



Original Article

Gallbladder Cancer: Diagnosed at Advanced Stage – A Conundrum

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Abstract

Introduction: Gallbladder cancer typically remains silent until an advanced and often noncurative stage with the shortest median survival after diagnosis. This study was conducted to find out the factors responsible for diagnosis of carcinoma gallbladder at advanced stage.

Materials and Methods: This observational study was conducted in the Bangabandhu Sheikh Mujib Medical University from July 2022- June 2023 on 110 patients of carcinoma gallbladder. The patients were grouped into early (stage I, II) and advanced stage (stage III, IV) on the basis of imaging or histopathology report. All the variables related to diagnosis of carcinoma gallbladder were evaluated and factors related to delayed diagnosis were worked out.

Results: 28 (25.5%) patients of this study group were incidental, 16 (14.5%) were early and 66 (60%) were advanced gallbladder carcinoma. Rural residence, low educational level and poor economic status of our people, lack of specific symptom at early stage of the disease, lack of sensitivity of most commonly performed imaging (USG) and absence of sensitive tumour marker at early stage were responsible for delayed diagnosis of the disease.

Conclusion: Clinicians should be very suspicious to diagnose gallbladder carcinoma at early stage. Patients presenting with symptoms of benign biliary disease should be investigated properly, when there is suspicious gallbladder wall thickness, CA 19-9 and CECT or MRI should be warranted.

Keywords: Carcinoma Gallbladder, Incidental carcinoma gallbladder, late diagnosis.

Introduction

Gallbladder cancer is the commonest malignancy of the biliary tract worldwide; though uncommon in western countries, it is quite common in Indian subcontinent.^{1,2} It is also the most aggressive cancer

of the biliary tract with the shortest median survival after diagnosis.^{3,4} Gallbladder cancer is generally considered to confer a poor prognosis as this tumour typically remains silent until an advanced and often noncurative stage. This poor prognosis is due, in part, to an aggressive biologic behavior and a lack of sensitive screening tests for early detection resulting in delayed diagnosis at advanced stage.^{2,5}

Over two-thirds of patients with gallbladder cancer are only diagnosed during surgery or postoperatively. Symptomatic patients most commonly present with advanced disease.^{6,7} Right upper quadrant or epigastric pain is the most common symptom (54–83%), followed by jaundice (10–46%), nausea and vomiting (15–43%), anorexia (4–41%), and weight loss (10–39%).^{8,9}

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Ultrasonography is most frequently the initial diagnostic study with a sensitivity and specificity of 85% and 80%, respectively; however, in early disease, ultrasound examination often fails to detect any abnormality, particularly when the tumour is flat or sessile and is associated with cholelithiasis.^{10,11} The most common evaluative imaging in gallbladder cancer is the CT scan, with 75.9% specificity and 82.5% sensitivity. MRI is superior to CT scan for differentiating T1a lesions from T1b or greater and as such may be useful in preoperative management planning.^{12,13} Image-guided FNA including ultrasound-guided or CT-guided biopsy has the potential for a diagnostic accuracy of 80–90%.^{14,15} In the future, the development of potential diagnostic markers for the disease will yield screening opportunities for those at risk of gallbladder malignancy.

Improved outcomes greatly depend on the recognition of the major risk factors, accurate initial staging, and meticulous surgical excision. Improved imaging modalities as well as accurate diagnostic markers will potentially help outcomes as early diagnosis is imperative and surgery can be curative. Lack of preoperative clinical suspicion, absence of definitive clues on history and physical examination at early stage, lack of specific features on radiology and absence of sensitive serological markers are likely contributing factors for advanced stage diagnosis of this disease with poor outcome.

Materials and methods

This observational study was conducted at the Department of Hepatobiliary Pancreatic and Liver

Transplant surgery of Bangabandhu Sheikh Mujib Medical University between July 2022-June 2023. During the study period, a total 110 patients diagnosed as carcinoma gallbladder, attending in OPD or admitted in ward, operated or not, meeting the selection criteria were included in the study. After taking informed written consent, detailed clinical history and relevant physical examination was done in each patient. After that, all relevant investigations were checked and appropriate biochemical reports were recorded. Furthermore, a new set of investigations were advised to each patient for proper evaluation of the current disease status and for study purpose. The diagnosis was confirmed on the basis of FNAC or core biopsy in case of patients who were not operated and by histopathology reports who underwent surgical resection. Then the patients were staged into stage I, II, III, IV on the basis of imaging report in case of patients who were not operated and by histopathology reports in case of postoperative patients. Then the patients were grouped into incidental, early (stage I, II) and advanced (stage III, IV) carcinoma gallbladder. All the variables related to diagnosis of carcinoma gallbladder were evaluated and factors related to delayed diagnosis were found out by comparing the early and advanced group.

