

“PREDICTORS OF INCIDENTAL GALL BLADDER CANCER IN CASES OPERATED FOR BENIGN GALL BLADDER DISEASE.”

General Surgery

Dr. Nabu Kumar Senior Resident, General Surgery, MGMMCH Jamshedpur.

Dr. Sanjay Singh* Senior Resident, General Surgery, SNMMCH, Dhanbad. *Corresponding Author

Dr. Zenith Harsh Kerketta Assistant Professor, General Surgery, RIMS, Ranchi.

ABSTRACT

Aims and Objective: “Study the predictors of incidental gall bladder cancer in cases operated for benign gall bladder disease – A Single Center Study” **Background:** Previous reports shows that Incidental gall bladder cancer occurs in approximately less than 2% of patients undergoing routine cholecystectomy. Gallbladder cancer, though generally considered rare, is the most common malignancy of the biliary tract, accounting for 80%–95% of biliary tract cancers. An early diagnosis is essential as this malignancy progresses silently with a late diagnosis, often proving fatal. Incidental gallbladder cancer (iGBC) is defined as gallbladder malignancy identified on postoperative histopathologic examination with no pre- or intraoperative findings suspicious of malignancy. **Methods:** A prospective study was done in RIMS, Ranchi, Department of General Surgery in patients who presented with history of jaundice, biliary colic, fever, obesity, cholangitis, cholecystitis(both calculus and acalculus), cholelithiasis, gall bladder polyp, primary sclerosing cholangitis, mucocele of gall bladder, Empyema of GB, Emphysematous cholecystitis, cholesterosis, cholecystoenteric fistula, Gall stone ileus, Anamolous junction of pancreaticobiliary duct taking into consideration the chief complains, clinical features, lab reports, X-ray findings, intra-operative findings and biopsy report. The patients confirmed by biopsy report to have a gall bladder cancer would be included in the study and predictors in these population would be kept under this study. **Result:** In this study the incidence of incidental gall bladder cancer was 2.9% of 205 patients who presented with benign disease of the GB and underwent surgical intervention. The mean age was 46.67 years (minimum age was 34 years and maximum age was 60 years) and 83.33% of incidental GB cancer cases were female. Among the incidental Ca GB patients, one patients had laparoscopic cholecystectomy. Rest 5 cases underwent open cholecystectomy (2 extended cholecystectomy included). **Conclusion:** The rate of incidental Ca GB in this study is 2.9%. These predictors might help in early diagnosis and treatment as most of the patients who were diagnosed with iGBC presented very late and half of the patients had metastasis at the time of presentation.

KEYWORDS

Incidental Gall Bladder Cancer, Gall Bladder Cancer, Cholecystectomy, Extended Cholecystectomy, Chronic Cholecystitis

INTRODUCTION

Gallbladder cancer, though generally considered rare, is the most common malignancy of the biliary tract, accounting for 80%–95% of biliary tract cancers¹. An early diagnosis is essential as this malignancy progresses silently with a late diagnosis, often proving fatal. Its carcinogenesis follows a progression through a metaplasia–dysplasia–carcinoma sequence¹. Incidental gall bladder cancer (iGBC) is defined as gall bladder malignancy identified on postoperative histologic examination with no pre- or intraoperative findings suspicious of malignancy².

