

Incidental gallbladder cancer: Missing links in Pakistani population

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ABSTRACT

Aims: To determine frequency of incidental gallbladder cancer (IGBC) in Pakistani population, its demographic/histopathological features and type of surgical resections performed. **Methods:** This observational study was conducted at Combined Military Hospital (CMH)/Armed Forces Institute of Pathology (AFIP) Rawalpindi, Pakistan from July 2009 to July 2015. Clinical as well as pathological records of all patients who underwent laparoscopic cholecystectomy (LC) / open cholecystectomy (OC) were reviewed and data was obtained regarding IGBC and benign gallbladder pathology. Patients diagnosed

with cancer underwent staging investigations and were offered definitive surgery. Overall frequency and clinicopathological features of IGBC were studied. **Results:** One hundred sixty-four patients out of 10,549 had IGBC (1.55%). Mean age of presentation in IGBC and benign gallbladder pathology patients was 59.23 ± 12.17 and 45.73 ± 13.11 years respectively (p -value < 0.001). Cancer patients had significantly more comorbid (73.17% versus 39.43%, p -value < 0.001) and larger stones (p -value < 0.001). Histopathology revealed adenocarcinoma in 148 (90.24%), adenosquamous carcinoma in 08 (4.88%), undifferentiated in 04 (2.44%), squamous cell carcinoma in 02 (1.22%), sarcoma and melanoma in one patient each (0.61%). Most of the tumors were well differentiated (36.59%) and liver was most commonly infiltrated organ (52.44%). Thirty-four patients had stage I, 38 patients had stage II, 49 patients had stage III and 43 patients had stage IV cancer (20.73%, 23.17%, 29.88%, 26.22% respectively). Surgical resection included no further treatment in 31 patients as cholecystectomy proved adequate vis-à-vis stage, extended cholecystectomy in three patients (1.83%), radical cholecystectomy in 17 (10.37%), pancreaticoduodenectomy (Whipple) in 6 (3.66%), palliation/symptomatic management in 42 (25.61%) patients while 65 (39.63%) patients refused surgery. Adequate lymphadenectomy was performed only in 50 (30.49%) patients while 44 (26.83%) showed positive resection margins. **Conclusion:** IGBC must be kept in mind while performing cholecystectomy and every specimen should undergo routine histopathological examination. Radical surgery should be offered and may improve outcome in carefully selected cases.

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INTRODUCTION

Gallbladder cancer (GBC), a highly lethal disease, is the third most prevalent gastrointestinal tract cancer with multifactorial etiology [1]. Strikingly distinct ethnic, gender and geographical variations superimpose vague clinical picture, leading to late diagnosis at advance stage usually in the seventh decade and disastrous clinical course with dismal survival rates, in spite of growing awareness and recent advances in medical sciences [2].

Global rates for GBC exhibit striking variability closely following worldwide prevalence of gallstones, reaching epidemic levels for Mapuche Indians of Chile (35/100000) followed by Hispanics, North American, Indians, and Japanese [3]. Asian subcontinent exhibits extraordinarily high disease incidence, where an increased frequency of GBC occurs in north Indian females (21.5/100000), Pakistani females (13.8/100000) and Korean males [4].

Adenoma-carcinoma sequence and dysplasia-carcinoma sequence are the most common theories as exact etiology of GBC is still not known. Intrinsic genetic predisposition orchestrated by environmental triggers play critical role in eliciting cancer [5]. Gallstones represent most significant risk factor being present in 85% cases [6]. Progression is frequently rapid and silent with early spread through vascular, lymphatic, intraperitoneal, neural and intraductal routes, most common route being lymphatics. Metastases usually occur in liver, adjacent organs and peritoneum, liver being involved in 76–86% cases [7].