Statistical analyses of the results was done by using computer based statistical software SPSS version 25. Means, percentage and frequencies was determined as indicated. The comparison between the two groups was made using Chi-square (χ^2) test and Fischer Exact test as required for qualitative variables. A p-value of less than 0.05 was considered significant.

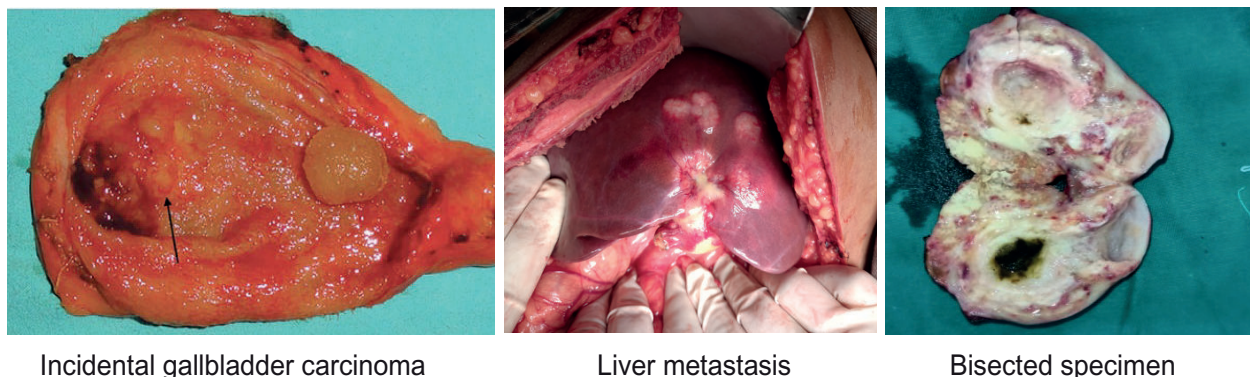


Figure-1: Pictures of gallbladder carcinoma

Results

Among the 110 patients of this study group 28 (25.5%) patients were diagnosed incidentally by postoperative biopsy report of gallbladder operated due to a benign cause. The rest of the patients were either in the early gallbladder carcinoma group (n-16; stage I- 6, stage II- 10) or in the advanced gallbladder carcinoma group (n-66; stage III- 44, stage IV- 22).

Table I: Different study group of patients of gallbladder cancer with staging (N=110)

Group	Number of patients n (%)
Incidental Gallbladder Carcinoma	28 (25.5)
Stage I	20 (18.5)
Stage II	8 (7)
Early Gallbladder Carcinoma	16 (14.5)
Stage I	6 (5.5)
Stage II	10 (9)
Advanced Gallbladder Carcinoma	66 (60)
Stage III	44 (40)
Stage IV	22 (20)
Total	110

Table-II: Difference in patients clinico-pathological variables between early and advanced gallbladder carcinoma (N=82)

Variables	Early Gallbladder Carcinoma n (%)	Advanced Gallbladder Carcinoma n (%)	P Value
BMI			
<18.5	0 (0)	9 (14)	0.237 ^a
18.5-24.9	10 (63)	24 (36)	
25-29.9	5 (31)	25 (38)	
>30	1 (6)	8 (12)	0.273 ^b
Family history			
Positive	0 (0)	5 (8)	
Negative	16 (100)	61 (92)	
Exposure			
No exposure	12 (75)	31 (47)	0.109 ^b
Smoking	2 (12.5)	17 (26)	
OCP	2 (12.5)	18 (27)	
Total	16 (20)	66 (80)	

^a Chi-square test was done to measure the level of significance; ^b Fisher's Exact test was done to measure the level of significance. Figure within parenthesis indicates in percentage.

Table-III: Association of gallbladder and biliary pathologies in early and advanced carcinoma gallbladder (N=82)

Variables	Early Gallbladder Carcinoma n (%)	Advanced Gallbladder Carcinoma n (%)	P Value
Gallbladder & biliary pathologies			0.764 ^b
None	8 (50)	20 (30)	
Gallstone	1 (6)	5 (8)	
GB polyp	0 (0)	2 (3)	
Porcelain GB	0	3 (4)	
Choledochal cyst	2 (13)	5 (8)	
Pancreatico-biliary maljunction			
Total	16 (20)	66 (80)	

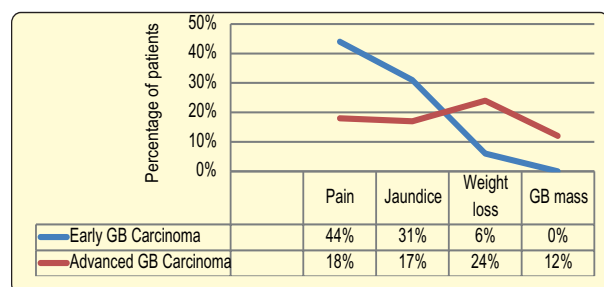
^b Fisher's Exact test was done to measure the level of significance. Figure within parenthesis indicates in percentage.

