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CLINICAL CHARACTERISTICS AND SURGICAL OUTCOME OF INCIDENTAL GALL BLADDER CANCERS DURING OR AFTER CHOLECYSTECTOMY

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Abstract

Objective: *To measure the frequency of incidental gall bladder carcinoma (GBC) during and after cholecystectomy and compare the clinical characteristics and surgical outcomes between both groups.*

Study design: *Quasi-experimental study*

Place and duration of study: *Surgery department of Army Liver Transplant Unit Pak Emirates Military Hospital (PEMH) from July 2023 to July 2024.*

Methodology: *After ethical approval, we collected a sample of 52 patients who were diagnosed with incidental gall bladder cancers during or after cholecystectomy. We studied and compared their clinical characteristics, risk factors and surgical outcomes.*

Results: *Total 10 (19.23%) patients had Isolated Cholecystectomy, and 42(80.76%) patients had radical cholecystectomy. Chronic cholecystitis was found in 7(70.0%) patients in group DDLC and 42(100.0%) patients in DALC with p value 0.005. Acute cholecystitis was found in all patients in group DDLC and 27(64.3) patients in group DALC with p value of 0.002.*

Conclusion: *We concluded that the frequency of incidental gall bladder cancers is higher during histopathology than during laproscopic cholecystectomy and surgical outcomes are affected by this. The demographic characteristics, risk factors and clinical features do not differ significantly from the surgical outcome and mode of diagnosis.*

INTRODUCTION

Gallbladder cancer (GBC) accounts for eighty percent of biliary tree tumors in autopsy studies conducted globally with female predominance. It is the most prevalent carcinoma of the biliary tract, which mostly presents with nonspecific signs and symptoms, making it difficult to differentiate from benign gallbladder (GB) conditions. It is often asymptomatic until it reaches advanced stages or has non-specific symptoms which complicate early diagnosis.[1] Gallstones and chronic inflammation are most frequently observed clinical signs of GBC and patients who exhibit such symptoms, long-term survival is generally achievable, as these individuals may be diagnosed at an earlier stage of the disease.[2] The most frequently observed radiological finding is wall thickening. However, this thickening can also result from concurrent benign conditions, such as cholelithiasis, which can obscure the diagnosis of

GBC. Furthermore, the radiological characteristics of GBC are not unique and can overlap with benign GB diseases like GB polyps. As a result, GBCs often go undetected.[3] The global incidence of Incidental gall bladder cancers discovered during cholecystectomy or pathological examination is 1.2% and Incidental gallbladder cancer (IGBC) account for up to 50% of all gallbladder cancers (GBCs).[4] In Pakistan, a significant portion of the population is impacted by gallstones, with prevalence rates varying between 9% and 60%but incidence of GBC is 1-3% patients according to retrospective study done between 1988-2007 in Karachi.[5]

Cholelithiasis is recognized as an important risk factor for GBC. Additional risk factors for gall bladder cancer include older age, cholelithiasis, female gender, and obesity.[6] The rates of pathological examinations conducted after cholecystectomy can vary by country and insurance policies. If pathological examinations are not performed consistently in all cases, the incidence rate of incidental gallbladder cancer (IGBC) may be either overestimated or underestimated. Benign GB diseases are often diagnosed preoperatively but gall bladder cancer is typically identified during or after cholecystectomy.[7] In this study, we aim to study the clinical characteristics and outcomes of incidental gall bladder cancers diagnosed during and after cholecystectomy as when suspected during laproscopic cholecystectomy, it is converted to open surgery to allow radical resection. When GB cancer is diagnosed after routine cholecystectomy, reoperation for radical resection is the only option. However, not all patients undergo reoperation for radical surgery due to various factors, including refusal to proceed with radical surgery, poor medical condition, or cancer progression.[8] The identification of clinical characteristics will give an insight to this disease so that we can develop an index of suspicion and develop strategies to help eradicate it.

