



## HISTOPATHOLOGICAL EVALUATION OF GALLBLADDER CARCINOMA WITH THE EXPRESSION STATUS OF CYTOKERATINS 7 AND 20 BY IMMUNOHISTOCHEMISTRY – A HOSPITAL BASED STUDY.

**Dr Ena Dowerah**

Professor, Department of Pathology, Fakhruddin Ali Ahmed Medical College & Hospital.

**Dr Kakoli Bora\***

Post graduate Student, Department of Pathology, Fakhruddin Ali Ahmed Medical College. \*Corresponding Author

### ABSTRACT

The gallbladder carcinoma is highly aggressive tumour and is the sixth among GI tract-related organs. Its incidence is much higher in North and North-Eastern population as compared to South India. Surgical removal of gall bladder for its diseases is common. However, not much is known about the incidence of incidentally detected gallbladder carcinoma in our population and immunohistochemical expression of CK7 & CK20. Objective of our study is to find out the percentage of gallbladder carcinoma among the cholecystectomy specimens and to evaluate their histopathological and immunohistochemical findings.

**Materials and Methods:** The present study was conducted at a tertiary care hospital in Lower Assam, over a period of one year. Special emphasis was given on incidentally detected gallbladder carcinoma cases and CK7 and CK20 expression status in the gallbladder carcinoma cases.

**Results:** Among 340 cholecystectomy specimens, 12 cases (3.5%) of primary gallbladder carcinoma were detected, out of which 4 cases were detected incidentally (1.17%). Association with gall stones were found in 10/12 cases (83%). CK7 positivity was found in 91.6% (11/12) cases and CK20 was positive in 16.7% (02/12) cases.

**Interpretation & Conclusion:** Incidentally detected gallbladder malignancy was quite high. So, it is important that all gallbladder specimens must be submitted for histopathological reporting. Immunohistochemically, CK7 positivity was quite high compared to CK20 positivity in the gallbladder carcinoma cases.

**KEYWORDS :** Gallbladder carcinoma, histopathology, IGBC, immunohistochemistry, CK7 & Ck20.

### INTRODUCTION

Gallbladder cancer (GBC) is the sixth most common cancer of the gastrointestinal system, with a worldwide annual incidence of 2.2 per 100,000 and 5-year mortality rate of 90%-95%<sup>1,2</sup>. Clinical presentation may not be distinguished from cholelithiasis or cholecystitis and most patients are diagnosed intraoperatively or in the postoperative histologic examination.<sup>3</sup>

Gallstones represent most significant risk factor being present in 85% cases<sup>4</sup>. Clinical and pathological staging is most important determinant dictating treatment strategy and outcome. Adenocarcinoma is the most common histopathological type and immunohistochemistry helps differentiate difficult cases<sup>5</sup>. It is reported that GBC incidentally detected by histopathological examinations after open or laparoscopic cholecystectomy is encountered in 0.2–2.9 % of patients undergoing cholecystectomy<sup>6,7</sup>.

### MATERIALS AND METHODS:

The present cross sectional study was conducted at a tertiary care hospital in Lower Assam, over a period of one year from June 2020 to May 2021. All cases diagnosed clinically & radiologically and operated as cholecystitis with or without cholelithiasis, gall bladder polyp, porcelain gall bladder etc. were included in the study. Immunohistochemical examination of gallbladder carcinoma cases was done using CK7 & CK20 IHC markers.

### RESULTS

A total of 340 patients underwent gall bladder surgery during this period. Out of 340 cases, 12 cases were found to be gallbladder carcinoma with a percentage of 3.5% and incidentally detected gallbladder carcinoma cases was 04 (1.17%). The age group of gallbladder carcinoma cases was ranged from 25-65 years with a mean age of 49.8 years. Females (83%) were more commonly affected than males (17%) with male : female ratio of 1:5. Among the 12 gallbladder carcinoma cases, gallstones were present in 10 cases with a percentage of 83.3%.

Histopathologically, most common type of gallbladder carcinoma was adenocarcinoma NOS (08/12; 66.6%) and among them, well differentiated adenocarcinoma (06/08; 75%) was most common type. (Table 1). Most common pathological staging (pT) of the gallbladder carcinoma cases was pT1 (06/12; 50%) followed by pT2 (05/12; 41.6%) and lastly pT3 (01/12; 8.3%) (Table 1). Out of total 12 gallbladder carcinoma cases; Perineural invasion (PNI) was observed in 02 cases and both were diagnosed as moderately differentiated adenocarcinoma and pathological pT staging of the cases were pT2a & pT2b. Lymphovascular invasion (LVI) was not observed in any of the cases.

