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Research article

Diagnostic performance of preoperative CT in differentiating between benign and malignant origin of suspicious gallbladder lesions

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ABSTRACT

Purpose: To determine diagnostic performance of preoperative CT in differentiating between benign and malignant suspicious gallbladder lesions and to develop a preoperative risk score.
Method: All patients referred between January 2007 and September 2018 for suspicion of gallbladder cancer (GBC) or incidentally found GBC were retrospectively analyzed. Patients were excluded when preoperative CT or histopathologic examination was lacking. Two radiologists, blinded to histopathology results, independently reviewed CT images to differentiate benign disease from GBC. Multivariable analysis and internal validation were used to develop a risk score for GBC. Model discrimination, calibration, and diagnostic performance were assessed.
Results: In total, 118 patients with 39 malignant (33 %) and 79 benign (67 %) lesions were included. Sensitivity of CT for diagnosing GBC was 90 % (95 % confidence interval [CI]: 76–97). Specificity rates were 61 % (95 % CI: 49–72) and 59 % (95 % CI: 48–70). Three predictors of GBC (irregular lesion aspect, absence of fat stranding, and locoregional lymphadenopathy) were included in the risk score ranging from -1 to 4. Adequate performance was found (AUC: 0.79, calibration slope: 0.89). In patients allocated >0 points, the model showed higher performance in excluding GBC than the radiologists (sensitivity 92 % [95 % CI: 79–98]). Moreover, when allocated >3 points, the risk score was superior in diagnosing GBC (specificity 99 % [95 % CI: 93–100]).
Conclusions: Sensitivity rates of CT for differentiation between benign and malignant gallbladder lesions are high, however specificity rates are relatively low. The proposed risk score may facilitate differentiation between benign and malignant suspicious gallbladder lesions.

1. Introduction

Although gallbladder cancer (GBC) is rare, it is the sixth most common malignancy of the gastro-intestinal tract [1,2]. It is characterized by locally aggressive behavior with early spread to regional lymph nodes [1]. Complete resection is the only curative treatment [3].

At present, overall 5-year survival rates are up to 13 % [4,5]. This poor prognosis is due to the unfavorable anatomical position of the gallbladder and non-specific symptoms, which make it difficult to diagnose clinically [6]. Only in patients with T1b/T2 tumors undergoing radical resection, long-term survival has been reported, with a 5-year survival rate of 53 % [5]. However, in the majority of cases, GBC is found at an advanced stage, when surgery is no option anymore [7]. To offer patients the best treatment, it is important to correctly diagnose GBC. Moreover, selecting those patients who should be treated in a dedicated hepato-pancreato-biliary (HPB) hospital would lead to better

Abbreviations: GBC, gallbladder cancer; IQR, interquartile range; HPB, hepato-pancreato-biliary; MDT, multidisciplinary team; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; AUC, area under the curve; ROI, region of interest; OR, odds ratio.

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use of specialized healthcare.

Even though ultrasound is the key imaging modality for diagnosing gallbladder disorders, other techniques, such as computed tomography (CT), have been increasingly used to evaluate gallbladder lesions [8]. However, differentiating benign from malignant disorders remains challenging, since benign gallbladder disease may mimic GBC, and vice versa [8–10]. Presence of specific radiological lesion characteristics can indicate either benign gallbladder disease or GBC [11,12]. A risk score based on radiological predictors might facilitate the discrimination between benign and malignant disease, but has not been established yet.

The preoperative diagnostic value of CT for differentiating benign from malignant gallbladder disorders has been studied before. However, it concerned only small studies, or only one type of lesion was included [13–15].

The purpose of this study was to analyze the diagnostic performance of preoperative CT in the differentiation between benign and malignant origin of suspicious gallbladder lesions. Moreover, we aimed to develop a risk score for GBC based on radiological lesion characteristics.

2. Material and methods

This retrospective study was approved by the Ethics Committee of our hospital (IRB number: 201800272), and necessity of obtaining informed consent was waived.

2.1. Patients

All consecutive patients referred to our tertiary hospital between January 2007 and September 2018 for a suspicion of GBC or for an incidentally found GBC after cholecystectomy, who underwent preoperative contrast enhanced CT imaging in portal venous phase and in whom histopathological confirmation was available, were included. A suspicion of GBC was defined as a polyp with a diameter >10 mm, a focal or diffuse wall thickening, a massive lesion, or a porcelain gallbladder (which has been associated with an increased risk of GBC) [1]. Patients referred for incidental GBC were only included when CT was performed prior to cholecystectomy.

Patients were retrospectively identified from a prospectively maintained surgical institutional database. In addition, treatment options for all patients are discussed during multidisciplinary team (MDT) meetings, and therefore, each MDT patient list was manually searched to ensure inclusion of each eligible patient.