Methodology:

The ethical committee of the hospital permitted us to perform study with IERB number A/28/ERC/631/23. We performed our study at surgery department of Army Liver Transplant Unit Pak Emirates Military Hospital (PEMH) from July 2023 to July 2024. The study design was quasi-experimental and WHO sample size calculator was used to calculate sample size. The sample size was calculated keeping level of significance 5%, power of test 90%, the frequency of isolated cholecystectomy in GBC patients who were incidentally found during laproscopic cholecystectomy to be 29%[9] and the frequency of isolated cholecystectomy in GBC patients who were incidentally found on histopathology to be 89%[9]. The sample came out to be 12. We collected samples through non-probability consecutive samplings to include all cases of gall bladder carcinoma who were diagnosed incidentally from July 2023 to July 2024 from a population of 3280 who underwent laparoscopic cholecystectomy after application of criteria furnished. **Inclusion criteria:** The study included patients of both genders with an age range 25-65 years who emerged as suspected cases either during or after cholecystectomy, with no prior suspicion of malignancy at the preoperative assessment. The patients had no suspicion of gall bladder carcinoma on ultrasonography.

Exclusion criteria:

The Patients who were operated upon for radical cholecystectomy through resection and lymphadenectomy were not included. The patients with metastatic diseases or some other malignancies were also not included.

We were able to collect a sample of 52 patients out of which 8 patients were diagnosed incidentally during laparoscopic cholecystectomy and 44 were diagnosed incidentally during histopathology. The outcomes were of two types: Clinical and surgical. The presence or absence of the following clinical characteristics were noted for all patients: Nausea, vomiting, biliary colic, weight loss, cholelithiasis, dyspepsia, chronic cholecystitis and acute cholecystitis. Regarding surgical outcomes: There were two types of surgical outcomes: Isolated cholecystectomy and Radical cholecystectomy. Isolated cholecystectomy included routine laparoscopic cholecystectomy and radical resection included en bloc removal of the gallbladder along with gallbladder fossa, extra hepatic bile ducts and regional lymph nodes.[10] The demographics included age, gender, BMI, histopathological differentiation and risk factors (cigarette smoking and obesity).

The data was analyzed using SPSS software. Normality of data was checked first. For qualitative variables, frequency and percentages were calculated and for quantitative variables means and standard deviation were computed. Chi-square analysis and T-test were used were applicable. P value less than 0.05 was considered significant. The study diagram is presented in Figure-I.