Significant overlap between benign gallbladder pathology and GBC defies early detection leading to incidental diagnosis in majority at advanced stage. Persistent right upper quadrant pain, jaundice, anorexia, nausea and weight loss are most common symptoms while palpable gallbladder is present in a few only. Deranged liver functions represent most common laboratory finding [8]. Though ultrasonography (USG) is most widely used initial screening as well diagnostic tool, it lacks sensitivity and specificity for early cancer. Other preferred investigations are endoscopic ultrasound

(EUS), computed tomography (CT) scan, magnetic resonance cholangiopancreatography (MRCP) and fluorodeoxyglucose positron emission tomography (FDG-PET) [9]. Although there is currently no single tumor marker helping clinch diagnosis, promising one include cancer antigen (CA) 242, CA-125, and CA-19-9.

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 [10]. Early diagnosis and radical surgical resection offers only chance of long-term survival. Unfortunately, only 10% or so are resectable at the time of diagnosis. Incidental gallbladder cancer may be defined as a malignancy detected only on histopathological examination without prior preoperative suspicion of malignancy. Current study was performed to determine frequency of IGBC in Pakistani population, its demographic as well as histopathological features and type of surgical resections performed.

MATERIALS AND METHODS

After approval of Hospital Ethical Committee, clinical as well as pathological records of all patients who underwent laparoscopic cholecystectomy (LC)/open cholecystectomy (OC) at hepatobiliary department CMH/AFIP Rawalpindi, a tertiary care referral center, from July 2009 till December 2015, were studied. Incidental gallbladder cancer was defined as a malignancy detected only on histopathological examination without prior preoperative suspicion of malignancy. Only those cases having complete clinical as well as pathological record were included.

Gallbladder disease was confirmed through history, physical examination, laboratory tests and USG. Choledocholithiasis was treated with preoperative endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy/stenting after confirmation of diagnosis with MRCP/CT scan while gallstone pancreatitis was also treated with LC in the same admission after settlement of acute pancreatitis. Laparoscopic cholecystectomy was initial procedure and converted to open when indicated or felt appropriate. Patients diagnosed with IGBC on histopathological examination underwent staging investigations and were staged according to 7th edition of the American Joint Committee on Cancer (AJCC) Manual, 2010 [11]. Second stage surgical resection was offered to those patients having stage II/III disease if R0 was deemed possible while simple cholecystectomy was considered sufficient for Tis/T1a disease and palliative care offered for stage IV disease. Extended cholecystectomy comprising of cholecystectomy, resection of 2 cm non-neoplastic liver tissue and skeletonization of hepatoduodenal ligament was performed in patients having T1b lesions. Radical cholecystectomy consisting cholecystectomy,

excision of medial liver segments 4b/5 and regional lymphadenectomy was carried out in T2 lesions while T3 lesions underwent removal of additional extra hepatic bile ducts or other organs as dictated by tumor spread. Palliation involved nonsurgical/surgical biliary drainage and symptomatic relief accordingly [12]. Definitive surgery was performed by same surgical team comprising two consultants and five registrars.

Analysis was carried out on formalin fixed and paraffin embedded (FFPE) tissue specimens by single consultant over the period of the study as per college of American pathologist (CAP) protocol version 3.1.0.2. Immunohistochemistry (IHC) help was sought in difficult cases and Leica Microsystems®, USA Cytokeratin (CK) 7 and 20 were employed. CK 7 positivity while CK 20 negativity confirmed GBC [13]. Cases diagnosed with IGBC were discussed in multidisciplinary team (MDT) meeting comprising operating surgeon, histopathologist, gastroenterologist and oncologist.

All the data reviewed was entered into Statistical Package for Social Sciences (SPSS) software version 21 for windows (SPSS Inc., Chicago, IL, USA) and analyzed through its statistical package. Mean±SD was used for quantitative data like age while frequency and percentage was calculated for qualitative data. Chi-square and t-test were applied for categorical and numerical variables respectively. P-value of less than < 0.05 was taken as significant.

