PATHOLOGICA 2022;114:138-145
DOI: 10.32074/1591-951X-291

Original Article

Descriptive analysis of incidental and operable gallbladder carcinoma cases: a UK centre experience

Sanwandana Karunaratne, Amila Gamage, Izhar N. Bagwan

Department of Histopathology, Berkshire Surrey Pathology Services, Royal Surrey County Hospital, Guildford, UK

Summary

Objective. To identify and compare significant or relevant prognostic factors in pre-operatively diagnosed, surgically resectable, gallbladder cancer and in incidentally detected gallbladder cancer cases.

Material and methods. Gallbladder resections (October 2009-March 2016) were identified on the histopathology Winpath database. Cases with a final histological diagnosis of gallbladder cancer (GBC) were categorised into: Group A: clinically suspected operable GBC (n = 13). Group B: incidental GBC with staged liver bed resection (n = 5). Group C: incidental GBC without staged liver bed resection (n = 15). The clinicopathological features were analysed in each group separately.

Results. The overall incidence of primary (GBC) was 0.66% and all the cases were adenocarcinomas, of which, 6 of 33 (18.2%) were grade 1 and 15 of 33 (45.4%) were grade 3. Male to female ratio is 1:2.3. Of the 33 patients with GBC 14 (42.4%) has died of disease at 18-month follow-up. 15 of 33 had perineural invasion and 10/21 (47.6%) cases showed lymph node matastasis. Six cases had positive surgical margin and 9/15 showed direct liver invasion. Higher stage disease (T3/T4) was seen in 10/14 cases.

Conclusion. The prognosis of primary GBC is poor and best clinical outcomes can be achieved with early diagnosis followed by radical cholecystectomy and staged liver resection with negative margins.

Key words: gallbladder, carcinoma, incidental, operable, prognosis

Received: April 11, 2021
Accepted: August 8, 2021

Correspondence
Izhar Bagwan
Department of Histopathology, Royal Surrey County Hospital, Egerton Road, Guildford GU2 7XX
E-mail: izhardrster@gmail.com

How to cite this article: Karunaratne S, Gamage A, Bagwan IN. Descriptive analysis of incidental and operable gallbladder carcinoma cases: a UK centre experience. Pathologica 2022;114:138-145. https://doi.org/10.32074/1591-951X-291

Introduction

Gall bladder carcinoma is relatively rare type of malignancy, accounting for 0.3% of all the new cases in United Kingdom. However, it is the 5th most common cancer in the digestive tract and the commonest malignancy in the biliary tract[1]. The incidence is higher among Native Americans, Hispanics and parts of North India than all the other ethnic groups [1-3]. It is relatively low in Europeans and very rare in black people [4]. About approximately 50% of GBC cases present as an incidental finding in gallbladders excised for gallstone disease [3-6]. Histologically most malignancies are adenocarcinoma; however, other morphological types have also been described[4]. Prognosis of GBC is known to be poor due to widespread disease at the time of diagnosis, even with recent advances in diagnostic modalities and therapeutic options. The present study was conducted to assess various prognostic factors in pre-operatively diagnosed surgically resectable GBC and in incidentally detected carcinoma GBC cases.

Materials and methods

All gallbladder resections, including laparoscopic/open cholecystectomies and gallbladder with liver bed resections performed from October 2009 till March 2016 were identified on the histopathology Winpath database. Only cases with a final diagnosis of GBC on the histopathology database were included in the study. Advanced stage GBC cases that were not offered surgery, but offered only palliative chemotherapy were excluded. Haematoxylin and eosin stained slides were reviewed to confirm the diagnosis. Histological subtyping was performed using WHO classification of Tumours, 8th Edition. The following data were collected: differentiation, size, status of resection margin, provisional tumour stage (pT), lymph node status (N stage) and presence or absence of lymphovascular and perineural involvement. Demographic data (age & sex) and follow-up data were extracted from the Somerset cancer registry and medical records.

The GBC cases included in the study were categorised into the following three groups:

Group A: clinically suspected surgically resected GBC (n = 13).

Group B: incidental GBC diagnosed on histology with staged liver bed resection (n = 5).