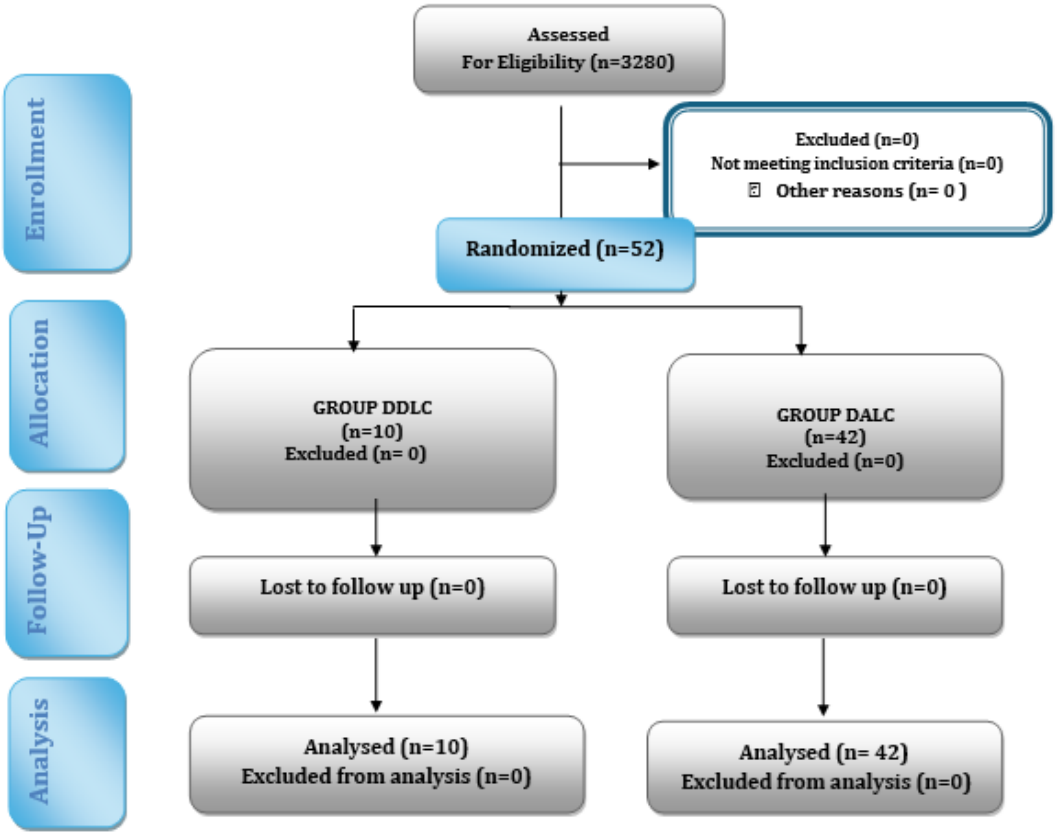

Fig-I: Consort flow diagram of study

Results:

There were 52 patients in the study who completed study till follow-up. Out of 52 patients, eight patients were diagnosed with carcinoma gall bladder during laproscopic cholecystectomy, and 42 patients were diagnosed during histopathology. Both groups had similar demographic traits. The mean age of group DDLC patients was 65±4.85 years and the mean age of DALC patients was 67±2.89 years. The BMI of DDLC group was 67.19±4.23 kg/m^2 and DALC group was 2 9.74±2.28 kg/m^2. There were 3(30.0%) males and 7(70.0%) females in study group DDLC. There were 6(14.3%) males and 36(85.7%) females in study group DALC. Both groups had greater number of female patients. Obesity was seen in 4(40.0) DDLC patients and 23(54.8%) DALC patients. Four (40.0%) percent of patients were smokers in group DDLC and 23(54.8%) were smokers in group DALC. The p values and frequencies are presented in Table-I.

Six (60.0%) patients in group DDLC had nausea, 2(20.0%) vomiting, 8(80.0%) had epigastric pain, 8(80.0%) had biliary colic and dyspepsia and 9(90.0%) patients had history of weight loss. Thirty (21.4%) patients in group DDLC had nausea, 14(33.3%) had vomiting, 32(76.2%) had epigastric pain, 31(73.8%) had biliary colic, 32(76.2%) had dyspepsia and 32(76.2%) had history of weight loss. There was no significant statistical difference in the above-mentioned clinical parameters. Chronic cholecystitis was found in 7(70.0%) patients in group DDLC and 42(100.0%) patients in DALC with p value 0.005. Acute cholecystitis was found in all

patients in group DDLC and 27(64.3) patients in group DALC with p value of 0.002. Seven (70.0) patients had single gall stone in group DDLC and 31(73.8%) patients in group DALC had single gall stone. Multiple stones were found in 3(30.0) patients in group DALC and 11(26.2%) patients in group DALC. The tumor differentiation was also similar in both groups. (Table-II).

Total 10 (19.23%) patients had Isolated Cholecystectomy, and 42(80.76%) patients had radical cholecystectomy (Table-III)

Table-I: The demographics parameters of the patients enrolled in study (n=52)

		DDLC Mean±SD n=10	DALC Mean±SD N=42	p value
Age (years)		65±4.85	67±2.89	0.180
BMI (kg/m^2)		67.19±4.23	29.74±2.28	0.023
		Frequency (%)	Frequency (%)	
Gender	Male	3(30.0)	6(14.3)	0.228
	Female	7(70.0)	36(85.7)	
Obesity	Yes	4(40.0)	23(54.8)	0.313
	No	6(60.0)	19(45.2)	
Smoking	Yes	4(40.0)	23(54.8)	0.09
	No	6(60.0)	19(45.2)	