RESULTS

Clinical as well as pathological records of 12578 patients were reviewed with regard to demographic/histopathological features and surgical intervention performed. Complete data was available in 10549 (83.87%) patients and were included in analysis. Out of 10549 patients 164 (1.55%) patients had IGBC. Mean age of presentation in IGBC and benign gallbladder pathology patients was 59.23±12.17 and 45.73±13.11 years respectively (p-value <0.001). Male: female ratio was 1:2.3 in IGBC and 1:3.2 in benign gallbladder pathology patients (p-value 0.042). Significantly more patients had concomitant disease in cancer group (73.17% versus 39.43%, p-value <0.001). BMI was also significantly high in cancer patients (29.73±3.44 IGBC and 28.19±3.99 benign gallbladder pathology, p-value <0.001). Higher ASA status was found in cancer patients which may be due to presence of comorbid/ advance age (p-value <0.001). Single stone was present in 61(37.2%) patients while multiple stones inflicted 91 (55.49%) cancer patients. Size of stone was significantly larger in IGBC patients (2.23±1.36 cm versus 1.27±0.66 cm p-value <0.001). Most of the surgeries were performed by consultants while acute cholecystitis and symptomatic cholelithiasis were most common presenting pathologies is given in Table 1.

One hundred and sixty-four patients (114 females and 50 males) were diagnosed histologically with IGBC. Among them, 93 (56.71%) patients presented with acute cholecystitis while 64 (39.02%) with symptomatic cholelithiasis and 07 (4.27%) had polyps. Majority had acute presentation while in 18 patients, length of disease was not known. Anorexia was the most common sinister symptom present in 53 (32.32%) patients followed by

