

Cohort study: occurrence rate of occult gallbladder carcinoma and its curative strategies

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Abstract

Background: Gallbladder specimen after cholecystectomy is one of the rarely come up against in routine histopathology. Accompanied by the great supposition, nearly all gallbladder specimens harbor the benign disease, but once in a while unexpected to find malignancy. Occult gallbladder carcinoma is uncommon, highly lethal, although it is fifth prevailing malignancy in the gastrointestinal tract. Gallbladder malignancy is possible to cure if diagnosed at early stage and promptly treated surgically. Aim of study to figure out the occurrence of incidental carcinoma of the gallbladder and its curative options after elective cholecystectomy detected in routine histopathology.

Methods: Cohort study was done in total 1522 specimens of gallbladder, that were submitted in the pathology department in Ziauddin University and Hospital, five years of duration from Jan 2011 to Dec 2015, that were searched retrospectively for incidence of occult gallbladder carcinoma.

Result: We found 16(1.05%) cases of occult gallbladder carcinoma out of 1,522 patients, 4(25%) well differentiated, 9(56.25%) moderately differentiated, 2(12.5%) poorly differentiated and 1(6.25%) was undifferentiated adenocarcinoma. The incidence rate of primary malignancy was 1.05% and commonly found in female with the complete number of laparoscopic cholecystectomies carried out in that time. During follow up two patients lost, rest of the patients no recurrence or metastasis seen at 6, 12 and 24 months but one patient still not completed two years follow up.

Conclusion: Gallbladder malignancy may be curable if diagnosed in early stages. Laparoscopic cholecystectomy may not worsen the prognosis in such cases. Therefore every gallbladder specimen should be examined histopathologically after cholecystectomy to detect possible occult gallbladder carcinoma.

Keywords: Cholecystectomy, cohort study, histopathology, carcinoma gallbladder, occult gallbladder carcinoma

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Introduction:

Carcinoma of the gallbladder is a disease with high mortality and is usually diagnosed as an incidental finding in the histopathology report after cholecystectomy for symptomatic gallstone disease^{1,11}. The incidence of gallbladder malignancy is 1.2/100,000 people in the United States; the frequency of gallbladder malignancy is higher in Mexican and Native Americans, the higher incidence is found in

the peoples of the Andes Mountains, in north-eastern Europeans peoples, and in the Israelis. The gallbladder malignancy ratio is about 3:1 as in female-male respectively; incidence of the malignancy peaks in the seventh decade of their life¹. The gallstone is the most common risk factor for gallbladder malignancy, present in 75-90% of gallbladder malignancies. The gallstones size plays an important role in the risk of developing malignancy. Diameter of the

gallstones that are greater than 3cm have a ten times greater risk for developing malignancy than do those containing gallstones 1cm in diameter. Causality is hard to develop but some other chronic inflammatory conditions such as cholecystoenteric fistula, sclerosing cholangitis, pancreaticobiliary maljunction, and some chronic *Salmonella typhi* infection have also been associated with a greater risk of malignancy in the gallbladder. Some recent studies reported about a 10% incidence of malignancy in porcelain gallbladders (calcified wall of the gallbladder) is a much lower rate than that reported in older studies. Stippled calcified mucosa is thought to carry a greater risk of malignancy in the gallbladder than does generalized calcification in the wall of gallbladder.²⁻³ With these associations, chronic inflammation can be involved in the pathogenesis of the gallbladder malignancy.¹² Carcinoma of the Gallbladder is often discovered incidentally during a gallstone disease workup and about 50% malignancy of the gallbladder is diagnosed incidentally in histopathology of the gallbladder specimen after elective cholecystectomy and at the time of diagnosis about 35% of patients have distant metastases. Adenocarcinoma is found in 90% of gallbladder malignancies histologically and squamous cell carcinoma is found in 2% of gallbladder malignancies. Sarcoma, adenosquamous carcinoma, oat cell carcinoma, carcinoid, lymphoma, melanoma, and metastatic tumors are rare types of carcinoma of gallbladder. There is number of histologic subtypes of adenocarcinoma, but papillary adenocarcinoma represent about 5% of carcinomas of the gallbladder, well-differentiated histologically and have a more favorable prognosis.⁴⁻⁵ Gallbladder specimen after cholecystectomy is one of the frequently encountered specimens in daily routine histopathology. With the great expectations the most of the specimens of the gallbladder harbor the benign disease but sometimes surprising to find malignancy. Cancer of the gallbladder is uncommon although it is the fifth most common carcinoma in the gastrointestinal tract. Gallbladder carcinoma is possible to cure when tumors are diagnosed