Table-II: The clinical outcomes of Gall Bladder Cancer (GBC) in the study samples (n=52)

		DDLC Frequency (%) n=10	DALC Frequency (%) N=42	p value
Nausea	Yes	6(60.0)	33(21.4)	0.204
	No	4(40.0)	9(21.4)	
Vomiting	Yes	2(20.0)	14(33.3)	0.314
	No	8(80.0)	28(66.7)	
Epigastric pain	Yes	8(80.0)	32(76.2)	0.582
	No	2(20.0)	10(23.8)	
Biliary colic	Yes	8(80.0)	31(73.8)	0.518
	No	2(20.0)	11(26.2)	
Dyspepsia	Yes	8(80.0)	32(76.2)	
	No	2(20.0)	10(23.8)	
Weight loss	Yes	9(90.0)	32(76.2)	0.314
	No	1(10.0)	10(23.8)	
Chronic cholecystitis	Yes	7(70.0)	42(100.0)	0.005
	No	3(30.0)	0(0)	
Acute cholecystitis	Yes	10(100.0)	27(64.3)	0.002
	No	0(0)	27(35.7)	
Single Gall Stone	Yes	7(70.0)	31(73.8)	0.545
	No	3(30.0)	11(26.2)	
Multiple Gall Stones	Yes	3(30.0)	11(26.2)	0.545
	No	7(70.0)	31(73.8)	

Differentiation grade	Well differentiated	5(50.0)	9(21.4)	0.845
	Moderate differentiated	4(40.0)	16(38.1)	
	Poorly differentiated	1(10.0)	17(40.5)	

Table-III: surgical outcome and frequency of Gall Bladder Carcinoma in study sample (n=52)

Surgical Outcome	Frequency (%)
Isolated Cholecystectomy	10 (19.23)
Radical Cholecystectomy	42(80.76)

Discussion:

The frequency of Gall bladder carcinoma was 1.58 percent in our study. A total of 52 patients of carcinoma gall bladder were identified in a year who did not have any suspicion of gall bladder malignancy preoperatively. Cholecystectomy is the standard procedure for symptomatic cholelithiasis but for advanced cancers liver resection and lymph node dissection, is recommended. Ten patients in our study were diagnosed during surgery in whom radical cholecystectomy was done and around three-quarters of subjects in our study were diagnosed with incidental gall bladder cancer after surgery and ultimately, they became candidates for revisional surgery. There is significant geographic heterogeneity in gallbladder cancer frequency and its clinical presentation. It has non-specific symptoms which mimic a diverse collection of disorders that is why diagnosis is a difficult clinical endeavor.

According to Davide Di Mauro[11] symptomatic cholelithiasis was the main reason of cholecystectomy with the median duration of abdominal symptoms was seven months. The connection of gallstones and gall bladder cancer is already established but it's still unknown whether gallstones increase the likelihood of the disease or if they can help it happen. According to single center study by Cha, Byung Hyo, it was recommended that since gall stone disease is the most important predictive factor for gall bladder carcinoma, every symptomatic cholelithiasis patient should undergo advanced work-up foe gall bladder carcinoma. They also noted that the characteristics of tumor were different between the suspected patients and patients with incidental GB cancer, and they also noted that patients with incidental gall bladder cancer had significantly better median five-year survival.[12]

The primary clinical challenge associated with incidentally discovered gallbladder (GB) cancer is decision of surgery. If all bladder cancers are identified through initial operation, transitioning to radical cholecystectomy is straightforward. But when cancers are detected postoperatively, reoperation for radical resection becomes both compulsory and critical.[13]The impact of incidentally diagnosed gallbladder (GB) cancers on prognosis and survival as compared to preoperatively diagnosed cancers is not researched extensively but some authors advocate that it is still unclear whether incidental cancers have a similar prognosis or worse than non-incidental GB cancer at the same stage. In patients with incidental GB cancers, the concurrent presence of cholecystitis is likely to complicate the diagnosis. Several studies have indicated that cholecystitis negatively affects survival, although the exact mechanisms behind this have not been explored.[14] In our study, all patients had a history of cholecystitis but there is need to develop an index of suspicion based on risk factors, and we should offer advanced workup to patients who have multiple risk factors of disease.