2.2. Data collection

Perioperative data (age, gender, date of surgery and CT, reason of referral) and histopathological records (pathology results, pTNM stage, tumor differentiation) were obtained from our institutional database. In case of missing data, electronic patient files were searched for additional information.

2.3. Surgical procedure

Patients with a suspicion of GBC underwent a radical cholecystectomy with frozen section of the gallbladder during laparotomy. If frozen section was positive and signs of disseminated disease were absent, a lymph node dissection of the hepatoduodenal ligament and a wedge resection of the gallbladder bed were performed.

Patients referred with incidental GBC underwent a similar approach after previous cholecystectomy in the referring hospital and after exclusion of disseminated disease on postoperative CT imaging [16].

2.4. Image evaluation

To characterize and stage the gallbladder abnormality detected at ultrasound or incidentally found after cholecystectomy, all patients underwent a full-dose contrast-enhanced CT scan in the arterial and portal venous phase with a reconstructed slice thickness of ≥2 mm. Fasting prior to CT was not part of the scan protocol. Two abdominal radiologists, both blinded to all data, independently reviewed the preoperative CT scans. A standardized form for image evaluation was used (Appendix Table A1). Attenuation of gallbladder lesions was determined in the portal venous phase using regions of interest (ROIs) at the largest part, measured twice and then averaged. Dilation of the extrahepatic bile ducts was defined as a diameter >5 mm up to the age of 50 years with an accepted increment of 1 mm per decade [17]. Intrahepatic bile ducts were considered dilated when the diameter exceeded 2 mm [18]. Vascular involvement included portal vein or hepatic artery involvement, and was defined as vessel wall irregularity or tumor reaching the vessel wall [19].

2.5. Final conclusion

Each reviewer independently provided a conclusion by using a five-point scale: (1) definitely benign, (2) probably benign (i.e. predominantly signs of benign disease, but less clear then for 'definitely benign' disease), (3) equivocal (i.e. equally suspicious of benign and malignant disease), (4) probably GBC (i.e. predominantly signs of malignant disease, but less clear then for 'definitely GBC'), (5) definitely GBC. The endpoints of this scale were predefined, based on the results of several previous studies [11,20]. Characteristics of an overt benign lesion (category 1) were: a diffuse gallbladder wall thickening, pericholecystic fat stranding, and presence of cholelithiasis without signs of malignant disease. Characteristics of overt GBC (category 5) were: a massive lesion, irregular lesion aspect, and involvement of adjacent liver parenchyma without signs of benign disease. Lesions defined by the radiologists as category 3–5 were considered malignant in the final conclusion, while lesions defined as category 1 or 2 were considered benign. After the independent evaluation session, a consensus reading was performed for lesions in which radiological variables differed between both radiologists.

2.6. Statistical analysis

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with 95 % confidence intervals (CI) of CT scans were calculated for each reviewer. Interobserver variability was calculated using Cohen's kappa.

To determine significant radiological differences between benign and malignant disease, univariable analysis was performed.

A multivariable logistic regression analysis was performed to identify predictors of GBC by selecting lesion characteristics based on literature and clinical expert opinion [11,21]. Lesion characteristics included in multivariable analysis were determined before running analyses and included four predictors: pericholecystic fat stranding, locoregional lymphadenopathy, irregular lesion aspect, and mean attenuation of the lesion. Final pathology (benign/malignant) was used as dependent factor. Only predictors with a P-value ≤ 0.157 were included in the risk score according to the Akaike criteria [22].

The model for the risk score was internally validated by bootstrapping 250 samples. To adjust for overoptimism, coefficients were multiplied by the shrinkage factor (calibration slope) obtained from bootstrapping. The area under the curve (AUC) was obtained to assess the performance of the risk score. A calibration plot was constructed to assess the agreement between observed and predicted risks.

Risk points were calculated for each predictor, by dividing each regression coefficient by the smallest regression coefficient. A risk score was developed by using these risk points. Based on clinical expert opinion, the total derived points were divided into three categories: low, intermediate, and high risk. Sensitivity, specificity, PPV, and NPV with 95 % CIs were calculated for the thresholds of risk categories.