This comprehensive study focuses on and explores the risks, management, and outcomes for primary gallbladder carcinoma. Epidemiological studies have identified striking geographic and ethnic disparities – inordinately high occurrence in American Indians, elevated in Southeast Asia, yet quite low elsewhere in the Americas and the world³. Age, female sex, congenital biliary tract anomalies, and a genetic predisposition represent important risk factors that are immutable. Environmental triggers play a critical role in eliciting cancer developing in the gallbladder, best exemplified by cholelithiasis and chronic inflammation from biliary tract and parasitic infections. The organisms that have been most commonly implicated are *Salmonella* (eg, *S. typhi* and *S. paratyphi*) and *Helicobacter* (eg, *H. bilis*) spp^{4,5}. The porcelain gallbladder is frequently (average 25%, range 12%–61%) associated with gallbladder cancer, in most of the cases^{6,7}. Further, gallbladder cancer rates correlate well with the prevalence of gallstone disease⁸. Previous reports show that incidental gall bladder cancer (iGBC) occurs in less than 2% of patients after routine cholecystectomy⁹. Occasionally, Gallbladder (Gb) malignancy is found on pathological reports after routine cholecystectomy. Recent studies have reported an increase in incidental Gb cancer (iGBC), with approximately 50%–58% of all new GBC cases^{10,11} being now discovered incidentally. Currently, a laparoscopic cholecystectomy (LC) is standard procedure for the treatment of benign Gb diseases. In the US, more than a million LC are performed each year¹². For that reason, iGBC discovered during or following LC has been increasing in the last decade. Some authors have reported an incidence of iGBC after LC of approximately 0.2%–2.1%^{13,14}.

In general, it is difficult to diagnose GBC in most routine

cholecystectomies performed for a preoperative diagnosis of benign GB diseases. There have been few reports on the predictive factors of iGBC. Those articles identified old age, female gender, Asian or African American heritage, elevated serum ALP and acute cholecystitis with jaundice as potential risk factors for iGBC¹⁵⁻¹⁷.

When iGBC is detected after cholecystectomy, additional procedures such as liver resection, lymph node dissection, and/or bile duct resection (BDR) may be performed depending on pathologic and imaging findings. Glenn and Hays¹⁸ first introduced 'radical cholecystectomy' (Glenn operation), a radical resection technique with regional lymphadenectomy. Pack et al.¹⁹ and Fahim et al.²⁰ have also reported combined hepatectomy and portal lymph node dissection in pT1b or more advanced GBC.

In general, it is difficult to anticipate GB malignancy in most routine cholecystectomies for preoperative diagnosis of benign GB diseases. Additionally, surgeons often encounter the concerns of tumor spread in perioperative GB perforation and of reoperation extent. To date, there have been few reports on the predictive factors of iGBC¹⁵.

Despite advancements in various diagnostic procedures, preoperative diagnosis of GB carcinoma is an exception rather than the rule, occurring in fewer than 20.0% of patients²¹.

Advanced stage of the disease because of delayed diagnosis leads to its poor prognosis except when diagnosed at early stages incidentally during routine cholecystectomies. Thus some of the surgeons recommend surgery even for the patient with asymptomatic gall bladder stones because of its likelihood to harbour occult malignancy²².

Univariate analysis revealed that older age (≥ 65 years), higher serum level of CA 19-9 (≥ 50 U/mL), acute cholecystitis, and GB empyema on preoperative diagnosis were adverse clinical factors of recurrence and survival. Also, in perioperative GB perforation subset, early recurrence was significantly greater and their 6-month, 1-year, and 3-year DFS rates compared with nonperforation group were 58% vs. 79%; 44% vs. 65%; and 36% vs. 59%, respectively ($P = 0.04$). However, OS was not significantly different between perforation and

nonperforation subgroups¹⁷.

Many authors reported that perforated GB during surgery is a prognostic factor for recurrence or survival²³⁻²⁷. iGBC should be preoperatively suspected, especially in old-aged patients. An age older than 65 years, lymph node metastasis, and lymphovascular invasion are important prognostic factors in iGBC patients who received subsequent EC with BDR¹⁷.

Incidental gall bladder adenocarcinoma is a rare event, and there is no definitely identifiable symptom and sign for prediction of this disease in the cases operated on with the impression of benign gall bladder diseases especially cholelithiasis and cholecystitis. Radiological findings including ultrasonography and CT would not add much information before surgery, in early stages of gall bladder cancer. The most important predictor of prognosis in incidental gall bladder cancer is the stage of the tumor. T1 cases have better prognosis even with simple or laparoscopic cholecystectomy²⁸.