at early stage and promptly treated surgically.⁹ Gallbladder polyps are common so it is important to identify these polyps because that can carry a high risk of malignancy in the gallbladder. Generally the size of a gallbladder polyp is the strongest predictor of transformation in malignancy.⁵ Benign lesions are relatively more common but adenomatous polyps are considered to have potential for gallbladder malignancy.⁸ The surgical approach to the carcinoma of gallbladder is early detection, appropriate staging histologically and curative tumor resection surgery.¹ But in unresectable disease have a median survival is 2-4 months and one year survival rate of < 5%.^{6,7} A good prognosis with five years survival rates is 90- 100%.¹⁰

Material and methods:

A total 1,522 cholecystectomies done in five years of duration and specimens of gallbladder that were submitted in pathology department in Ziauddin university and hospital from Jan 2011 to Dec 2015 that were searched retrospectively for occult gallbladder carcinoma in histopathology report. None of these cases had suspicion of malignancy preoperatively and whole data of all included patients was analyzed with full attention to pre and per-operative findings which could raise suspicion of malignancy of gallbladder. Data were analyzed using the statistical software namely SPSS version 21. Microsoft word and Excel have been used to generate graphs, tables, etc. Retrospectively data collected and analyzed for frequency, percentages, age ranges, mean age, gender frequency, male/female ratio and distribution of grading of occult gallbladder carcinoma in histopathology reports after elective cholecystectomy.

Results:

In this study of 1,522 patients, 1,142 were females and 380 were males (figure 1) (Table 1). All patients underwent for cholecystectomy for gallstone disease and all specimen of the gallbladder sent for histopathology. According to histopathology 382(25.1%) patients had acute on chronic cholecystitis with cholelithiasis,

Table 1: Age group and gender analysis (n=1522)

		Gender		Total	
		Female	Male		
Age Groups	< 20 years	Count	32	5	37
		% of total	2.1%	0.3%	2.4%
	21 - 40 years	Count	470	88	558
		% of total	30.9%	5.8%	36.7%
	41 - 60 years	Count	488	212	700
		% of total	32.1%	13.9%	46.0%
> 60 years	Count	152	75	227	
	% of total	10.0%	4.9%	14.9%	
Total	Count	1142	380	1522	
	% of total	75.0%	25.0%	100.0%	

Table 2: Histopathology analysis for carcinoma of gall bladder. (n=1522)

Tumor grade (Adenocarcinoma)	Age in years	Frequency /%
Well differentiated	50 to 62	4 (25%)
Moderately differentiated	39 to 80	9 (56.25%)
Poorly differentiated	50 to 68	2 (12.5%)
Undifferentiated	45	1 (6.25%)

773(50.8%) patients had chronic cholecystitis with cholelithiasis, 273(17.9%) had chronic cholecystitis cholelithiasis with cholesterolo-sis and rest of the patients had other benign pathology. Fifteen hundred and six patients (98.94%) had non neoplastic inflammatory disease of the gallbladder and sixteen (1.05%) patients had positive histopathology for occult gallbladder carcinoma. In our study we found 14(87.5%) patients were female and 2(12.5%) were male, having a male to female ratio of 1:7 (M:F=1:7). Mean age was 60.56 years with majority of patients falling in age group of 39-80 year (figure 1) (Table 1). With positive his-topathology for malignancy 1(6.25%) patient had undifferentiated adenocarcinoma, 2(12.5%) patients had poorly differentiated adenocarci-noma, 9(56.25%) moderately differentiated, and 4(25%) well differentiated adenocarci-noma (Table 2). Follow up done at 6, 12, and 24 months. Two patients lost during follow up, rest of the patients no recurrence or metasta-sis seen at 6, 12 and 24 months but one patient still not completed two years follow up.