P-values ≤0.05 were considered statistically significant. All

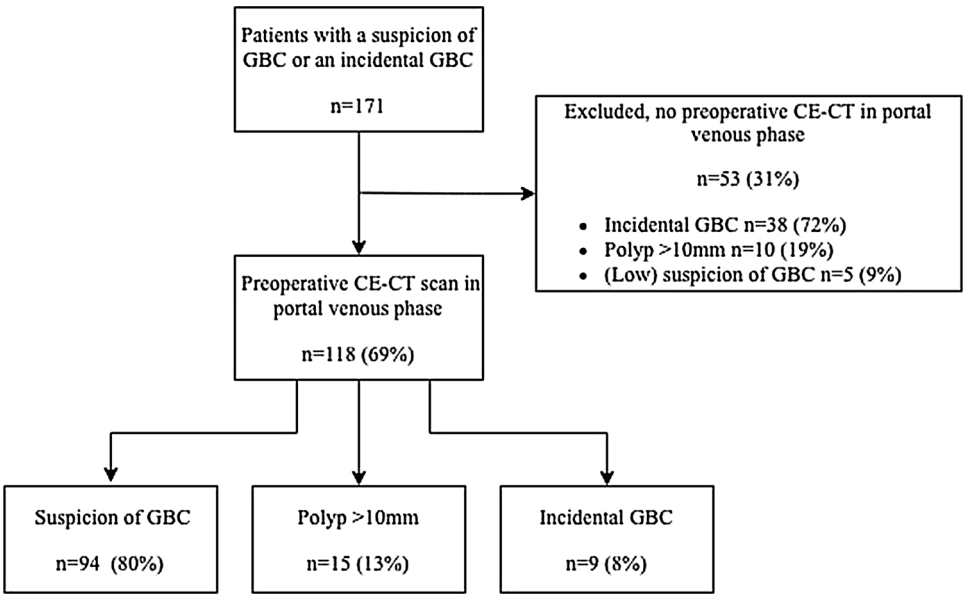

Fig. 1. Flowchart study sample.
GBC = gallbladder cancer, CE-CT = contrast enhanced computed tomography.

Table 1
Baseline characteristics.

Characteristic	Total n = 118	Benign n = 79	Malignant n = 39	P-value
Median age, in years (IQR)	66 (58–73)	64 (57–71)	69 (59–77)	0.047
Sex				
Female	73 (61.9)	50 (63.3)	23 (59.0)	0.69
Male	45 (38.1)	29 (36.7)	16 (41.0)	
Type of surgery				0.36
Simple cholecystectomy	51 (43.2)	50 (63.3)	1 (2.6)[b]	
+ wedge resection	40 (33.9)	24 (30.4)	16 (41.0)	
+ anatomical resection s4/5	5 (4.2)	4 (5.1)	1 (2.6)	
Completion resection (incidental GBC)	6 (5.1)	0 (0.0)	6 (15.4)	
Extended[a]	4 (3.4)	0 (0.0)	4 (10.3)	
Open-close procedure	9 (7.6)	0 (0.0)	9 (23.1)	
No (additional) surgery	3 (2.5)	1 (1.3)	2 (5.1)	

IQR = interquartile range.
[a] extended surgery was defined as ≥3 liver segments and/or a pancreatoduodenectomy.
[b] Melanoma metastasis. Numbers are presented as n (percentage of group).

statistical analyses were performed using SPSS version 23.0 (IBM Corporation, Armonk).

3. Results

3.1. Patient characteristics

A total of 171 patients with a suspicion of GBC on imaging or proven GBC were referred to the study center. Of these, 51 patients (30 %) were excluded because no preoperative CT was available. Another two patients (1%) were excluded because no portal venous contrast phase on CT was available. A total of 118 patients (69 %) were included in the study, consisting of 45 men (62 %) and 73 women (38 %) (Fig. 1). Median age was 66 years (interquartile range [IQR] 58–73). Reason for referral concerned a suspicion of GBC in 94 patients (80 %), a gallbladder polyp >10 mm in 15 patients (13 %), and an incidental GBC in 9 patients (8%). Details of surgical procedures are presented in Table 1. Three patients (2%) did not undergo any surgical procedure at our

Table 2
Histopathological results.
N0
13
33.3

Characteristic	Total n = 118	%
Benign	79	
Cholecystitis	54	68.4
Chronic	48	60.8
Xanthogranulomatous	5	6.3
Acute	1	1.3
Adenomyomatosis	15	19.0
Adenoma	3	3.8
Porcelain[a]	2	2.5
Other	5	6.3
Malignant	39	
Adenocarcinoma	33	84.6
Adenosquamous carcinoma	2	5.1
High-grade dysplasia	2	5.1
Metastases[b]	2	5.1
Differentiation[c]		
Good	3	20.0
Good-moderate	2	13.3
Moderate	6	40.0
Moderate-poor	3	20.0
Poor	1	6.7
pT stage		
T1	3	7.7
T2	14	35.9
T3	8	20.5
T4	1	2.6
Tx	13	33.3
pN stage		
N1	11	28.2
Nx	15	38.5
pM stage		
M0	5	12.8
M1	1	15.4
Mx	33	84.6

[a] Without signs of malignancy.
[b] Of cholangiocarcinoma (n = 1) and melanoma (n = 1).
[c] 24 missing values in pathology reports. Numbers are presented as n (percentage of group).