A total number of 04 cases are detected incidentally with incidence rate of 1.17% (04/340) and all cases were female. Age distribution was 25 years to 60 years with a mean age of 46.25 years. Out of total 04 cases; three cases were diagnosed as adenocarcinoma NOS and one was diagnosed as Intracystic papillary neoplasm with associated invasive carcinoma. Regarding differentiation; 02 cases were diagnosed as well differentiated adenocarcinoma and 01 case as moderately differentiated adenocarcinoma. Pathological pT staging of Incidentally detected gallbladder carcinoma (IGBC) cases : 02 cases – pT1 and 02 cases – pT2. (Table 1)

Immunohistochemically, CK7 positivity was found in 91.6% (11/12) cases and CK20 was positive in 16.7% (02/12) cases. Both CK7 & CK20 was positive in 16.7% and both CK7 & CK20 was negative in one case (8.33%); which was diagnosed as mucinous adenocarcinoma. (Table 1)

### DISCUSSION

Gallbladder cancer is the most common cause of death from biliary malignancies<sup>8</sup>. Most patients of gallbladder carcinoma are older than 50 years. Incidental gallbladder carcinoma is defined as whenever gallbladder carcinoma is found on histopathology after the gallbladder has been removed for symptomatic benign gallbladder disease with or without gallstones<sup>9</sup>.

In this study; age distribution for gallbladder carcinoma cases was 25 years to 65 years; which is comparable to Shah B et al<sup>10</sup> (40 – 68 Yrs), Dilasm G a et al<sup>11</sup> (29 – 75 Yrs), Bhattacharjee K P et al<sup>12</sup> (32 – 75 Yrs). Again, Females (83%) were more commonly affected than male (17%) with male:female ratio of 1:5 and all incidentally detected gallbladder carcinoma (IGBC) cases were observed in females (100%); which is comparable to other studies like Tiwari A et al<sup>13</sup> (1:5), Manuela S et al<sup>14</sup> (1:4.3) and Zhang WJ et al<sup>15</sup> (1:4). Gallstones were present in 83.3% of total 12 gallbladder carcinoma cases which is comparable to Povlidis T et al<sup>16</sup> (83.6%), Kumar H et al<sup>17</sup> (80%) and Tiwari A et al<sup>13</sup> (80%).

Incidence of gallbladder carcinoma was 3.5% which is comparable to Jokhi C D et al<sup>18</sup> (3%) and Tiwari A et al<sup>13</sup> (3%). Again, the incidence of incidentally detected gallbladder carcinoma was 1.17% which is comparable to the studies like Tiwari A et al<sup>13</sup> (1.25%), and Yadav R et al<sup>19</sup> (1.26%).

Again, among the total 12 malignant gallbladder cases; 08 cases were diagnosed as adenocarcinoma NOS (66.6%) followed by Intracystic papillary neoplasm with associated invasive carcinoma (03 cases) and lastly one case of Mucinous adenocarcinoma. This observation is comparable to Giang T H et al<sup>20</sup> (60%), Hussain N H et al<sup>21</sup> (57.6%),

Shah B et al<sup>10</sup> (71.4%) and Manuela S et al<sup>14</sup> (65.6%). There were 06 cases of well differentiated adenocarcinoma (75%) followed by 02 cases of moderately differentiated adenocarcinoma and 00 cases of poorly differentiated adenocarcinoma. This observation is comparable to other studies like Dutta U et al<sup>22</sup> (71.4%) and Manuela S et al<sup>14</sup> (52.3%). For pathological staging, there were 06 cases in stage pT1 (50%) followed by 05 cases in stage pT2 and one case in stage pT3. This observation is comparable to Siddiqui et al<sup>23</sup> (50%), Geramizadeh B et al<sup>24</sup> (55.5%) and Servet K et al<sup>25</sup> (61%).

Regarding immunohistochemistry findings, out of total 12 cases; 11 cases (91.6%) had shown CK7 positivity; which is higher than other studies. Again; 02 cases had shown CK20 positivity (02/12, 16.7%) which is lower than other studies. (Table 1)