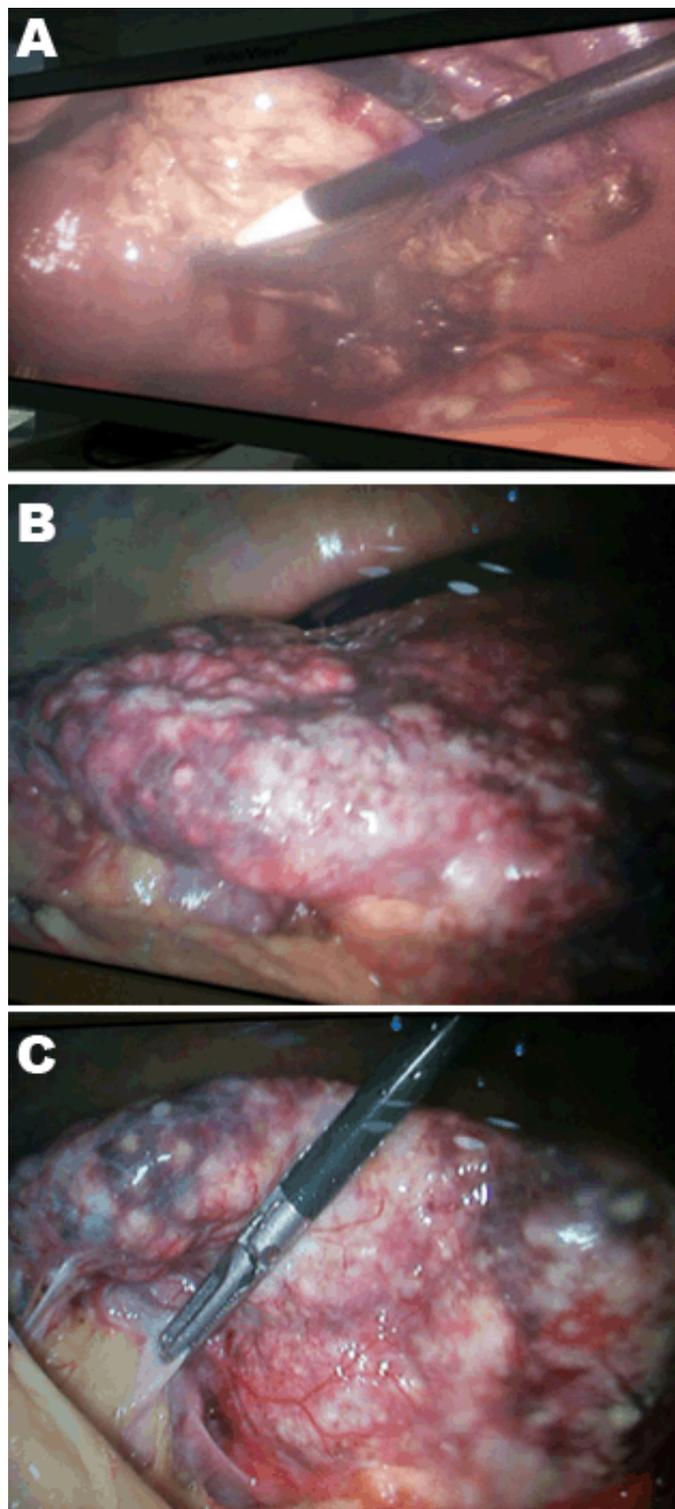


Figure 1: (A–C) Laparoscopic view of advance gallbladder cancer involving peritoneum and liver. Biopsy performed that revealed poorly differentiated adenocarcinoma.

weight loss in 52 (31.71%) and jaundice in 19 (11.59%) patients. Family history of cancer was more commonly found in female patients. Significantly more smokers with cancer were diagnosed as males (p-value <0.001). Simple cholecystectomy was performed in 72.81% while rest underwent biopsy only due to intraoperative suspicion (Figure 1) (Table 2).

Histopathological analysis revealed adenocarcinoma in 148 (90.24%) patients, adenosquamous carcinoma in 8 (4.88%), undifferentiated in 4 (2.44%), squamous cell carcinoma in 02 (1.22%), sarcoma and melanoma in one patient each (0.61%). Fundus (42.1%) of gallbladder was most common site followed by body and neck. Most of

tumors were well differentiated (36.59%) while 33.54% had poorly differentiated tumors. IHC was performed in 65 (39.63%) patients to reach at correct diagnosis. Thirty four patients had stage I (31 patients Tis/T1a while three patients had T1b lesion), 38 patients had stage II, 49 patients had stage III and 43 patients had stage IV cancer (20.73%, 23.17%, 29.88%, 26.22% respectively) according to AJCC 7th edition. Surgical resection included no further treatment in 31 patients, extended cholecystectomy in 3 (1.83%), radical cholecystectomy in 17 (10.37%), pancreaticoduodenectomy (Whipple) in 6 (3.66%), palliation/symptomatic management in 42 (25.61%) patients while 65 (39.63%) patients refused any

Table 1: Demographic variables of incidental gallbladder cancer and benign gallbladder pathology patients

Characteristics	Incidental gallbladder cancer		Benign Pathology		p-value
	Frequency	Percentage	Frequency	Percentage	
Male	50	30.5	2457	23.66	0.042
Female	114	69.5	7928	76.34	
Male :female ratio	1 : 2.3		1 : 3.2		
Age in years	59.23 ± 12.17		45.73±13.11		0.000
Concomitant disease	73.17%		39.43%		0.000
Diabetes mellitus	71	43.3	1575	14.88	
Hypertension	34	20.7	1890	17.86	
Ischemic heart disease	14	8.5	420	3.97	
Respiratory disease	01	0.6	210	1.98	
Surgeon					0.729
Consultant	115	70.1	7151	68.86	
Resident	49	29.9	3234	31.14	
Body Mass Index	29.73±3.44		28.19±3.99		0.000
ASA status					0.000
I/II	91	55.5	9305	89.6	
III/IV	73	44.5	1080	10.4	
Surgical anatomy					0.000
Single stone	61	37.2	1134	10.92	
Multiple stone	91	55.48	6689	64.41	
Size of the stone	2.23±1.36		1.27±0.66		0.000
Pre Op diagnosis					0.000
Ac cholecystitis	93	56.7	1638	15.77	
Symptomatic cholelithiasis	64	39	8117	78.16	
Polyp	07	4.3	105	1.01	
Other	0	0	525	5.06	

sort of surgical intervention. Liver was the most common organ to be involved by tumor (86 subjects 52.44%). Only 50 patients (30.49%) had adequate number of lymph node sent while in majority (55.49%) no comment was found in histopathology report. Resection margins were positive in 44 (26.83%) specimens while in 48 (29.27%) patients, margin status was not mentioned (Table 3).