Table 3
Diagnostic performance of CT and the CT-based preoperative risk score.

Diagnostic outcome	Reviewer 1	Reviewer 2	Risk score cut off >0 n = 83	Risk score cut off >3 n = 15
Sensitivity	90 % (76–97)	90 % (76–97)	92 % (79–98)	36 % (21–53)
Specificity	61 % (49–72)	59 % (48–70)	41 % (30–52)	99 % (93–100)
PPV	53 % (46–60)	52 % (45–59)	43 % (38–48)	93 % (66–99)
NPV	92 % (82–97)	92 % (82–97)	91 % (78–97)	76 % (71–80)

Data in parentheses are 95 % confidence intervals.

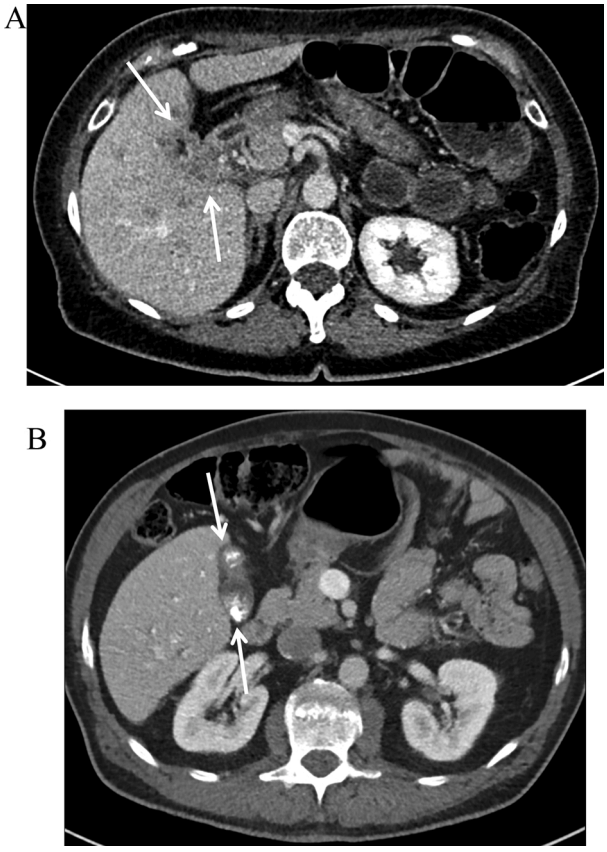

Fig. 2. A. Axial CT image in the portal venous phase of an 54-year-old woman showing a small gallbladder with irregular wall thickening and moderate heterogeneous enhancement. The wall thickening was considered malignant by both readers in the final conclusion. However, histopathological examination showed no signs of malignancy. **B.** Axial CT image in the portal venous phase of an 61-year-old man showing multifocal moderate wall thickening of the gallbladder with cholelithiasis. The gallbladder abnormalities were considered benign by both readers in the final conclusion. However, histopathological examination revealed adenocarcinoma.

hospital, due to unresectable disease on preoperative imaging (n = 1), due to an incidentally found T1b tumor with no need for further treatment (n = 1), and due to benign disease after revision of histopathology results (n = 1).

3.2. Histopathological results

Histopathological examination revealed 39 patients (33 %) with malignant disease, and 79 patients (67 %) with benign gallbladder disease. An extensive overview of the histopathological results can be found in Table 2. In all patients, the reference standard consisted of histopathological examination (n = 109 resection specimen, n = 9 core needle biopsy).

3.3. Diagnostic performance of CT

The median interval between CT scan and surgery or biopsy was 65 days (IQR 47–98). Derived sensitivity and specificity rates, PPV, and NPV are presented in Table 3. Interobserver agreement was moderate for the differentiation between benign and malignant lesions ($\kappa = 0.500$), and fair when using the five-point scale ($\kappa = 0.240$).

A total of 43 benign lesions (36 %) were considered malignant by the radiologists due to: allocation as 'equivocal' (n = 28), irregular lesion aspect (n = 7), vascular involvement (n = 2), liver involvement (n = 2), heterogeneous patchy moderate enhancement in portal venous phase (n = 2), a large mass (n = 1), or presence of a suspicious lung nodule (n = 1).

Seven malignant lesions (6%) were considered benign due to: absence of malignant characteristics at CT (n = 5), or diffuse relatively smooth wall thickening combined with presence of cholelithiasis (n = 2).

Fig. 2 shows examples of lesions with disagreement between the final radiological conclusion and histopathological diagnosis.