Group C: incidental GBC diagnosed on histology without staged liver bed resection (n = 15).

In three patients who had clinically suspected surgically resected carcinoma, the liver resection was not done as the lesions were polypoid and entirely within the lumen on CT scan.

The clinicopathological features were analysed in each group separately.

This was a retrospective data analysis on patient records and hence ethical approval exemption was given.

Results

A total of 10,047 gallbladder resections (including laparoscopic/open cholecystectomy, gallbladder with liver bed resections and gallbladder with pancreatic resections) had been performed at the tertiary cancer centre from October 2009 till March 2016. Of these, 9702 were found to be histologically benign. The remaining 345 gallbladder resections were associated with either primary or secondary malignancy. Three hundred and twelve of these 345 gallbladders were resected due to malignancies in the adjacent organs, mostly in liver or pancreas. Hence, 33 cases of surgically resectable primary GBC were identified on histopathology database.

During the same period, 34 cases of inoperable primary gallbladder carcinoma were diagnosed based on clinical and radiological examination in the institution and hence the total of GBC cases identified over a period of 6 years was 67 (33 + 34 = 67). The inoperable cases were treated by only chemotherapy without surgery. These cases were excluded from analysis in the current study. Histological assessment was performed on the 33 operable cases. These included five referral cases for histopathological review and for multi-disciplinary team (MDT) discussion. Therefore, the overall incidence of GBC was 0.66% (67 of 10,081 patients).

Clinical Data

The study included 10 males and 23 females for a 1:2.3 ratio. 32 of 33 patients were > 60 years of age, (one patient aged 38 years). The most common clinical presentation was chronic cholecystitis with/without cholelithiasis (18/33) followed by gallbladder/liver mass (13/33). Pre-operatively, GBC was suspected clinico-radiologically in 13 of 33 cases whereas 20 cases were identified incidentally only after histological examination (Tab. I).

Table I. Distribution of cases as per clinical/radiological presentation.

Clinical/Radiological presentation	Number of cases	Percentage
Chronic cholecystitis	10	31%
Cholelithiasis	8	24%
Benign polyp	2	06%
Gall bladder carcinoma	7	21%
Malignant polyp	4	12%
Malignant liver mass	2	6%

Histopathological Data

Three macroscopic tumour patterns were identified on gross examination (Fig. 1) – polypoid/mass forming, plaque and diffuse wall thickening (Tab. II). In 19 of 33 cases presence of calculi was identified on macroscopic examination (Fig. 1B & 1D). In some cases, the presence or absence of gallstones could not be entirely confirmed as the specimens were opened in theatre.

Exact tumour size was mentioned in 5 incidental cases (Group B & C) and in the remaining microscopic dimensions were assessed on histology slides. Five of 13 Group A cases (38.46%) showed a large tumour size in the range of 41-60 mm while four cases had tumour size < 20 mm.