Most of the patients of this study group were aged between 45-54 years (35%), most were female (55%) and highest proportion were residing in rural area (70%). 82% of advanced carcinoma gallbladder patients reported from rural area, rural residence was a significant factor for delayed diagnosis ($p < 0.05$). Low educational level and poor economic status of the patient was significantly different between early and advanced carcinoma gallbladder group ($p < 0.05$). Most of the patients in advanced group had history of exposure to OCP (18:2) or smoking (17:2) and were overweight (23:6) but they were not significant risk factors for delayed diagnosis. Gall stone (n=28), GB polyp (n=6), porcelain GB (n=2), choledochal cyst (n=3) and pancreatico-biliary maljunction (n=7) were associated with carcinoma gall bladder but there was no significant difference in their presence between early and advanced gallbladder carcinoma group ($p > 0.05$).

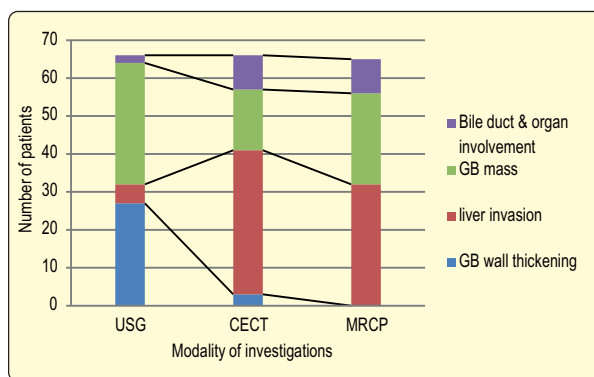
Table-IV Difference in tumour marker (CA 19-9 & CEA) elevation between early and advanced stage of carcinoma gallbladder (N=82)

Variables	Early Gallbladder Carcinoma n (%)	Advanced Gallbladder Carcinoma n (%)	P Value
Tumour marker			
CA 19-9			0.082 ^a
Normal (<37)	11 (69)	33 (50)	
Raised (>37)	5 (31)	33 (50)	
CEA			0.800 ^b
Normal (<3)	13 (81)	52 (79)	
Raised (>3)	3 (19)	14 (21)	
Total	16 (20)	66 (80)	

^a Chi-square test was done to measure the level of significance, ^b Fisher's Exact test was done to measure the level of significance. Figure within parenthesis indicates in percentage.

**Figure-2:** Line diagram shows difference in common presenting feature between early and advanced gallbladder carcinoma

There was significant difference in clinical presentation between early and advanced carcinoma gallbladder group, early gallbladder carcinoma mainly presented with pain (44%) and jaundice (31%) in comparison to advanced group who presented with weight loss (24%), pain (18%), jaundice (17%) and GB mass (12%). Asymptomatic patients or patients with PUD and chronic pancreatitis were largely diagnosed at advanced stage. Tumour marker CA 19-9 was raised in 46% patients with a better sensitivity than CEA which was raised in 21% patients.

**Figure-3:** Column diagram showing the role of different imaging modalities to identify different morphological feature of advanced gallbladder carcinoma

Imaging findings of early stage disease were GB wall thickening and GB mass; on the other hand advanced diseases were reported as liver invasion, Bile duct and visceral involvement, GB mass with or without GB wall thickening. MRI is better than CECT and USG to diagnose GB mass in early stage gall bladder carcinoma (15:10:2), CECT was better than MRCP and USG to detect liver invasion (38:32:5) and Bile duct and visceral involvement is better delineated by CECT and MRCP than USG (9:9:2).

Table-V: Variations in tumour locations in different groups of gallbladder carcinoma (N=82)

Variables	Early Gallbladder Carcinoma n (%)	Advanced Gallbladder Carcinoma n (%)	P Value
Tumour location			0.001 ^b
Fundus	1 (6)	32(48)	
Body	3 (19)	23(35)	
Neck	12 (75)	11(17)	
Total	16 (20)	66 (80)	

^b Fisher's Exact test was done to measure the level of significance. Figure within parenthesis indicates in percentage.

Tumour locations were significantly different between early and advanced gallbladder carcinoma group. Gallbladder neck was the predominant tumour location in early group (75%) and in advanced group the tumour was mainly located in fundus (48%) followed by body (35%) and neck (17%).