**Table 1: Showing the detailed parameters of the gallbladder carcinoma cases.**

S. no.	Age	Sex	Gall stone	IHC - CK7 & CK20	Histopathological diagnosis	pT staging
1	45 Yrs	F	Present	CK7 + & CK20 +	Well differentiated adenocarcinoma	pT1b
2	54 Yrs	F	Present	CK7 + & CK20 -	Well differentiated adenocarcinoma	pT2a
3	50 Yrs	F	Present	CK7 + & CK20 -	Well differentiated adenocarcinoma	pT1b
4	65 Yrs	F	Present	CK7 - & CK20 -	Mucinous adenocarcinoma	pT2a
5	55 Yrs	F	Absent	CK7 + & CK20 -	Intracystic papillary neoplasm with associated invasive carcinoma	pT1a
6	25 Yrs	F	Present	CK7 + & CK20 -	Moderately differentiated adenocarcinoma	pT2b
7	60 Yrs	F	Present	CK7 + & CK20 -	Well differentiated adenocarcinoma	pT2a
8	47 Yrs	M	Present	CK7 + & CK20 -	Well differentiated adenocarcinoma	pT1b
9	42 Yrs	M	Present	CK7 + & CK20 -	Moderately differentiated adenocarcinoma	pT2a
10	53 Yrs	F	Present	CK7 + & CK20 -	Intracystic papillary neoplasm with associated invasive carcinoma	pT3
11	50 Yrs	F	Absent	CK7 + & CK20 -	Intracystic papillary neoplasm with associated invasive carcinoma	pT1b
12	52 Yrs	F	Present	CK7 + & CK20 +	Well differentiated adenocarcinoma	pT1b

## CONCLUSION

From different studies including present study, it is observed that the incidentally detected gallbladder malignancy was quite high. Therefore, it is concluded that all gallbladder specimens must be submitted for histopathological reporting with careful gross examination of the specimens followed by microscopic examination to rule out malignancy. Immunohistochemically, CK7 positivity was quite high compared to CK20 positivity in the gallbladder carcinoma cases.

## REFERENCES:

1. Khuroo MS, Mahajan R, Zargar SA, Javid G, and Sapru S. Prevalence of biliary tract disease in India: A sonographic study in adult population in Kashmir. *Gut* 1989; 30:201-5.
2. Lammert F, Miguel JF: Gallstone disease: from genes to evidence based therapy. *J Hepatol* 2008; 48 Suppl 1:S124-35
3. Murat Ferhat Ferhatoglu, Kazım Şenol\*, Taner Kıvılcım, Abdulcabbar Kartal, Alp Gürkan. Clinicopathologic and Prognostic Features in Gallbladder Malignancies: Retrospective Analysis of 5206 Cases. *Med Bull Haseki* 2019; 57:147-152.
4. Solaimi L, Sharma A, Watt J, Iosifidou S, Chin Aleong JA, Kocher HM. Predictive factors for incidental gallbladder dysplasia and carcinoma. *J Surg Res* 2014 Jun 1; 189(1):17-21.
5. Shindoh J, Vauthey JN. Staging of biliary tract and primary liver tumors. *Surg Oncol Clin N Am* 2014 Apr; 23(2):313-22.
6. Preeti Singh, Vijay Kumar Jaiswal, Nidhi Verma, Monika Rathi, Bhavna Sharma, Amod Kumar Saroj. Histopathological spectrum of gall bladder lesions and association with cholelithiasis. *International Journal of Medical and Health Research*. Volume 4; Issue 9; September 2018; Page No. 134-138.
7. Sivaprakash Rat hanaswamy, Sanjeev Misra, Vijay Kumar, Chintamani, Jaipal reddy Pogal, Akash Agarwal & Sameer Gupta. Incidentally Detected Gallbladder Cancer- The Controversies and Algorithmic Approach to Management. *Indian J Surg* (May-June 2012) 74(3):248-254.
8. Khan R, Wahab S, Khan M, Siddiqui S, Maheshwari V. Advanced presentation of

