

Pathological differences between clinically suspected and unsuspected gallbladder carcinoma: A 5- year retrospective study

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Abstract

Introduction: Gallbladder carcinoma frequently presents as incidental finding in routine cholecystectomy specimens operated for gallstone diseases. The reason behind unrecognition of these tumors pre and intraoperatively and its significance need evaluation. **Objective:** We have done a 5 years retrospective study from December 2011 to November 2016 in a referral centre to evaluate the pathological features of unsuspected gallbladder carcinoma and to compare these with those of suspected carcinomas. **Methods:** A total record of 74 cases of gallbladder carcinomas are retrieved from the archives. These are 54 whole gallbladder specimens of simple and extended cholecystectomies and 24 small tissue pieces of gallbladder. Out of 54 whole gallbladder specimens 30 are clinically unsuspected and 24 are suspected carcinomas. **Result:** Majority of the unsuspected group have diffusely thickened gallbladder wall as their sole gross presentation or no grossly identifiable lesion at all. On the other hand, suspected gallbladder carcinomas have presented mostly as localized wall thickening, thickened wall with invasion of the adjacent structures or large intraluminal mass. Adenocarcinoma was the commonest histological type in suspected and exclusive type in unsuspected group. Most of the unsuspected carcinomas are well differentiated in contrast to the suspected carcinomas which are mostly poorly differentiated followed by almost equal prevalence of moderately differentiated and well differentiated tumors. Half of the unsuspected tumors are limited to gallbladder and no cases of pT4 stage are present. On the contrary, only one fourth of cases of the suspected carcinomas are limited to gallbladder and another one fourth are in pT4 stage. **Conclusion:** Unsuspected gallbladder carcinoma show different gross presentation and also tend to be better differentiated and in earlier stages than suspected carcinomas.

Keywords: Gallbladder, Adenocarcinoma, Unsuspected

Introduction

Gallbladder carcinoma is the 20th most common cancer in the world [1]. The highest incidence of gallbladder carcinoma is seen in South America and Asia, and the lowest incidence in Africa. Chile has the highest incidence (age standardized rate 9.7 per 1 lakh population) followed by Bolivia and Korea. Korea has the highest incidence of gallbladder carcinoma in male (7.8 per 1 lakh) and Chile has in female (12.8 per 1 lakh). High incidences are also reported from women in Delhi (India), South Karachi (Pakistan), Japan and Quito (Equador) [2]. Incidence of gallbladder cancer is

high in North, East and North East India, particularly in Delhi, Assam (Dibrugarh, Kamrup Urban and Cachar district), Tripura and Kolkata [3].

Gallbladder Cancer is a disease of adult and occur more commonly in female than male [4,5]. Many of the cases are not suspected clinically and are discovered incidentally during histopathological examination of gallbladder for gallstone diseases [6-16].

Gallbladder carcinomas are notorious for presenting in an advanced stage with attendant dismal prognosis [4,6,11,12,17]. Asymptomatic Cancer progression might be the major cause for this untoward event. In a

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highly prevalent zone, a relatively high proportion of unsuspected gallbladder carcinoma affects decision making for proper management in a large number of patients.

We have done a 5 year retrospective analysis to elucidate the causes for this clinical entity and also to evaluate the pathological significance of a missed out unsuspected carcinoma received after cholecystectomy due to some other reason.

Methods and Material

This is a 5 year retrospective study in a referral centre from December, 2011 to November, 2016. All the case records of gallbladder carcinomas from the registrar and the corresponding blocks and slides have been retrieved.

A total of 74 cases of gallbladder carcinomas are found, out of which 54 are whole gallbladder specimens (simple cholecystectomies with or without omentum and/or lymph nodes and extended cholecystectomies) and 20 are small tissue pieces of gallbladder.

Grossing & reporting including staging had been done using standard recommendations [18,19]. Suspected carcinomas include all the carcinomas that were suspected clinically either preoperatively or

intraoperatively. Unsuspected gallbladder carcinomas are those carcinomas which are first recognized during gross pathological examination or on microscopy. 30 out of 54 whole gallbladder specimens were not clinically suspected of carrying cancer. The 24 small tissue pieces were all from suspected gallbladder carcinomas.