However, in cases of iGBC the rate of bile spillage is very high (44%)²⁹ and although robust data are lacking, small studies and registry data show significantly worse survival in iGBC patients when bile spillage occurs^{25,30-31}. This corroborates the common-sense notion that spillage may convert curable iGBC into an incurable case of peritoneal carcinomatosis, which can lead to premature death, even in cases of the very earliest stage of iGBC (pT1a)²⁵. It was thus hypothesized that there may exist preoperative factors that are able to predict cases at high-risk of iGBC. These factors help general surgeons to avoid cases of unsuspected iGBC, and also to avoid spillage of cancer-cell-laden bile during cholecystectomy that would be associated with worse outcome, due to carcinomatosis.

Mortality rates closely follow incidence; those countries with the highest prevalence of gallstones experience the greatest mortality from gallbladder cancer. Vague symptoms often delay the diagnosis of gallbladder cancer, contributing to its overall progression and poor outcome. Surgery represents the only potential for cure. Some individuals are fortunate to be incidentally found to have gallbladder cancer at the time of cholecystectomy being performed for cholelithiasis.

Such an early diagnosis is imperative as a late presentation connotes advanced staging, nodal involvement, and possible recurrence following attempted resection. Malignant transformation is further implicated via chronic inflammation itself, and/or alterations of tumor suppressor genes (such as *tumor protein 53 [p53]*) or proto-oncogenes (such as mutations of *Kirsten ras oncogene homolog [K-ras]*)^{32,33}.

Overall mean survival is a mere 6 months, while 5-year survival rate is only 5%³⁴. The dismal prognosis, in part, relates to the gallbladder lacking a serosal layer adjacent to the liver, enabling hepatic invasion and metastatic progression. Improved imaging modalities are helping to diagnose patients at an earlier stage.

The last decade has witnessed improved outcomes as aggressive surgical management and preoperative adjuvant therapy has helped prolong survival in patients with gallbladder cancer. In the future, the development of potential diagnostic markers for disease will yield screening opportunities for those at risk either with ethnic susceptibility or known anatomic anomalies of the biliary tract. The anomaly is rare in western countries but more apparent in Asians, particularly those of Japanese origin³⁵.

Meanwhile, clarification of the value of prophylactic cholecystectomy should provide an opportunity for secondary prevention. Primary prevention will arrive once the predictive biomarkers and environmental risk factors are more clearly identified.

MATERIALS AND METHODS

Study area: Department of General Surgery, Rajendra Institute of Medical Sciences, Ranchi.

Study population: Benign gall bladder disease patients undergoing cholecystectomy at Rajendra Institute of Medical Sciences, Ranchi.

Study period: January 2018 to December 2019.

Sample size: 205 patients of benign gall bladder disease.

Inclusion criteria:

1. Age: Any age.

2. Sex: Both males and females to be selected for the study.

3. History: Patients admitted with history of jaundice, biliary colic, fever, obesity, cholangitis, cholecystitis (both calculus and acalculus), cholelithiasis, gall bladder polyp, primary sclerosing cholangitis, mucocele of gall bladder, Empyema of GB, Emphysematous cholecystitis, cholesterosis, cholecystoenteric fistula, Gall stone ileus, Anomalous junction of pancreaticobiliary duct.

Patients with 2 or more than two clinical symptoms would be incorporated in the study design.

4. Suspicion: Preoperative suspicion of Gall Bladder Cancer.

5. Consent: Family member must give informed consent.

6. Patient who give consent to undergo this study.

Exclusion criteria:

(a) Diagnosed case of carcinoma gall bladder by USG or CECT.

(b) Patient with a single clinical symptom at the time of presentation would be excluded.

(c) Critically ill patients.

Sample design: 205 patients of benign gall bladder disease, admitted through OPD or Indoor admissions between January 2018 to December 2019.

Study design: Prospective observational study.