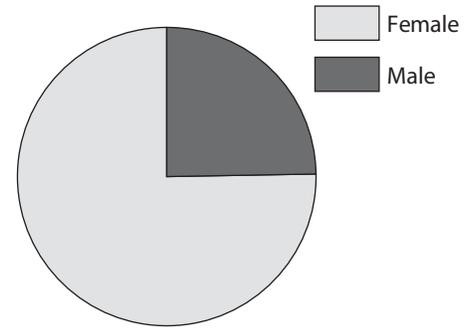


Figure 1: Gender distribution

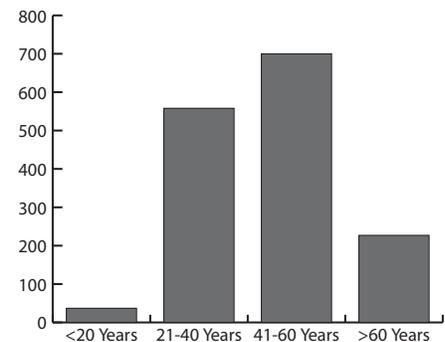


Figure 2: Distribution of patients who have undergone cholecystectomy in relation to their age

Discussion:

Diagnosis of the carcinoma of gallbladder preoperatively is an exception rather than the rule. The carcinoma of gallbladder is usually diagnosed incidentally in histopathology report after surgery for gallstone disease.¹³ It is the fifth most common malignancy of the biliary tract.¹⁴ In our study the frequency of occult gallbladder carcinoma is 16(1.05%) out of 1522 patients compared to in these studies.¹⁵⁻¹⁶ Similarly these international studies has been reported a figure of gallbladder carcinoma is 5 out of 1,308 patients (0.38%),¹⁷ 5 cases of carcinoma of gallbladder in 2,890 consecutive cases (0.17%),¹⁸ 13 cases of gallbladder cancer among 1,305 patients (1%).¹⁹ In our study one case of gallbladder polyp was identified, all occult gallbladder carcinoma were reported his-topathologically and diagnosed as adenocarci-noma, being graded undifferentiated, poorly, moderately and well differentiated. Most of the occult gallbladder carcinoma was reported in our study at early stages and they are well dif-ferentiated. All laparoscopic cholecystectomies

carried out at that time, no recurrence found at 6, 12 and 24 months follow up. Similar findings have been reported in these studies.²⁰⁻²¹ Further curative recourses of occult gallbladder carcinoma depend upon the stage of the cancer and general fitness of the patient. Surgical resection of the tumor is potential curative treatment when performed at an early stage of the cancer.²² Role of Chemotherapy and radiotherapy as an adjuvant treatment for carcinoma of gallbladder remains unclear.²³ Incidence of gallbladder polyps is ranging from 4.6% to 6.9%.²⁴ Routine histopathology of all gallbladder is well justified after cholecystectomy for gallstone disease as findings in pathology report, definitely affects the management plan and outcome of disease.

Conclusion:

It is concluded that occult gallbladder cancer may be curable if diagnosed at early stage. As an occult gallbladder carcinoma and cholecystectomy may not worsen the prognosis in such cases. In our study no association could be found between pre and per operative findings that could raise a suspicion of malignancy of gallbladder and so use of retrieval bag as a routine measure may reduce the incidence of port site metastasis. Therefore every gallbladder specimen after cholecystectomy should be examined histopathologically to detect possible incidence of occult gallbladder carcinoma.

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Role and contribution of authors:

Dr Irum Masood, Design the study, data collection, tabulate and write-up intro, discussion, result, conclusion

Dr Haris Rasheed Consultant and laparoscopic General surgeon Ziauddin University and hospital Karachi, Supervise and Design the study, initial methodology, Final Review

Ahmed Raheem Statistician Department of Pathology & Laboratory Medicine Agha Khan

University and Hospital Karachi, did Statistical analysis

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