All the carcinoma specimens are considered for assessment of age, sex, histological type and grade, but only whole gallbladder specimens are considered for study of gross morphology, stages of carcinoma and correlation of grades with stages. Normal gallbladder wall thickness measures up to 0.3 cm [20]. So, gallbladder wall more than 0.3 cm thick is considered to be thickened gallbladder wall.

The term diffuse thickening is used to mean diffuse increase in thickness of wall without any grossly recognizable site of tumor. This group is again divided into mild (0.4cm to 0.6cm) moderate (0.7cm to 1.0cm) and marked (>1.0cm) thickening.

The term 'no gross lesion' means that gallbladder wall is grossly unremarkable. In assessment of PT0 nonpapillary tumors inflammatory atypia due to acute cholecystitis is excluded. The data are presented in table format for description and draw summary.

Result

Age and sex distribution:

Table 1. Shows the age and sex distribution of the suspected and unsuspected gallbladder carcinoma patients.

Age group	Unsuspected		Suspected	
	Male	Female	Male	Female
<30 years	0	1	0	1
30 - <40 years	2	3	0	8
40 - <50 years	0	7	4	10
50 - <60 years	3	4	1	9
60 - <70 years	3	6	2	7
>70 years	0	1	1	1
Total	8	22	8	36

It is seen that gallbladder carcinomas are seen over a wide age range of 30 years to 70 years. The mean ages for the suspected and unsuspected groups are 50.5 years and 47.7 years respectively. Unsuspected cancers are 2.7 times and suspected cancers are 4.5 times commoner in females.

Gross morphology:**Table 2-** displays the distribution of different type of gross morphology among the cases.

Gross Pattern	Unsuspected	Suspected
Diffuse wall thickening	9	2
Localized wall thickening	5	6
Thickened wall with invasion of liver and omentum	0	6
Papillary lesion without wall thickening	1	3
Papillary lesion with wall thickening (localized or diffuse)	4	1
Large intraluminal mass	0	4
Induration of wall without thickening	1	1
No grossly indentifiable lesion	10	
Total	30	24

It is seen that unsuspected group have mostly presented with diffuse wall thickening (30%) and no grossly identifiable lesion (33.3%). Some cases have also shown localized wall thickening (13.3%). On the other hand suspected group have mostly presented as localized wall thickening (25%), thickened wall with invasion of liver and omentum (25%), large intraluminal mass (16.7%) and papillary lesion without wall thickening. Out of the unsuspected diffuse thickening group, 6 cases have mild and 3 have moderate wall thickening. On the other hand suspected diffuse thickening group show one each in mild and moderate wall thickening.

Histological type of the tumor- It is seen that all the 30 unsuspected carcinomas and 40 of 44 suspected carcinomas are conventional adenocarcinomas including papillary type. Rest of the suspected carcinomas are one each of squamous cell carcinoma, small cell carcinoma, clear cell adenocarcinoma and signet ring cell adenocarcinoma.

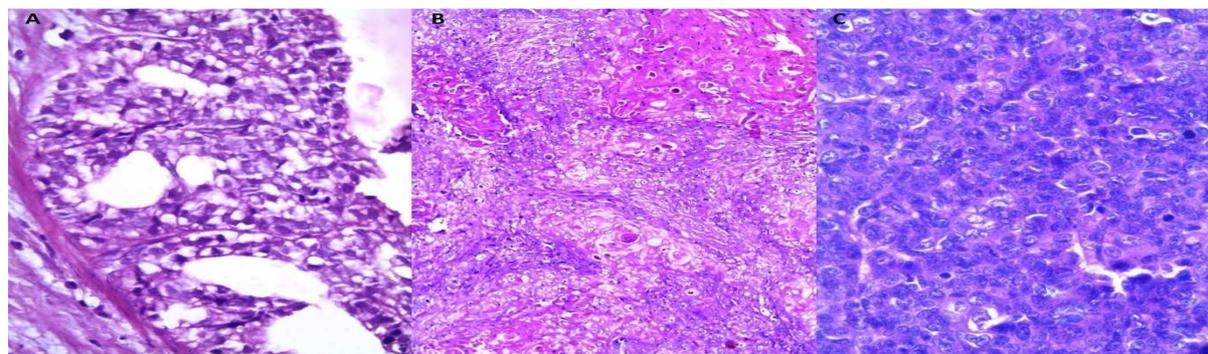


Figure-1: Some unusual histological types of gallbladder cancer. A. Clear cell adenocarcinoma (H & E, 40X). B. Squamous cell carcinoma (H & E, 10X). C. Small cell carcinoma (H & E, 40X)