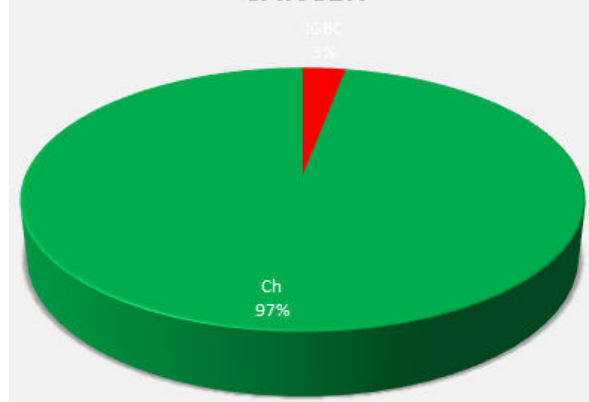
Study techniques: Prospective observational study recording data from 205 patients of benign gall bladder disease between January 2018 to December 2019.

CASES OF INCIDENTAL GALL BLADDER CANCER:

Chronic Cholecystitis	IGBC	Total
199	6	205

- Out of 205 cases 6 cases were found to have incidental gall bladder cancer.
- 2.92 % of cases were found to have incidental gall bladder cancer in the population which were operated for benign gall bladder diseases.

CASES OF INCIDENTAL GALL BLADDER CANCER



IGBC : Incidental Gall Bladder Cancer

Ch:Chronic Cholecystitis

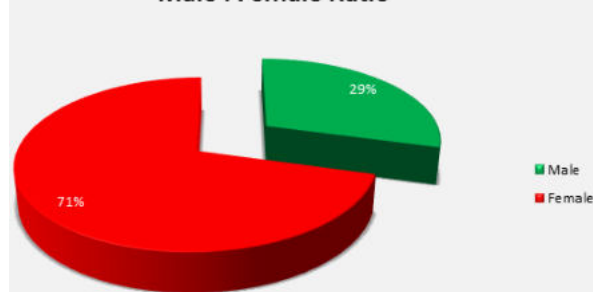
MALE : FEMALE RATIO:

SEX	NUMBER OF CASES	PERCENTAGE
MALE	60	29.2
FEMALE	145	70.8
TOTAL	205	100

- Out of 205 cases taken for study 60 cases were male and 145 cases were female.

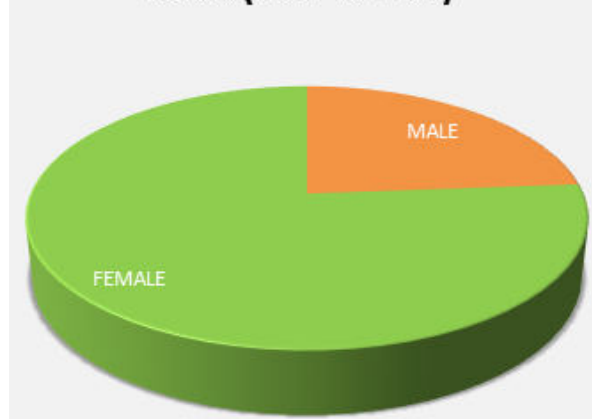
- 29.2% comprised of male population.

- 70.8% comprised of female population.

Male : Female Ratio**INCIDENTAL GALL BLADDER CANCER (MALE : FEMALE RATIO):**

SEX	NUMBER OF CASES	PERCENTAGE
MALE	1	16.7
FEMALE	5	83.3
TOTAL	6	100

- Out of 6 cases that came out to be incidental gall bladder cancer, 1 patient was male and 5 patients were female.
- 16.7% comprised of male patient.
- 83.3% comprised of female patient.