The morphological subtype was adenocarcinoma

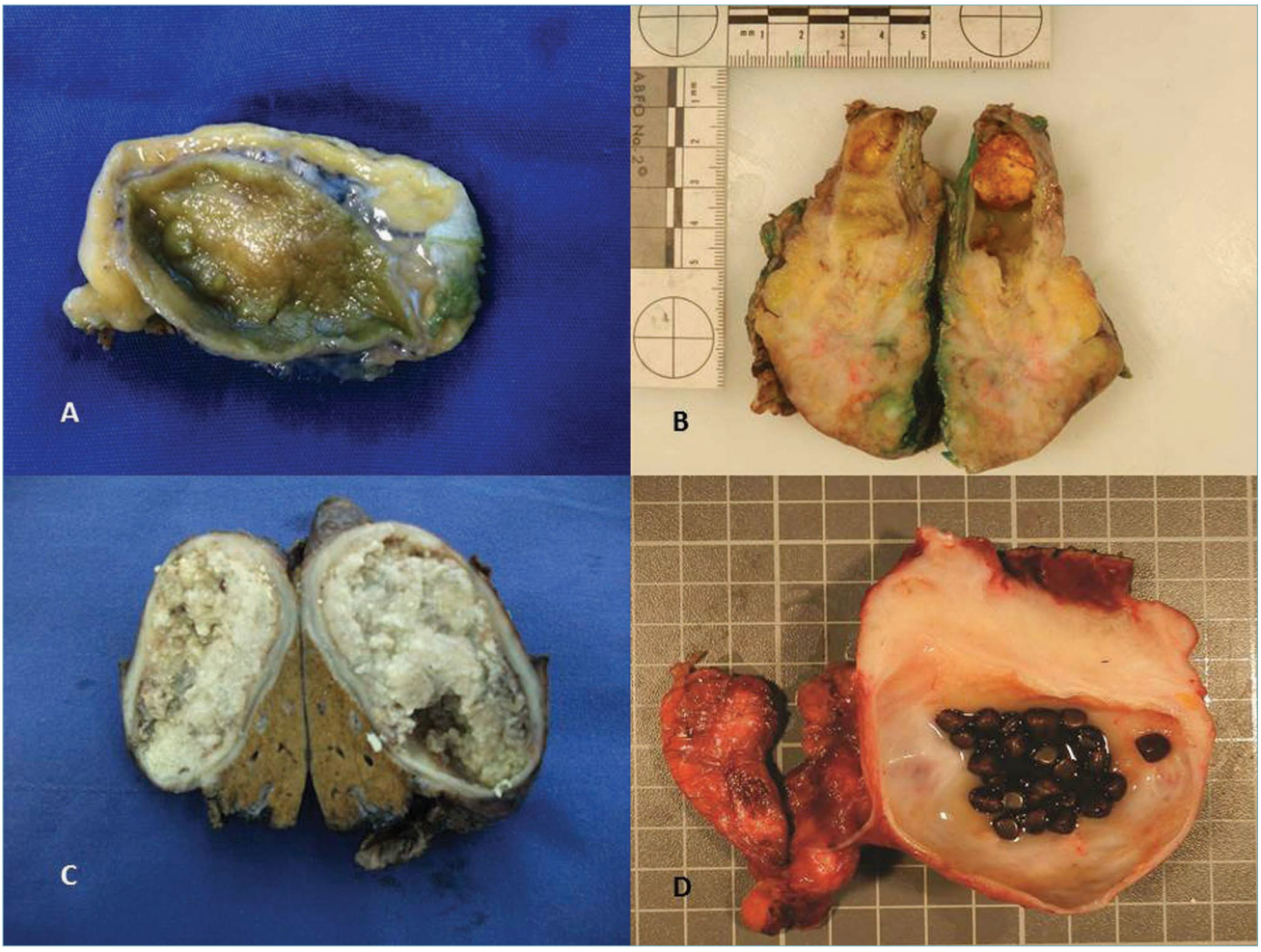

Figure 1. Macroscopic appearances of gallbladder cancer. (A) Incidental gallbladder cancer presenting as slightly raised plaque like lesion. (B) Advanced operable gallbladder cancer with extensive infiltration into the adjacent liver. Note the large gallstone. (C) Operable polypoid tumour completely obliterating the gallbladder lumen. (D) Note the diffuse thickening of the wall by the tumour with associated gallstones.

(Fig. 2A-E) in all cases with pure mucinous adenocarcinoma present in four of 33 cases. Other morphological subtypes like adenosquamous carcinoma, squamous cell carcinoma or neuroendocrine carcinoma were not identified. Well differentiated adenocarcinoma (grade 1) was seen only in Group B & C (6 cases), whereas in Group A the tumours were either moderate or poorly differentiated (grade 2 or 3). Altogether, 15 of 33 cases showed grade 3, poorly differentiated adenocarcinoma (45.4%).

Table II. distribution of cases as per macroscopic appearances.

Macroscopic appearances	Group A	Group B	Group C
Polypoid lesion	09	00	02
Plaque-like lesion	02	02	06
Diffuse wall thickening	02	03	07
Total	13	05	15

Perineural invasion was seen in 8/13 Group A cases, in 1/5 Group B cases and in 6/15 Group C cases. Lymphovascular invasion was seen in 8/13 Group A cases and in 7/15 Group C cases, but none in Group B cases. Altogether, perineural and lymphovascular invasions (Fig. 2F) were present in 15 of 33 cases (45.4%).