3.4. Radiological predictors of GBC

An extensive overview of the lesion characteristics can be found in Table 4. In univariable analysis, type of lesion ($p = 0.04$), irregular lesion aspect ($p < 0.001$), dilatation of intrahepatic bile ducts ($p = 0.01$), presence of lymphadenopathy ($p < 0.001$), vascular invasion ($p = 0.02$), and invasion of the adjacent liver parenchyma ($p = 0.05$) were significantly associated with GBC. In multivariable analysis, only presence of locoregional lymphadenopathy (odds ratio [OR] 6.7, $p = 0.002$), and irregular lesion aspect (OR 7.1, $p = 0.004$) were significantly associated with GBC (Table 4). Examples of typical benign and malignant lesions are shown in Fig. 3.

3.5. Preoperative CT-based risk score

Three out of four predictors (i.e. an irregular lesion aspect, presence of locoregional lymphadenopathy, and absence of pericholecystic fat stranding) had a P-value ≤ 0.157 in multivariable analysis and were included in the CT-based preoperative risk score for GBC (Table 5). Median lesion attenuation had a P-value >0.157 in multivariate analysis (Table 4), and therefore, was excluded from the risk score [22].

The predicted and observed cases of malignancy of this risk score are plotted in Fig. 4. Internal validation provided a shrinkage factor (calibration slope) of 0.89 to correct predictor coefficients for overoptimism. The AUC of the risk score was 0.80 (95 % CI: 0.72–0.89), and after internal validation 0.79 (95 % CI: 0.71–0.89).

Three different risk categories were determined: low (≤0 points), intermediate (1–3 points), and high risk (>3 points) (range: -1 to 4). The risk score categorized 35 patients (30 %) as low risk (benign: n = 32 [91 %], malignant: n = 3 [9%]), 68 (58 %) as intermediate risk (benign: n = 46 [68 %], malignant: n = 20 [29 %]), and 15 (13 %) as high risk (benign: n = 1 [7%], malignant: n = 14 [93 %]). The predicted risk of GBC was 0.07 (observed risk 0.09) and 0.83 (observed risk 0.93) in the low and high risk category, respectively (Fig. 5). Sensitivity, specificity, PPV, and NPV with 95 % CI of the thresholds of the risk categories are presented in Table 3.

4. Discussion

This study analyzed the diagnostic performance of CT in the differentiation between benign and malignant suspicious gallbladder lesions. Obtained sensitivity of CT for diagnosing gallbladder cancer was 90 % for both reviewers, with a specificity of 59–61 %. A risk score for

Table 4
Univariable and multivariable analysis of lesion characteristics at CT scans.

				Univariable analysis	Multivariable analysis		
Characteristic	Total n = 118	Benign n = 79	Malignant n = 39	P-value	OR	95 % CI	P-value
Median attenuation, HU (IQR)[a]	76 (61–92)	78 (62–92)	69 (61–90)	0.23	0.99	0.97 - 1.01	0.21
Type of lesion				0.04			
Lesion not visible	7 (5.9)	7 (8.9)	0 (0.0)				
Focal	58 (49.2)	34 (43.0)	24 (61.5)				
Polypoid	5 (4.2)	2 (2.5)	3 (7.7)				
Diffuse	48 (40.7)	36 (45.6)	12 (30.8)				
Location of lesion				0.38			
Lesion not visible	6 (5.1)	6 (7.6)	0 (0.0)				
Diffuse	44 (37.3)	32 (40.5)	12 (30.8)				
Fundus	36 (30.5)	23 (30.4)	12 (30.8)				
Fundus + corpus	7 (5.9)	4 (5.1)	3 (7.7)				
Corpus	12 (10.2)	6 (7.6)	6 (15.4)				
Neck	8 (6.8)	4 (5.1)	4 (10.3)				
Neck + corpus	4 (3.4)	2 (2.5)	2 (5.1)				
Neck + fundus	1 (0.8)	1 (1.3)	0 (0.0)				
Aspect of lesion				<0.001			0.004
Smooth	39 (33.1)	36 (45.6)	3 (7.7)		1.00	–	
Irregular	79 (66.9)	43 (54.4)	36 (92.3)		7.13	1.85 – 27.46	
Cholelithiasis				0.96			
No	76 (64.4)	51 (64.6)	25 (64.1)				
Yes	42 (35.6)	28 (35.4)	14 (35.9)				
Fat stranding				0.07			0.056
No	87 (73.7)	54 (68.4)	33 (84.6)		1.00	–	
Yes	31 (26.3)	25 (31.6)	6 (15.4)		0.32	0.10 – 1.03	
Dilatation IHBD				0.01			
No	95 (80.5)	69 (87.3)	26 (66.7)				
Yes	23 (19.5)	10 (12.7)	12 (33.3)				
Dilatation EHBD[b]				0.35			
No	104 (88.9)	71 (91.0)	33 (84.6)				
Yes	13 (11.1)	7 (9.0)	6 (15.4)				
Locoregional lymphadenopathy				<0.001			0.002
No	95 (80.5)	72 (91.1)	95 (80.5)		1.00	–	
Yes	23 (19.5)	7 (8.9)	23 (19.5)		6.72	2.04 – 22.16	
Liver invasion				0.046			
No	95 (80.5)	68 (86.1)	27 (69.2)				
Yes	23 (19.5)	11 (13.9)	12 (30.8)				
Vascular invasion				0.02			
No	106 (89.8)	75 (94.9)	31 (79.5)				
Yes	12 (10.2)	4 (5.1)	8 (20.5)				
Suspicion of metastases				0.06			
No	109 (92.4)	76 (96.2)	33 (84.6)				
Yes	9 (7.6)	3 (3.8)	6 (15.4)				