Grades of the tumor- It is found that 19 (63.3%) of unsuspected tumors are well differentiated, 6 (20%) are moderately and 5 (16.7%) are poorly differentiated. The corresponding figures for suspected cancers are 13 (29.4%), 12 (27.3%) and 19 (43.2%) respectively

Stages of the tumors:**Table-3:** Shows the distribution of stages of the tumors in each grade

Grades Stages	pT 0	pT 1	pT 2	pT 3	pT 4	Total
Well differentiated (including papillary)	6(3)	3(1)	5(2)	5(2)	0(0)	19(8)
Moderately differentiated	0(0)	1(0)	0(0)	5(2)	0(3)	6(5)
Poorly differentiated	0(0)	0(0)	0(0)	5(8)	0(3)	5(11)
Total	6(3)	4(1)	5(2)	15(12)	0(6)	30(24)

The figures in brackets are for suspected cases and those without brackets are for unsuspected cases.

Table 3 Shows that well differentiated tumors are predominantly limited to gallbladder, but moderately differentiated tumors have mostly and poorly differentiated tumors have exclusively extended beyond gallbladder in both unsuspected and suspected groups.

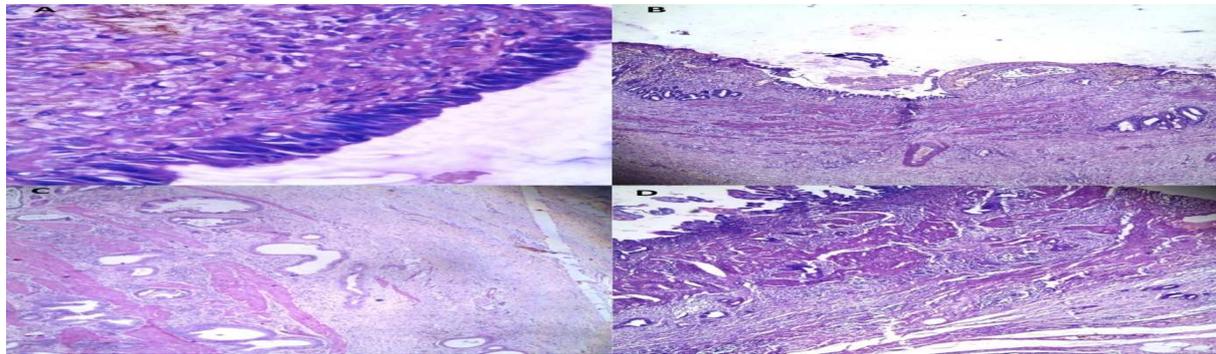


Figure-2: Photomicrograph displaying stages of gallbladder cancer. A. Flat dysplasia or pT0 (H & E, 40X) B. Stage pT1 tumor infiltrating the muscularis propria partially (H & E, 4X) C. Stage pT2 tumor infiltrating the muscularis propria completely but not up to the serosa (H & E, 10X) D. Stage pT3 tumor infiltrating upto serosa (H & E, 4X)

Table-4: Relative percentages of suspected and unsuspected tumors in each stage

Category	Stages				
	pT0	pT1	pT2	pT3	pT4
Unsuspected	20%	13.3%	16.7%	50%	0%
Suspected	12.5%	4.2%	8.3%	50%	25%

Table 4 shows that half of all unsuspected tumors are detected in a stage limited to gallbladder with a high proportion of pT0 and pT1 stage tumors. But only 25% of the suspected tumors are detected in a stage limited to gallbladder. No unsuspected tumors are present in pT4 stage, but 25% of the suspected tumors are found in this stage.

Discussion

Unsuspected carcinomas constitute 40.5% of all gallbladder carcinomas in our study. The mean age for suspected group is 47.7 years and that for unsuspected group is 50.5 year. This is comparable to study from Nepal (mean age of 54 year) [5]. However studies from North America (Canada) and South America (Chile) have reported average age of presentation 61.23 year and 61.5 year respectively[4,11]. This disparity could probably be attributed to racial and environmental influences. We have found that unsuspected gallbladder carcinomas are 2.75 times and suspected carcinomas are 4.5 times more common in female. Several other studies have also shown that gallbladder carcinomas are 4-5 times more common in female [4,11]. However, we have found that female predominance is less marked in unsuspected than suspected cancers which require further studies for confirmation.