- Gallbladder cancer: epidemioclinicopathological study to evaluate the risk factors and assess the outcome. *J Pak Med Assoc* 2010;60.
9. Misra MC, Guleria S. Management of cancer gallbladder found as a surprise on a resected gallbladder specimen. *J Surg Oncol*. 2006;93:690-8.
10. Bimal Shah, Sarang Degloorak. A retrospective audit of gall bladder histopathology following cholecystectomy. *IP Journal of Diagnostic Pathology and Oncology*, April-June, 2018; 3(2):123-126.
11. Dilasma Ghartimagar, Adarsh Kumar Jhunjhunwala, Arnab Ghosh, Manish Kiran Shrestha. Thirty-five cases of gallbladder carcinoma out of 4914 cholecystectomy specimens from a Nepalese tertiary care hospital – A retrospective cohort study. *Annals of Medicine and Surgery* 69 (2021) 102753.
12. Prasanta Kumar Bhattacharjee, Durgaprasad Nanda. Prospective observational study on cholelithiasis in patients with carcinoma gall bladder in a tertiary referral hospital of Eastern India. *J Can Res Ther* 2019; 15:153-6.
13. Archana Tiwari, Ramji Rai, Surendra Kumar Jain. Importance of Routine Histopathological Examination of Gallbladder Specimen in Detecting Incidental Malignancies. *J Lumbini. Med. Coll.* 2016; 4(1):15-19.
14. Manuela Stancu, Irina-Draga Căruțu, Simona Giușcă, Gioconda Dobrescu. Hyperplasia, metaplasia, dysplasia and neoplasia lesions in chronic cholecystitis – a morphologic study. *Romanian Journal of Morphology and Embryology* 2007, 48(4):335-342.
15. Wei-Jie Zhang, Gui-Fang Xu, Xiao-Ping Zou, Wei-Bing Wang, Jun-Chi Yu, Guo-Zhong Wu, Chun-Lei Lu. Incidental gallbladder carcinoma diagnosed during or after laparoscopic cholecystectomy. *World J Surg*. 2009 Dec; 33(12):2651-6.
16. T Pavlidis, C Lazaridis, K Atmatzidis, JMakris, B Papaziogas and T Papaziogas. Gallbladder specimen pathology for presumed gallstone disease. *HPB* 2000; 2(1):33-37.
17. Kumar H, Kini H, Tiwari A. Histological evaluation of 400 cholecystectomy specimens. *Journal of Pathology of Nepal* (2015) Vol. 5, 834-840.
18. Cyrus Dara Jokhi, Sujata R Kanetkar, Nikita V Vohra. Study of histopathological findings in gallbladder diseases. *Indian Journal of Pathology and Oncology* 2019; 6(4):627-635.
19. Rita Yadav, Mala Sagar, Sanjeev Kumar, Shyam Kumar Maurya. Incidental Gallbladder Carcinoma in North Indian Population: Importance of Routine Histopathological Examination of All Benign Gallbladder Specimens. *Cureus* 2021; 13(7): e1 61 56. DOI 10.7759/cureus.16156.
20. Tran H Giang, Tran TB Ngoc and Lewis A Hassell. Carcinoma involving the gallbladder: a retrospective review of 23 cases – pitfalls in diagnosis of gallbladder carcinoma. *Diagnostic Pathology* 2012, 7:10; 1-8.
21. Nissar Hussain Hamdani, Sumyra Khurshid Qadri, Ramesh Aggarwalla, Vishnu Kumar Bhartia, Sumit Chaudhuri, Sanjay Debakshi, Sarfaraz Jalil Baig, NK Pal. Clinicopathological Study of Gall Bladder Carcinoma with Special Reference to Gallstones: Our 8-year Experience from Eastern India. *Asian Pacific J Cancer Prev*, 13(11), 5613-5617.
22. Utpal Dutta, Projnan Saikia, Gayatri Gogoi, Mondita Borgohain. Clinicopathological evaluation of gallbladder carcinoma with special emphasis on incidentally detected cases- A hospital based study. *Indian Journal of Pathology and Oncology*, April-June, 2019; 6(2):309-314.
23. Faisal G Siddiqui, Ahmer A Memon, Arshad H Abro, Nazeer A Sasoli and Lubna Ahmad. Routine histopathology of gallbladder after elective cholecystectomy for gallstones: waste of resources or a justified act? *BMC Surgery* 2013, 13:26:1-5.
24. Bitu Geramizadeh, Ali Kashkooe. Incidental Gall Bladder Adenocarcinoma in Cholecystectomy Specimens: A Single Center Experience and Review of the Literature. *Middle East J Dig Dis* 2018; 10(4):249-253.
25. Servet Kocaöz, Gülay Turan. Preneoplastic and neoplastic gallbladder lesions detected after cholecystectomy. *Gastroenterology Review* 2019; 14(3):193-197.
26. Jennie V. Duval, MD; Louis Savas, BS; Barbara F. Banner, MD. Expression of Cytokeratins 7 and 20 in Carcinomas of the Extrahepatic Biliary Tract, Pancreas, and Gallbladder. *Arch Pathol Lab Med*—Vol 124, August 2000, 1196-1200.
27. Harikleia Kalekou, Dimosthenis Miliaras. Cytokeratin 7 and 20 expression in gallbladder carcinoma. *PoJ Pathol* 2011; 1: 25-30.
28. Nevra Dursun, MD; Oscar Tapia Escalona, MD; Juan Carlos Roa, MD; Olca Basturk, MD; Pelin Bagci, MD; Asli Cakir, MD; Jeanette Cheng, MD; Juan Sarmiento, MD; Hector Losada, MD; So Yeon Kong, MPH; Leslie Ducato, BS; Michael Goodman, MD; N. Volkan Adsay, MD. Mucinous Carcinomas of the Gallbladder - Clinicopathologic Analysis of 15 Cases Identified in 606 Carcinomas. *Arch Pathol Lab Med*. 2012; 136:1347-1358.