DISCUSSION

Gallbladder cancer is a highly lethal disease harboring dismal outcome. Cancer epidemiology (frequencies, pattern of distribution and determinants) are of immense importance as identification of risk factors provides insight into pathogenesis thus establishing platform for effective preventive and treatment strategies [14]. Early diagnosis and radical surgical resection is the only

Table 2: Clinical features of incidental gallbladder cancer patients with respect to gender

Characteristics	Male		Female		p-value
	Frequency	Percentage	Frequency	Percentage	
Clinical Presentation					
Acute cholecystitis	27	54	66	57.89	0.87
Symptomatic cholelithiasis	21	42	43	37.72	
Polyp	2	4	5	4.39	
Duration of cholelithiasis					
< 10 years	27	54	65	57	0.92
>10 years	17	34	37	32.46	
Not Known	6	12	12	10.53	
Sinister symptoms					
Anorexia	15	30	38	33.33	0.67
Jaundice	6	12	13	11.40	0.91
Weight loss	15	30	37	32.46	0.76
Family history					
Yes	4	8	27	23.68	0.18
No	46	92	87	76.32	
Parity					
Nulliparous			5	4.39	
Multipara			109	95.61	
Smoking					
Yes	42	84	13	11.4	0.000
No	8	16	101	88.6	
Surgical procedure					
Simple cholecystectomy	38	6	83	72.81	0.67
Biopsy	12	24	31	27.19	
Suspicion of cancer during surgery					
No	38	6	83	72.81	0.67
Yes	12	24	31	27.19	
Year wise cancer case					
2009	3	6	12	10.53	0.39
2010	4	8	16	14.03	
2011	4	8	15	13.16	
2012	6	12	16	14.03	
2013	9	18	15	13.16	
2014	12	24	17	14.91	
2015	12	24	23	20.18	

effective weapon in treatment armamentaria at present [15].

Incidental gallbladder cancer is a realistic hope allowing considerable leverage of tactical maneuverability as disease stage is the most important determinant of surgical success [16]. Diagnosis of IGBC remains enigma due to paucity of clinical features and inability of investigations to identify the disease [17]. Recognizing important risk factors and associated clinical jargons may provide clue for picking IGBC early [18].

Current study focuses on frequency of IGBC at tertiary care referral center, its demographic/histopathological variables and overview of definitive surgeries performed. Clinical as well as pathological record of 10549 patients was studied. Incidental gallbladder cancer was found in 164 (1.55%) patients. Patients with IGBC were

significantly older than those having benign gallbladder pathology (59.23±12.17 versus 45.73±13.11 years, p-value <0.001). Figures are in concordance with international literature as cancer usually affects elderly female in seventh/eighth decade while cholelithiasis is a disease of fourth decade [19]. Significantly more patients had concomitant disease in cancer group (p-value <0.001), higher ASA status (p-value <0.001) and larger stones (p-value <0.001) conforming to reports of various other authors [20]. Acute cholecystitis (56.7%) was most common presentation while anorexia was most frequent sinister symptom present in 32.3% of IGBC patients. Significantly more smokers with cancer were diagnosed as males (p-value <0.001). However, family history was more frequently found in female patients which may confer to more prevalence of gallstones in

Table 3: Histopathological features of incidental gallbladder cancer with respect to gender