Background gallbladder mucosa showed high grade glandular dysplasia in 25 of 33 cases and low-grade dysplasia in one case (26/33-78.8%). Therefore, overall, 78.8% cases show a background of dysplastic changes. Intestinal metaplasia was seen in six cases

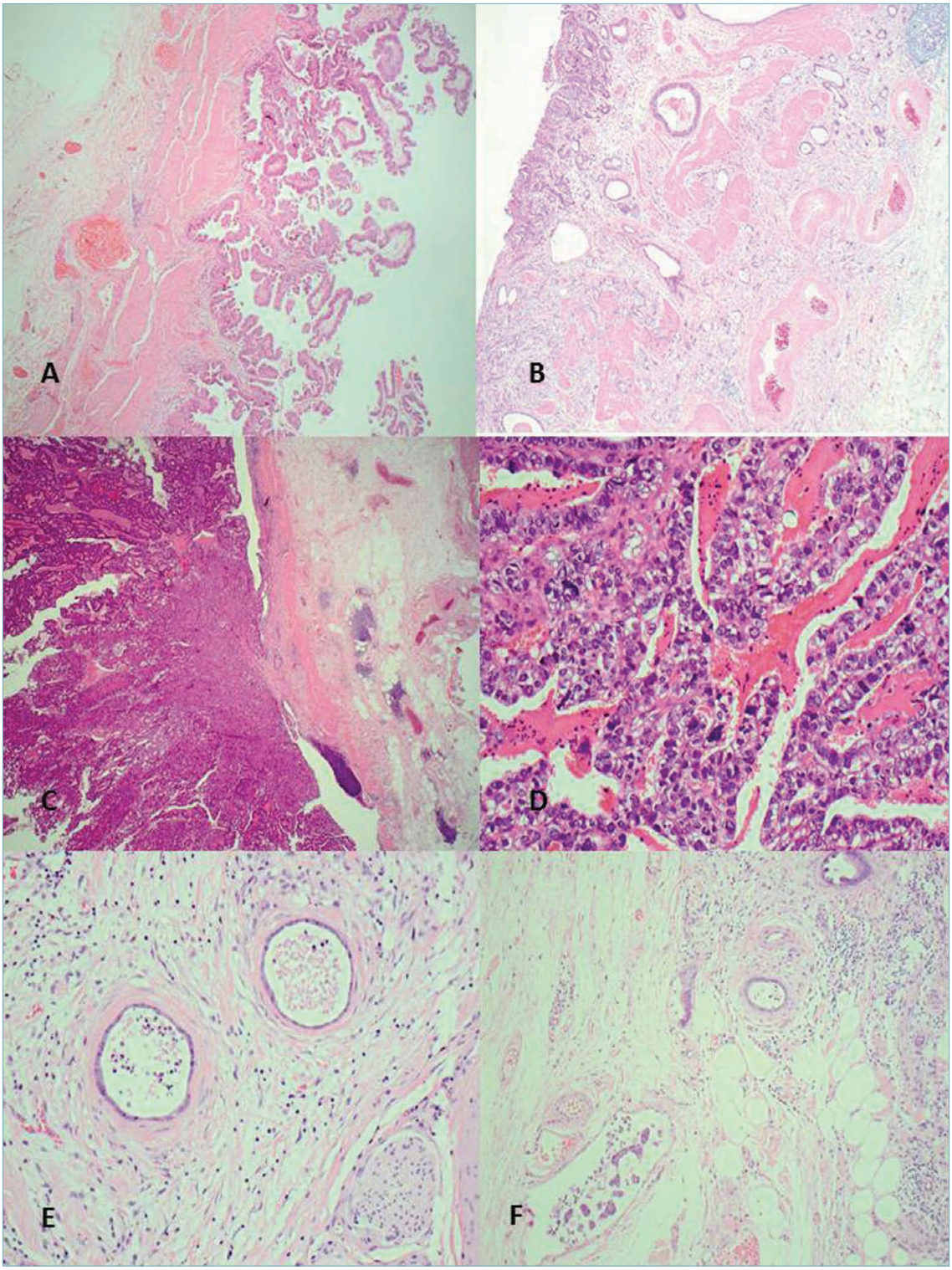

Figure 2. Histological appearances of gallbladder carcinoma. (A) Incidentally detected well differentiated adenocarcinoma with background high grade dysplasia (H & E 20X). (B) Moderately differentiated adenocarcinoma deeply infiltrating the gallbladder wall (H & E 40X). (C) Adenocarcinoma with polypoid tubulo-papillary architecture (H & E 20X). (D) Poorly differentiated/grade 3 adenocarcinoma (H & E 400X). (E) Higher magnification showing infiltrating well differentiated glands present within adventitial fat (H & E 400X). (F) Presence of lymphovascular invasion (H & E 200X).

(18.2%), chronic cholecystitis in 28 cases (84.8%) and acute on chronic cholecystitis was observed in three cases. One case of adenocarcinoma was associated with background mucosa associated lymphoid tissue (MALT) lymphoma.

Lymph nodes for histological assessment were present in 21 of 33 cases; metastases were seen in eight cases of Group C, one case of Group B and one case of Group A (total 10/21 cases-47.6%). The sites of lymph node metastases were cystic duct lymph node (9/10) and hepatic artery lymph node (1/10).

Liver resection was performed in 10 of 13 Group A cases, eight of which showed direct liver invasion. In the three cases that presented as intra-luminal polypoid lesions on radiology, the liver resection was not performed. In Group B, only one of five cases showed direct liver involvement.

Altogether, 6 out of 33 cases (18.2%) showed cystic duct resection margin involvement, including five in Group C and one in Group A. None of Group B cases showed margin involvement.

Tumour Staging (Tab. III)

The distribution of staging as per the groups is shown in Table III. The staging information in Group C was incomplete due to the fact these patients had not received staging liver resection; it was therefore considered provisional. The commonest tumour stage was pT2 (14/33-42.4%), followed by pT3 (10/33-30.3%). In Groups B & C, pT2 was the commonest stage whereas in Group A it was pT3 (6/13-46%).