[a] 7 missing values (lesion not visible).
[b] 1 patient with dilatation due to portal biliopathy, excluded from this analysis. HU = Hounsfield Units, IQR = interquartile range, IHBD = intrahepatic bile ducts, EHBD = extrahepatic bile ducts. Numbers are presented as n (percentage of group).

gallbladder cancer on preoperative CT imaging was developed for suspicious lesions, including irregular lesion aspect, absence of pericholecystic fat stranding, and presence of locoregional lymphadenopathy. The risk score showed adequate performance (AUC: 0.79, calibration slope: 0.89).

Few studies on the diagnostic value of CT for the differentiation between benign and malignant gallbladder disease have been published. Reported sensitivity and specificity rates of the differentiation between benign lesions and GBC at CT were 72 % and 91 % for polypoid lesions, 71–88 % and 65–92 % for xanthogranulomatous cholecystitis, and 30–50 % and 93–98 % for adenomyomatosis, respectively [13–15,20]. Variations in study size and in- and exclusion criteria could explain differences in diagnostic performance of CT compared to the present study. Previous studies included only one type of benign lesion, instead of including all different types, the latter being more representative for daily practice. Moreover, in the study of Jang et al., advanced stages of GBC were excluded [15]. In addition, differences in CT machines and protocols could lead to varying results. However, a strong collaboration exists between the referring hospitals and our center, and CT protocols and image quality were harmonized as much as possible.

A moderate interobserver agreement was found regarding the final conclusion of benign or malignant disease. Comparable κ-values have been reported in previous studies [13,14,20]. An important explanation for interobserver disagreements in this study could be the use of a 5-point scale. Although this scale corresponds most with conclusions of radiologists in daily practice, it can complicate interpretation of final diagnoses (benign vs. malignant) in statistical analyses. In this scale the score 'equivocal' was considered malignant, since the origin of the suspicious gallbladder lesion remains unclear prior to surgery, and therefore, these patients should be treated at a specialized center. However, this division might overestimate the actual number of malignant suspicions. Other factors influencing correct final radiological diagnosis were irregular lesion aspect and presence of cholelithiasis. Although irregular lesion aspect was significantly associated with GBC and presence of cholelithiasis was significantly related with benign lesions, these factors can be reported vice versa [11,23]. This illustrates the challenges clinicians face on a daily basis when evaluating CT images.

According to our data, 33 % of patients with a suspicion of GBC that underwent surgery were finally diagnosed with malignant disease, emphasising the need for correct preoperative diagnosis. For efficient use of tertiairy HPB healthcare, it is important to reduce the number of patients undergoing major surgery for benign gallbladder disease. Even more important, imaging techniques with high diagnostic accuracy are