When survival outcomes of laparoscopic procedures versus open procedures was done for treating gallbladder cancer, no significant difference was found between the two methods, indicating that laparoscopic cholecystectomy does not affect survival adversely.[15] However, one study suggested that laparoscopic cholecystectomy may carry a higher hazard as it can disseminate tumor cells that's why open surgery is preferable in patients who have suspected GB cancer.[16] We converted all laparoscopic surgeries to open surgeries when we incidentally gall bladder cancer was diagnosed.

Gallbladder cancer (GBC) is also prevalent in our geographic regions. Early diagnosis followed by radical resection is the only reasonable management approach which guarantees a favorable prognosis but many patients with gall bladder cancer are unfortunately diagnosed at advanced stage.[17] In our study, we only compared the clinical outcomes of incidental gallbladder cancer during laparoscopic cholecystectomy with those diagnosed on histopathology, but we did not follow for prognosis. We did not identify significant differences in demographics and risk factors between both groups. We found that the primary reasons for cholecystectomy in our patient were gallstones, with accompanying cholecystitis. There were no gallbladder polyps and wall thickening in our patients and there was no ultrasonography feature of malignancy.

Many epidemiological studies have indicated that a history of cholelithiasis may be a potential risk factor for gallbladder cancer[18] but in Pakistan gall bladder disease is considered as very trivial surgery from both patient and surgeons' perspective. The waiting time for surgery is two weeks to one month in our setup and only ultrasonography is done to confirm diagnosis. The report of histopathology is often not shown to surgeons. According to Faisal G Siddiqui et al[19] the gallbladder's histological spectrum is quite varied, and it is not uncommon for gallbladder cancer to be diagnosed incidentally but the standard procedure for routine histopathology of all gallbladder specimens is not followed. Under such circumstances, subclinical malignancies would go undetected with catastrophic consequences. They recommended that all cholecystectomy specimens undergo regular histology. We ensured the meticulous histopathology of our patient population to collect study samples. This could be a source of bias in our study as some samples get lost and some patients do not follow up which can lead to under-reporting of cancer prevalence.

Recent research has shown that cholelithiasis is the primary basis for cholecystectomy and it incidentally leads to gallbladder cancer, but the incidence is very low (0.25%).[20] Furthermore, prophylactic cholecystectomy for asymptomatic cholelithiasis to prevent GBC is not justified due to low incidence. The clinical features and radiologic indicators that could identify early GBC or premalignant lesion remain unknown. Adenomatous gall bladder polyps have potential for malignancy.[21] In our study, none of patients had polyp, but all patients had CA gall bladder.

Conclusion: We concluded that the frequency of incidental gall bladder cancers is higher during histopathology than during laparoscopic cholecystectomy and surgical outcomes are affected by this. The demographic characteristics, risk factors and clinical features do not differ significantly from the surgical outcome and mode of diagnosis.

Recommendations:

There is need of large-scale randomized controlled trials to improve the diagnosis of gall bladder carcinoma and advanced work-up may be used along with ultrasonography to make a difference. It is essential to differentiate patients at high risk for incidental gallbladder cancer (IGBC) from those with benign conditions before making surgical decisions, regardless of symptoms. Identifying valid predisposing risk factors for early GBC in patients is need of time as this disease mimics benign condition and can be easily misdiagnosed.

Limitations of Study:

We shared experience single center experience. We did not follow patients for long term survival.

Conflict of Interest: None

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Authors Contributions:

Author 1 & Author 2: Drafting of work, design analysis, data acquisition, data interpretation and approval of final version to be published

Author 3 & Author 4: Data analysis, data acquisition, drafting of work, critical revision, approval of final version to be published

Author 5 & Author 6: Drafting of work, critical review, approval of final version to be published.

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