Table III. Distribution of tumour stage (n = 33).

T Stage	Group A	Group B	Group C*	Total
pT1	03	00	04	07
pT2	02	05	07	14
pT3	06	00	04	10
pT4	02	00	00	02

*The staging in this group was incomplete as staged liver resection was not performed, hence considered provisional in this group.

Follow-up

Eighteen months follow-up was available for analysis. Seven of 13 cases in Group A and seven of 15 cases in Group C died of the disease, whereas all 5 cases in Group B showed no evidence of disease at the end of 18 months follow-up. Overall, 14 of 33 (42.4%) patients died of disease, six patients were alive with recurrent disease and 13 of 33 patients were free of disease.

In those patients who died of their disease, grade 3 adenocarcinoma was seen in 9/14 cases (64.28%), while the remaining 5 cases showed grade 2 differentiation. Perineural and lymphovascular invasions were seen in 9 of 14 cases (64.28%). Positive surgical margin was noted in 6 cases while the remaining 8 cases had clear margins. Lymph node metastasis was present in 5 of 14 cases. Six of these 14 cases showed direct liver involvement, all of which these belonged to Group A. Higher stage disease (T3/T4) was seen in 10 cases while 4 cases had T2 stage (Tabl. IV).

Table IV. Distribution of histological features in patients who died of disease (n = 14).

Histological Features	Group A (n = 7)	Group C (n = 7)
Histological Grade (G2/G3)	G2 (n = 3); G3 (n = 4)	G2 (n = 2); G3 (n = 5)
Perineural Invasion Present	5	4
Lymphovascular Invasion Present	6	3
Liver Involvement Present	6	0
Surgical Margin Positive	1	5
Lymph node metastasis Present	0	5
Tumour Stage (pT)	pT3 (n = 6); pT4 (n = 1)	pT2 (n = 4); pT3 (n = 3)
Background Dysplasia Present	6	3
Background Cholecystitis	7	7

In addition, patients who died of their disease showed poor differentiation (G2/G3 in all 14 cases), higher stage of disease and higher rate of positive margins as compared to patients who remained alive at the end of 18 months of follow-up (Tab. V).