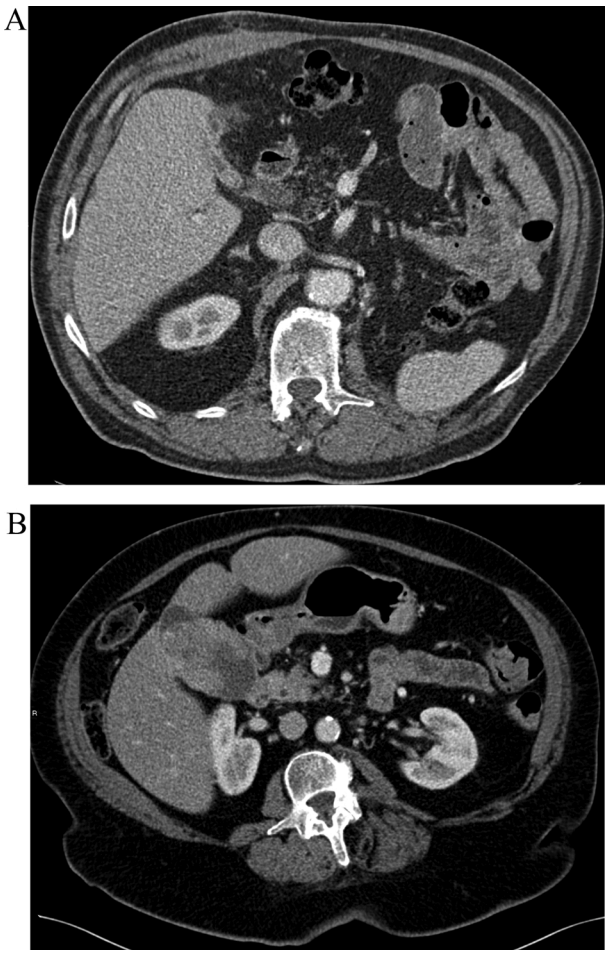

Fig. 3. A: Axial CT image in the portal venous phase of an 80-year-old man showing relatively smooth diffuse gallbladder wall thickening with increased enhancement and fat stranding around the gallbladder fundus. A gallstone with low calcium content was present in the gallbladder neck. Histopathological analysis of the gallbladder after cholecystectomy revealed chronic inflammation without signs of malignancy. **B:** Axial CT image in the portal venous phase of an 72-year-old woman showing a large enhancing mass in the gallbladder with irregular contours, highly suggestive of malignancy. Enlarged lymph nodes were present in the liver hilus (not shown). The patient underwent open cholecystectomy, resection of surrounding liver parenchyma, and regional lymphadenectomy. Adenocarcinoma of the gallbladder was confirmed at histopathological examination.

Table 5
Final model and preoperative CT-based risk score.

Predictor	Odds ratio	P-value	CFC	Adj CFC	Points
Presence of pericholecystic fat stranding	0.4 (0.1–1.8)	0.10	−0.97	−0.86	−1
Irregular lesion aspect	8.8 (2.4–33.1)	0.001	2.18	1.93	2
Locoregional lymphadenopathy	7.2 (2.3–22.6)	0.001	1.98	1.75	2

CFC = coefficient, adj = adjusted. Data in parentheses are 95 % confidence intervals. Only predictors with P-value ≤ 0.157 in multivariable analysis (Table 4) were included in the risk score.

needed. This would minimize the risk of missing a malignacy and enable early diagnosis of GBC, thereby offering patients best treatment options, and leading to most efficient use of specialized HPB healthcare.

Differentiation between between benign disease and GBC might be facilitated by determining CT-based preoperative risk factors for malignancy. In our study, a focal lesion type, presence of irregular lesion aspect, vascular and liver invasion, dilatation of intrahepatic bile ducts and presence of locoregional lymphadenopathy were significantly associated with GBC at univariable analysis. Moreover, although not significant, suspicion of metastases and absence of pericholecystic fat stranding were more frequently observed in patients with malignant lesions. At multivariable analysis, irregular lesion aspect and presence of locoregional lymphadenopathy emerged as independent predictors of GBC with high OR. However, the CIs were wide, indicating low precision. Although almost each patient with GBC had irregular lesion aspect, it should be noted that slightly more than 50 % with a benign lesion also had irregular lesion aspect and therefore, this could result in many false positives. In a study of Goshima et al., a significant association between GBC and liver invasion and dilatation of the intrahepatic bile ducts at preoperative CT has also been reported [23]. In addition, Levy et al. also concluded that biliary obstruction and lymph node metastases are frequently associated with GBC [24]. Moreover, Chang et al. concluded that a focal lesion, absence of pericholecystic fat stranding, and presence of lymph node enlargement were significantly more often observed in GBC than in xanthogranulomatous cholecystitis [11]. In addition, hyperenhancement of a thick inner layer, non or faintly enhancement of a thin outer layer, and discontinuity in mucosal lining have been reported to be associated with GBC [11,23,25]. In the current study, the

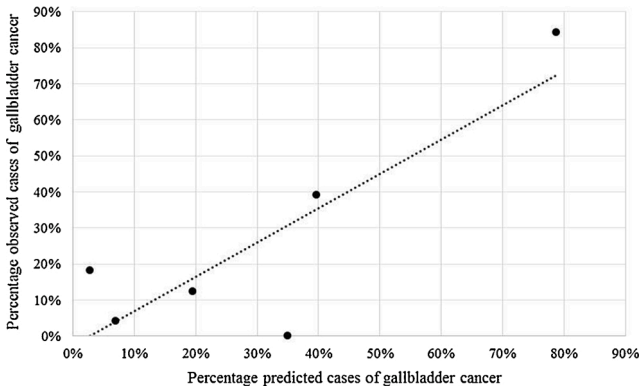

Fig. 4. Calibration plot with percentage predicted and observed cases of gallbladder cancer.
The slope has a target of 1. A calibration slope with a value above 1 implies that predicted risks are too moderate (i.e. too high for patients at low risk and too low for patients at high risk), while a slope value below 1 implies that predicted risks are overestimated (i.e. too high for patients at high risk and too low for patients at low risk). The points represent the different risk scores. The calibration of this slope was 0.89, indicating adequate performance.