Discussion

Gallbladder malignancy is a rare entity, but common in the gastrointestinal tract. Most are diagnosed at advanced stage with dismal prognosis having 5 years survival rate of less than 5.0%. Detection at early stage has excellent prognosis increasing up to 90.0-100.0% 5 years survival rate.^{3,6,10} However, early detection is not possible due to delayed onset of symptoms or is masked off by chronic cholecystitis, and is usually detected during simple cholecystectomy as incidental finding. Lack of preoperative clinical suspicion, absence of definitive clues on history and physical examination at early stage, lack of specific features on radiology and absence of sensitive serological markers are likely contributing factors for advanced stage diagnosis of this disease.^{1,14}

An Indian study reported higher incidence of this carcinoma is reported in relation to poor socioeconomic condition, low level of education and lifestyle factors like smoking, tobacco chewing and alcohol consumption.³ In our study, 82% of advanced carcinoma gallbladder patients reported from rural area. The reason behind this might be the lack of health care facility in the rural area and lack of proper referral system fails to diagnose the disease at early stage. In advanced carcinoma gallbladder group a major proportion of patients' educational level was not up to the mark and most of the patients were from low income family (n=36, 54%). As gallbladder carcinoma does not become symptomatic in the early stages and the poor illiterate people of our country ignores mild health problems, presents late to appropriate health care provider and at that time their disease becomes advanced.

Persistent insult to gallbladder mucosa is the reason upheld for association of gallstone disease with carcinoma gallbladder. Presence of gallstone, duration of gallstone disease, number of gallstones, and size of gallstones are various factors which are directly associated with chronic insult to gallbladder mucosa. Gallbladder polyp of ≥ 10 mm is considered a risk factor for malignant transformation.¹² In this study we found that gall stone, gallbladder polyp, porcelain gallbladder, choledochal cyst and pancreatobiliary maljunction were associated with gallbladder carcinoma but not significantly different between early and advanced group.

It was found that symptoms related to gallbladder cancer are usually non-specific and include jaundice, abdominal pain, nausea, GB mass and weight loss. Due to non-specific symptoms, most of the patients present in an advanced stage with metastasis.⁶ In our study early gallbladder carcinoma mainly presented with pain and jaundice in comparison to advanced group who presented with weight loss, pain, jaundice and GB mass.

Tumor markers such as CEA, and CA 19-9 have been widely used for the diagnosis of different types of cancer (e.g., liver, gastric, colorectal, and pancreatic). Valle et al., and Creasy et al., observed inconsistent results when these markers were used individually for the diagnosis of gall bladder carcinoma.^{8,12} In our study we observed that CA 19-9 and CEA level were not significantly different between early and advanced carcinoma group and CA 19-9 had a better sensitivity than CEA to diagnose gall bladder carcinoma. As CA 19-9 is not specific for GBC and it should be combined with other imaging tests to diagnose GBC.

Differentiation of the cause of gallbladder wall thickening remains a challenging task even with advances in imaging modalities. It was found in a 2013 study that USG is sensitive for evaluation of the gallbladder mural thickening or mass and local extension into liver but its role in staging is limited as it is less reliable for detection of lymph nodes and peritoneal metastasis.¹⁴ In our study we found that MRI is better than CECT and USG to diagnose GB mass in early stage gall bladder carcinoma.

Tumour location in the gallbladder is an important factor to produce symptoms before its progression to an advanced stage. In this study gallbladder neck was the predominant tumour location in early group and in advanced group the tumour was mainly located in fundus and body. Tumour located in the neck of gall bladder produces symptoms at early stage and helps in early diagnosis of the disease.

The study was conducted in a single centre in Dhaka city which may not be representative for the whole population. The sample size was small in the present study, which compromises the generalizability of the study.

Clinicians should be very suspicious to diagnose the disease at early stage. As the early stage gallbladder disease presents with symptoms like benign biliary and gallbladder cancer. If there is doubtful wall

thickness, patients should be investigated by an experienced sonologist, tumour marker (CA 19-9) and better imaging (CECT or MRCP).

Conclusion

Gallbladder carcinoma is a female predominant disease arising in 5th or 6th decades of life mostly residing in rural area. rural residence was a significant factor for delayed diagnosis. Low educational level and poor economic status of the patient was significantly influenced delayed diagnosis. Lack of specific symptom at early stage of the disease and poor sensitivity of USG and lack of sensitive tumour marker at early stage is responsible for delayed diagnosis of the disease. Tumour located at fundus also presented late.

Conflict of Interests

The authors declare that they have no conflict of interest.

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