Table V. Comparison of histological features in patients who died of disease (n = 14) and alive during 18 months of follow-up.

	Died during 18 months follow-up	Alive during 18 months follow-up
Number	14(42.4%)	19(57.6%)
Perineural invasion	9(64.28%)	6(31.57%)
Lymphovascular invasion	9(64.28%)	6(31.57%)
Positive margin	6(42.85%)	0
Direct liver involvement	6(42.85%)	3(15.78%)
Back ground dysplasia	9(64.28%)	17(89.47%)
Back ground cholecystitis	14(100%)	17(89.47%)
Tumour grade	G1-0 G2-9/14(64.28%) G3-5/14(35.71%)	G1-6/19(31.57) G2-7/19(36.84) G3-6/19(31.57)
High tumour stage	T3/T4-10/14(71.42%)	T3/T4-2/19(10.52%)

Discussion

The first case of GBC was reported by De Stoll in 1771 [6]. Although it is the fifth most common malignancy in the gastrointestinal tract and the commonest malignancy in the biliary tract, it is quite still rare with an incidence of 0.3-1.5% [6]. In the present study, the overall incidence of primary gallbladder carcinoma in patients undergoing a cholecystectomy was 0.66% (67 of 10,081 patients) thus confirming its rarity [2].

Nearly half of the GBC diagnosed incidentally are seen in resected gallbladder specimens of patients with symptoms due to cholelithiasis [7]. GBC usually presents at a late stage, even when found incidentally. The sign and symptoms are not specific, often resembling those of chronic cholecystitis [7]. Similar findings were noted in present this study, with the commonest presentation being chronic cholecystitis with or without cholelithiasis. Right upper quadrant abdominal pain is also seen as a presenting feature. Very rarely patients with GBC demonstrate signs of paraneoplastic syndrome, which may be the first manifestation of the disease [8].

GBC is more prevalent among women and a case control study from India, the following factors were noted to increase risk; mentioned that early menarche, late menopause, multiple pregnancies and childbirths appear to increase the risk [9]. Similarly Everson et al. described the mechanism by oestrogens increase the formation of gallstones, probably by elevating biliary cholesterol [10]. In present study the M:F ratio was 1:2.3 and apart from one, all the patients were > 60 years of age. It has been observed in various studies that GBC mortality increases with aging [11].

In 2017, Do et al. assessed the clinicopathologic characteristics in young Korean patients. In this patients cohort they observed a higher frequency of polypoid tumors arising in adenomas, a rare association with background intestinal metaplasia and dysplasia and a favourable prognosis [12]. However, in present study, the only young patient (age 38 years) had a poor outcome, after initial diagnosis, developing recurrence within the first year and going on to die from the disease. The patients had presented with an incidental grade 3 adenocarcinoma, margin positivity and involved lymph nodes. Background cholelithiasis with cholecystitis was seen in this case, but no adenoma or dysplasia was noted. Hence, disease progression in young patients is difficult to predict.

Arroyo et al. in 2016 observed that within South American population, age, female gender and genetic makeup were non-modifiable risk factors; however, cholelithiasis, typhoid disease, consumption of red chilli pepper contaminated with aflatoxin and very low socioeconomic status were risk factors (that could be intervened) [11]. Similarly, in 2016 Tomimaru et al. analysed incidental gallbladder cancers among Japanese population and observed as follows: Cholelithiasis in 48.5% of patients, polypoid lesions in 24.3% of patients, cholecystitis in 21.2% of patients and adenomyomatosis in 6% of patients [13]. However, in the current study out of 20 cases of incidental GBC, the clinicoradiological diagnosis was as follows: cholecystitis (50%), cholelithiasis (40%) and benign polyp (10%).

In present study, background cholecystitis (with/without cholelithiasis) and background dysplasia was observed in at least 80% of cases.