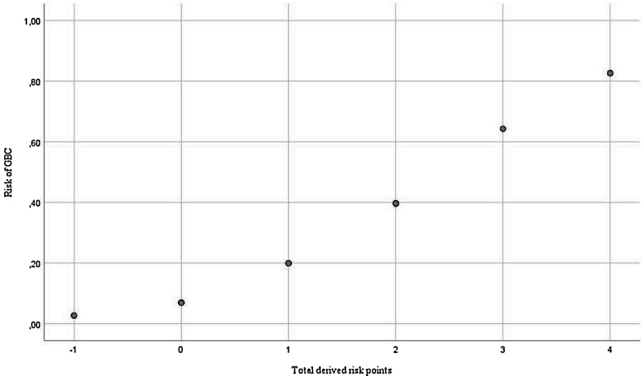

Fig. 5. Predicted risk of gallbladder cancer per risk score.
GBC = gallbladder cancer.

different layers of the gallbladder wall were often difficult to distinguish at CT, and therefore, the density of the wall thickening was determined as a proxy of the enhancement pattern. Perhaps, MRI is more suitable to distinguish the different gallbladder wall layers.

In this study, a CT-based preoperative risk score was constructed including the following factors: irregular lesion aspect, absence of pericholecystic fat stranding, and presence of locoregional lymphadenopathy. This risk score ranging from -1 to 4 can be a valuable tool for clinicians to optimize correct diagnosis of GBC in suspicious gallbladder lesions. In patients allocated a total risk score >0, the model showed a higher performance in excluding GBC than that obtained by the radiologists (sensitivity 92 % vs. 90 %). Moreover, in those patients classified as high risk, the predictive model was better in diagnosing GBC than the radiologists (specificity 99 % vs. 59–61 %). Calibration and discrimination of the risk score showed adequate performance [26,27]. Hence, although external validation is necessary, the model could be used by clinicians as an additional tool to estimate the risk of GBC at CT imaging in suspicious gallbladder lesions.

This study has several limitations. First, due to its retrospective design, a selection bias might exist, and patients in whom no preoperative CT scan was performed, had to be excluded. To overcome any selection bias, future research should be designed as large prospective studies. In addition, this offers the opportunity to externally validate our model. Second, the selection of patients in the current study might impede generalizability of the results. However, this selection method enabled us to define the value of CT in determining which patients with a suspicious gallbladder lesion should be treated in a dedicated HPB hospital. This could lead to better use of academic healthcare. Third, since the study sample consisted of a relatively low number of malignant events, we could only include four predictors in multivariable analysis [28]. A larger study sample containing more GBC cases potentially leads to a larger number of predictive factors.

In conclusion, sensitivity rates of CT for the differentiation between benign and malignant suspicious gallbladder lesions are high, however specificity rates are relatively low. Use of the proposed preoperative CT-based risk score may facilitate differentiation of suspicious gallbladder lesions into benign and malignant origin, and thereby optimize treatment and use of specialized HPB healthcare.

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CRediT authorship contribution statement

Hendrien Kuipers: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing - original draft. **Frederik J.H. Hoogwater:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Gea A. Holtman:** Methodology, Software, Validation, Formal analysis, Writing - review & editing. **Jules J.G. Slangen:** Investigation, Resources, Writing - review & editing. **Robbert J. de Haas:** Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Supervision. **Marieke T. de Boer:** Conceptualization, Methodology, Resources, Writing - review & editing, Supervision.

Declaration of Competing Interest

None.

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Appendix A

Table A1
Standardized form for evaluation of CT scans.

Intravenous contrast
Oral contrast
Phase (pre-contrast, arterial, portal venous, delayed)
Type of lesion (focal, diffuse, massive, polypoid)
Location of gallbladder wall thickening (fundus, corpus, neck, diffuse)
Lesion aspect (smooth or irregular)
Shortest and largest diameter of gallbladder wall thickening
Attenuation (Hounsfield units)
Presence of cholelithiasis
Presence of pericholecystic fat stranding
Dilation of the intrahepatic and/or extrahepatic bile ducts
Locoregional lymphadenopathy
Invasion of adjacent liver parenchyma
Vascular involvement
Suspicion of metastases

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