Characteristics	Male		Female		p-value
	Frequency	Percentage	Frequency	Percentage	
Tumor type					
Adenocarcinoma	43	86	105	92.11	0.26
Adenosquamous	3	6	5	4.39	
Undifferentiated	2	4	2	1.75	
SCC	0	0	2	1.75	
sarcoma	1	2	0	0	
Melanoma	1	2	0	0	
Tumor Site					
Body	21	42	39	34.21	0.59
Fundus	20	40	49	42.98	
Neck	9	18	26	22.81	
Wall of gallbladder					
Normal	9	18	22	19.30	0.16
Thick contracted	21	42	29	25.44	
Proximal	1	2	11	9.65	
Circumferential	18	36	48	42.11	
Cystic duct margin	1	2	4	3.51	
Type of growth					
Ulcerated	17	34	50	43.86	0.47
Papillary	16	32	29	25.44	
Polypoidal	17	34	35	30.70	
Mucosa of gallbladder					
Normal	15	30	27	23.68	0.68
Ulcerated	19	38	46	40.35	
Hemorrhagic	16	32	41	35.96	
Grade of tumor					
Well differentiated	18	36	42	36.84	0.89
Moderately differentiated	14	28	35	30.70	
Poorly differentiated	18	36	37	32.46	
Stage of the disease					
I	12	24	22	19.3	0.72
II	13	26	25	21.93	
III	14	28	35	30.70	
IV	11	22	32	28.07	
Second stage surgery					
None	10	20	21	18.42	0.75
Radical/extended cholecystectomy	5	10	15	13.58	
Whipple	3	6	3	2.63	
Palliation	11	22	31	27.19	
Refused by patient	21	42	44	38.60	
Invasion					
Lymphovascular	23	46	48	42.11	0.64
Perineural	29	58	56	49.12	0.29
Liver	23	46	63	55.26	0.27
Lymph node status					
Not sent	27	54	64	56.14	0.64
<3	11	22	25	21.93	
>3	4	8	10	8.77	
Negative	8	16	15	13.16	
Resection margins					
Positive	10	20	34	29.82	0.39
Negative	25	50	47	41.23	
Not mentioned	15	30	33	28.95	
Immunohistochemistry					
Yes	21	42	44	38.60	0.68
No	29	58	70	61.40	

females worldwide. Majority of females were multipara (95.6%). Simple cholecystectomy was most frequent operation performed while biopsy was performed in those having suspicion of malignancy preoperative. Histological diagnosis of malignancy was followed by staging investigations, discussion in MDT meeting and then treatment as per stage. Number of cases increased with advancing years which may be due to more surgeries being performed at our center. Histopathological analysis was performed in all specimens regardless of diagnosis as per guidelines [21].

Most common tumor found was adenocarcinoma (90.24%) followed by adenosquamous carcinoma. Zhou et al. quoted that 93.1% patients in their series had adenocarcinoma [22]. Most of tumors in our series were well differentiated and fundus was most common site, the results are in concordance with study conducted by Cui et al. [23]. Majority of the patients had either stage II or stage III disease. Surprisingly, most of the patients (36.6%) refused second stage surgery while radical cholecystectomy was most common definitive surgical procedure performed in 17 (10.37%) patients. Other surgeries performed included pancreaticoduodenectomy in six, extended cholecystectomy in three and palliation in 42 patients. Simple cholecystectomy proved adequate in 31 patients. IHC was performed in 62 (37.8%) patients to reach at diagnosis. Liver was the most common organ infiltrated by tumor. Lymph node analysis revealed that majority had either none sent or inadequate number which is also in concordance with international data [24]. Resection margins were found negative in majority (37.8%), however, no comment was found in case of 48 (29.3%) patients.

Our results are consistent with international figures quotes worldwide [25–27]. A study conducted by Zhou et al. [22] showed a frequency of 2.06% while another study by He et al. [12] revealed higher age but similar findings as for as stage and treatment strategies are concerned. Haq et al. [28] conducted a study at Fauji Foundation hospital, Rawalpindi, Pakistan and showed frequency of 0.68%. A review performed by Piccolo et al. [24] showed that frequency of IGBC varied from 0.25–3%. They also revealed that in most studies proper number of lymph nodes were either not resected or not sent which is case with our study as well. A meta-analysis involving 986 articles by Choi et al. [8] found that most important clinical dilemma with IGBC is decision of second stage surgery both at clinician as well as patient end. Same dilemma is visible in our series where majority of patients refused definitive surgery in spite of thorough counseling. Most of cancer patients had acute cholecystitis which is consistent with results quoted by You et al. [13]. Most of female cancer patients in our cohort were multipara as also reported by Chan et al. [29].