A study conducted by Ethun et al. from the United States in 2017, revealed that 60% of gallbladder carcinomas were clinically suspected and only 40% were non-incidental GBC [14]. There was a greater number of clinically suspected patients who had R2 resection (43% *vs* 19%), advanced T stage (T3/T4:70% *vs* 40%), high grade tumour (50% *vs* 31%), lymphovascular invasion (64% *vs* 45%) and positive lymph nodes (60% *vs* 43%) than the patient with incidental GBC [14]. (Interestingly, in the present study 39% were clinically suspected cases and 61% were incidental cases of gallbladder carcinoma.) Additionally, a greater number of clinically suspected cases had a clear resection margin than the incidental cases (92.3% *vs* 75%), had advanced T stage (T3/T4:61.5% *vs* 20%), higher grade tumour (100% *vs* 70%) and lymphovascular and perineural invasion (61.5% *vs* 35%).

Due to minimal invasive nature, more than three quarters of cholecystectomies for clinical diagnosis of cholelithiasis/cholecystitis are performed laparoscopically. This is due to the improved post-operative recovery from the minimally invasive technique. However, this approach for treating GBC remains controversial and less than 10% of patients have tumours that can be actually removed at the time of surgery by this approach [15]. Open technique is recommended for performing radical cholecystectomy due to increased risk of organ perforation, bile spillage during surgery and port site recurrences in laparoscopic cholecystectomy[15]. In patients with incidental GBC, it was observed in various studies that the prognosis was closely related to the tumour stage [16]. Similarly, neither the type of surgery nor the timing of tumour diagnosis (during or after cholecystectomy) influenced the outcome provided curative resection was achieved [16]. In 2011, Fuks et al. in their study observed that re-resection of liver bed significantly increased the survival in patients with T2 and T3 disease especially with R0 resection [17]. They also mentioned that bile duct resection increased post operative morbidity but did not improve survival [17]. In the present study, five of seven Group C patients who

died of disease had lymph node metastasis and positive cystic duct resection margin thus highlighting the importance of R0 resection and lymph node status on prognosis. In contrast, 4 of 5 Group B cases who had R0 staged liver resections showed no evidence of disease on follow-up. In 2014, Birnbaum et al. also mentioned in their series that nodal status predicted outcome in locally advanced GBC [18].

Chen et al. retrospectively analysed 338 Chinese patients with advanced GBC and confirmed that an advanced T stage does not preclude curative resection. The authors concluded that the range of liver resection with or without common bile duct resection would not influence the prognosis provided R0 resection was achieved [19]. In this study lymph node metastasis, positive resection margin, higher tumour grade and presence of ascites were identified as independent risk factors for poor prognosis in patients with curative intent resection [19]. Similar findings were observed in present study wherein higher tumour grade, lymphovascular invasion, margin positivity and lymph node metastasis acted as independent poor prognostic factors in Group C advanced T3/T4 tumours wherein around 60% patients succumbing to disease. In 2016, Margonis et al. from the United States assessed the incidence and patterns of recurrence following GBC resections and observed recurrence of the disease in 35% of patients during the follow-up, while the median time to recurrence was 9.5 months from the surgery. Additionally, T3 stage, presence of lymphovascular invasion and residual disease were identified as the increased risk of recurrence [20].

Conclusion

This study highlights that GBC is a rare disease in UK with dismal prognosis in the majority of patients who received surgical intervention. Best clinical outcomes can be achieved with early diagnosis followed by radical cholecystectomy and staged liver resection with negative margins. Advanced T stage does not preclude curative resection of GBC. Additionally, margin clearance seems extremely important, which is challenging in incidental cases. Developing high quality cancer registries with involvement in research and clinical trials is required to contribute to the better management of these patients.

Conflict of interest

The Authors declare no conflict of interest.

Funding

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

1 Krishnatreya M, Saikia A, Kataki AC et al. Variations in spatial distribution of gall bladder cancer: a call for collaborative action. Ann Med Health Sci Res 2014;4 (Suppl 3):S329-331. https://doi.org/10.4103/2141-9248.141984.

2 Haq N, Khan BA, Imran M et al. Frequency of gall bladder carcinoma in patients with acute and chronic cholecystitis. J Ayub Med Coll Abbottabad 2014;26:191-193.

3 Sharma JD, Kalita I, Das T et al. A retrospective study of post-operative gall bladder pathology with special reference to incidental carcinoma of the gall bladder. Int J Res Med Sci 2014;2:1050-1053.