In the present study, most of the unsuspected gallbladder carcinomas have presented with diffuse thickening of the wall (30%) and no grossly identifiable lesion (33.3%). Relatively higher proportion of carcinomas presenting with diffuse wall thickening and with no grossly identifiable lesion have been reported in some other studies also[4,10]. Roa et al have reported diffuse thickening in 12.3% and unapparent lesion in 38.8% of their cases as gross presenting features. On the other hand localized wall thickening (25%), thickened wall with invasion of the surrounding structures (25%) and large intraluminal mass (16.7%) represents greater portion of suspected gallbladder carcinomas in the present study.

Adenocarcinoma is the most common histological type of gallbladder carcinoma [4,5,9,20]. All the unsuspected carcinomas and 95% of the suspected carcinomas in the present study are adenocarcinoma. Suspected group show 29.5% well differentiated, 27.3% moderately differentiated and 43.2% poorly differentiated tumors. Similar results are reported by Ivan Roa et al[4]. They have found 21.5% of their cases to be well differentiated and 78.5% cases to be moderately

and poorly differentiated. However the clinically unsuspected group in our study show a different picture. 63.3% cases of unsuspected group are well differentiated and rest are almost equally divided between moderately differentiated and poorly differentiated grades.

In the present study half of the unsuspected carcinomas are limited to gallbladder and a significant portion of these are carcinoma in situ and early carcinoma limited to muscle layer only. No cases of PT4 are present. But the suspected carcinomas show only one fourth of the cases limited to gallbladder and another one fourth in PT4 stage.

Table-5: Stage distribution of gallbladder carcinoma cases in multiple studies found in literature expressed as percentages of total cases.

Study	PT 0	PT 1	PT 2	PT 3	PT 4
Kimura W et al[6]					
Asymptomatic cases (15)*	13.3	20	46.7	20	0
Symptomatic cases (65)*	0	0	0	9.3	90.7
L. Hu et al[13] (38)* (All cases are unsuspected)	-	31.7	36.8	28.9	2.6
M. D' Hondt et al[11]					
Incidental (30)*	0	10	63.3	26.7	0
Non incidental (12)*	0	16.7	41.7	33.3	8.3
M.G.P. Veloso et al[12]					
Preoperatively diagnosed(7)*	-	-	-	7	
No preoperative diagnosis(17)*	-	5	-	12	
Waghmare R.S.et al[10] (7)* (All are unsuspected)	0	1	6	0	0
Present study					
Unsuspected (30)*	20	13.3	16.7	50	0
Suspected (24)*	12.5	4.2	8.3	50	25

*Figures in brackets indicate total number of cases in that study.

All the studies in table 5 show that unsuspected or incidental or asymptomatic group show more prevalence of earlier stages than suspected, non incidental or symptomatic cases. However a major difference of our study with all other studies is that only 50% of the patients in the unsuspected group in our study presented in a stage limited to gallbladder. The corresponding figures for Kimura W et al, L Hu et al and M D' Hondt et al are 70%, 68.5% and 73.3% respectively [6,11,13]. This might be due to the influence of genetic and environmental variations between the population of our study and that of other studies.

Another important observation in our study is that well differentiated tumors whether clinically suspected or not shows more tendencies for presentation in earlier stages than moderately and poorly differentiated tumors. Jorge Albores-Saavedra et al[21] also found that 10 of the 13 intramucosal carcinomas in their study were well differentiated.

Conclusion

A significant portion of gallbladder carcinomas in the present study are found as clinically unsuspected incidental findings on routine gross and microscopic examination. They show relatively less female predominance than suspected cases.

Most of these unsuspected lesions show diffuse thickening of wall as their gross presentation or no grossly identifiable lesion at all. They have a tendency

to be better differentiated and in earlier stages than the clinically suspected carcinomas. Well differentiated tumors show more prevalence of earlier stages in the both suspected and unsuspected groups.

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Author contribution- PH is involved in study concept, literature search, data acquisition, manuscript preparation, editing and overall supervision. RD has took part in literature search and manuscript preparation. MKS is involved in data acquisition and manuscript preparation. All the three authors have read and approved the final manuscript.

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