Incidental gallbladder cancer represent an important area of research as early diagnosis will considerably affect morbidity as well as mortality. Alterations in oncogenes, tumor suppressor genes, microsatellite instability and

methylation of gene promoter areas act in synergy with recurrent or chronic mucosal inflammation to induce cancer although exact cause is not known [30]. Gallstones especially chronic one pose most significant risk although other suspected culprits [31] are advance age, female sex, positive family history, cholelithiasis, obesity (BMI > 30), parasitic infestations, chronic bacterial cholangitis especially by *Salmonella* and *Helicobacter* [32], porcelain gallbladder, large polyps >10 mm, heavy metals exposure and abnormal pancreaticobiliary duct junction [33]. Clinical features are ominous but those harboring clue include persistent right upper quadrant pain, jaundice, nausea and weight loss [8]. Biochemical investigations are nonspecific. Ultrasound features that may give rise to suspicion include wall thickness >3 mm and enhanced vascularity. Currently EUS along with fine needle aspiration cytology (FNAC) has become modality of choice to distinguish benign from malignant lesion and stage disease [34]. Computed tomography diagnostic features of GBC are heterogeneously enhanced wall area, irregular distorted gallbladder filled with mass and it determines accurately possibility of surgical resection (93% for T stage). Multiplanar and 3D volume rendered CT is current addition to diagnostic battery [35]. All-in-one MRI protocol (MRCP, magnetic resonance angiography) quite accurately detects bile duct or vascular invasion, with sensitivity and specificity approaching 100%. Diffusion-weighted imaging (DWI) is revolutionizing the use of MR [36]. PET/CT may have a promising role in the diagnosis of unsuspected metastases thus changing staging and treatment early in the disease course [37]. Although no current tumor marker is available but most promising is CA-242 which may be regarded as marker of early infiltration [38]. Histopathology is current gold standard for diagnosis and provides framework for future management options [21]. Staging is the most significant factor determining treatment and prognosis in short as well as long-term [39]. A minimum of three regional lymph nodes are required for accurate “N” staging while adequate clearance requires at least six as per SEER guidelines [3].

Surgery is the only cure available at present and options include simple cholecystectomy (stage 1/Tis, T1a), extended cholecystectomy (stage 1/T1b), radical cholecystectomy (stage II/T2), major hepatic/ bile duct resection or pancreaticoduodenectomy (stage III/T3) and palliation (surgical/nonsurgical) for stage IV disease [27, 40]. Regional lymphadenectomy is a must but currently neglected part of oncological clearance [41]. Factors that may point towards sinister diagnosis during surgery include thick wall, stiff uneven pale surface, miliary nodules, enlarged regional lymph nodes, plastered atrophied gallbladder, intraluminal nodules/mass or local gallbladder wall thickening and necrotic tissue/blood clot found in gallbladder lumen [42]. There is still no effective adjuvant or neoadjuvant chemo radiotherapy for GBC although combination

chemotherapies and targeted molecular therapies are rapidly emerging [43, 44].

The results of this study should be interpreted with care as it was single center study. Although small number of patients limited the accuracy of the study but low incidence of gallbladder cancer makes it difficult to acquire larger cohorts. Moreover, there was no data reported regarding results of definitive surgery and patient survival thus missing extremely important aspect. Larger multicenter studies are required to further extend the results of our work. Various aspects of IGBC like risk factors, tumor markers and survival rates need to be studied further. The results of current study will help us to identify at risk patients and formulate guidelines for appropriate surgical intervention in conjunction with oncologist/gastroenterologist feedback [45].

CONCLUSION

The clinical and radiologic diagnosis of gallbladder cancer at early stage is challenging despite recent advances in technology. A detailed clinical history, high index of suspicion, good ultrasonologist and competent histopathologist is the linchpin for early diagnosis. The surgical strategy and prognosis differ strikingly according to T-stage and RO resection is still the only chance of cure. Interdisciplinary collaboration among surgeon, ultrasonologist, oncologist, endoscopy expert and histopathologist is hallmark of improved vigilance and better long term outcome. Prognosis is very ominous due to high recurrence, morbidity and mortality.

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Author Contributions

Muhammad Tanveer Sajid – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Syed Mukarram Hussain – Substantial contributions to conception and design, Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

Shoab Nayyar Hashmi – Substantial contributions to conception and design, Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

Qurat ul Ain Mustafa – Acquisition of data, Analysis and interpretation of data, Drafting the article, Final approval of the version to be published

Neelofar Shaheen – Acquisition of data, Revising it

critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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