4 Adsay NV, Klimstra DS. Benign and malignant tumours of the gallbladder and extrahepatic biliary tract. In: Odze RD, Goldblum JR, eds. Surgical pathology of the GI tract, liver, biliary tract and pancreas (3rd edition). Philadelphia: Saunders Elsevier 2015, pp. 1021-1054.

5 Wyatt J, Huebscher S, Goldin R. Dataset for histopathology reporting of liver resection specimens (including gall bladder) and liver biopsies for primary and metastatic carcinoma (2nd edition). London: The Royal College of Pathologists 2012.

6 Weinstein D, Herbert M, Bendet N et al. Incidental finding of gall bladder carcinoma. Isr Med Assoc J 2002;4:334-336.

7 Duffy A, Capanu M, Abou-Alfa GK et al. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). J Surg Oncol 2008;98:485-489. https://doi.org/10.1002/jso.21141

8 Uribe-Uribe NO, Jimenez-Garduno AM, Henson DE et al. Paraneoplastic sensory neuropathy associated with small cell carcinoma of the gallbladder. Ann Diagn Pathol 2009;13:124-126. https://doi.org/10.1016/j.anndiagpath.2007.08.003

9 Pandey M, Shukla VK. Lifestyle, parity, menstrual and reproductive factors and risk of gallbladder cancer. Eur J Cancer Prev 2003;12:269-272. https://doi.org/10.1097/00008469-200308000-00005

10 Everson GT, McKinley C, Kern F Jr. Mechanisms of gallstone formation in women. Effects of exogenous oestrogen (Premarin) and dietary cholesterol on hepatic lipid metabolism. J Clin Invest 1991;87:237-246. https://doi.org/10.1172/JCI114977

11 Arroyo GF, Gentile A, Parada LA. Gallbladder cancer: South American experience. Chin Clin Oncol 2016;5:67. https://doi.org/10.21037/cco.2016.10.01

12 Do SI, Lee HW, Sohn JH et al. Clinicopathologic characteristics of young patients with gallbladder cancer. Pathol Res Pract 2017;213:189-193. https://doi.org/10.1016/j.prp.2016.12.021

13 Tomimaru Y, Noguchi K, Nagase H et al. Clinicopathological study of incidental gallbladder cancer diagnosed after laparoscopic cholecystectomy. Gan To Kagaku Ryoho 2016;43:1605-1607.

14 Ethun CG, Le N, Lopez-Aguiar AG et al. Pathologic and prognostic implications of incidental versus non incidental gallbladder cancer: a 10 institution study from the United States extrahepatic biliary malignancy consortium. Am Surg 2017;83:679-686.

15 Goetze TO. Gallbladder carcinoma: prognostic factors and therapeutic options. World J Gastroenterol 2015;21:12211-12217. https://doi.org/10.3748/wjg.v21.i43.12211

16 Miller G, Jarnagin WR. Gallbladder carcinoma. Eur J Surg Oncol 2008;34:306-312. https://doi.org/10.1016/j.ejso.2007.07.206

17 Fuks D, Regimbeau JM, Le Treut YP et al. Incidental Gallbladder cancer by the AFC-GBC-2009 Study Group. World J Surg 2011;35:1887-1897. https://doi.org/10.1007/s00268-011-1134-3

[18] Birnbaum DJ, Vigano L, Ferrero A, et al. Locally advanced gallbladder cancer: which patients benefit from resection? Eur J Surg Oncol 2014;40:1008-1015. https://doi.org/10.1016/j.ejso.2013.10.014

[19] Chen C, Geng Z, Shen H et al. Long-term outcomes and prognostic factors in advanced Gallbladder cancer: focus on the advanced T Stage. PLoS One 2016;11:e0166361. https://doi.org/10.1371/journal.pone.0166361

[20] Margonis GA, Gani F, Buettner S, et al. Rates and patterns of recurrence after curative intent resection for gallbladder cancer: a multi-institution analysis from the US Extra-hepatic Biliary Malignancy Consortium. HPB (Oxford) 2016;18:872-878. https://doi.org/10.1016/j.hpb.2016.05.016