IGBC (M:F RATIO)

- **IGBC : Incidental Gall Bladder Cancer**
- **M : Male**
- **F : Female**

AGE DISTRIBUTION OF THE CASES:

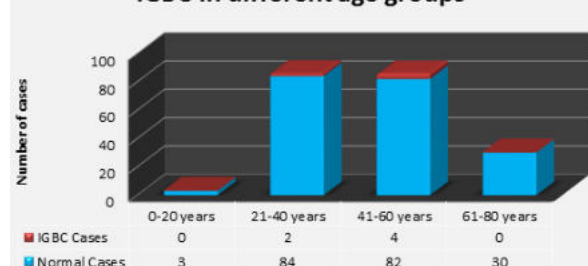
AGE GROUP	NUMBER OF CASES	%
0-20 years	3	1.4
21-40 years	86	41.9
41-60 years	86	41.9
61-80 years	30	14.8
TOTAL	205	100

- 3 cases came under the age group of 0-20 yrs.
- 86 cases belong to the age group of 21-40 yrs.
- 86 cases were in the 41-60 yrs age group.
- 30 cases came under the age group of 61-80 yrs.
- Maximum number of cases were between the age group of 21-60 yrs - 172 cases (83.9%)

Number of cases**INCIDENTAL GALL BLADDER CANCER : AGE DISTRIBUTION**

AGE GROUP	NORMAL CASES	IGBC CASES
0-20 years	3	0
21-40 years	84	2
41-60 years	82	4
61-80 years	30	0

- Out of 6 cases that came out to be IGBC cases out of 205 study population, 2 cases fall under the age group of 21-40 years and rest 4 came under 41-60 yrs of age.
- The cases that fell under the age group of 21-40 years were above 30 years of age.
- It can be concluded that 30-60 yrs of age group had maximum IGBC cases preponderance.

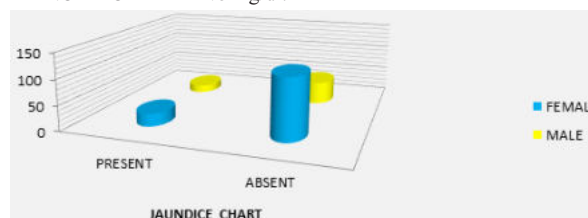
IGBC in different age groups**IGBC : Incidental Gall Bladder Cancer**

Normal Cases : Cases whose biopsy report came out to be chronic cholecystitis

PRESENCE OR ABSENCE OF JAUNDICE:

JAUNDICE	PRESENT	ABSENT	PERCENTAGE
MALE	15 (1)*	45	25 % of male population
FEMALE	25	120	17.2% of female population
TOTAL	40 jaundice cases	165	19.51% of total population

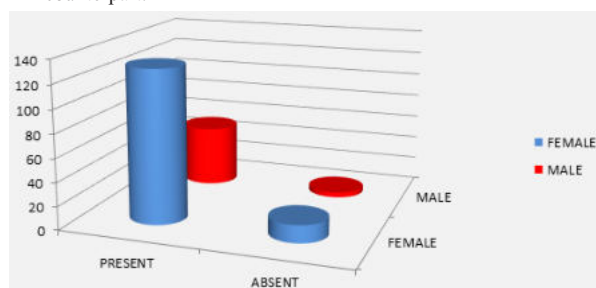
- 19.51 % of total study population presented with jaundice(40 out of 205 cases).
- 25 % of male population and 17.2% of female population had jaundice.
- Jaundice was more prevalent in the female population.
- (1)* Only 1 case of IGBC presented with jaundice out of 6 IGBC cases. In this case the subject was a male patient who presented with jaundice.
- All the cases that presented with jaundice had bilirubin level of NOT MORE THAN 5 mg/dl.

**PRESENCE OR ABSENCE OF PAIN:**

PAIN	PRESENT	ABSENT	PERCENTAGE
MALE	52 (0)*	8	86.67 % of male population
FEMALE	130 (5)*	15	89.65 % of female population
TOTAL	182	23	88.78 % of total population

- 88.78 % of total population presented with pain (182 out of 205 cases).
- Pain was the chief complain of most of the patients mainly involving the right upper quadrant. 86.67 % comprised of the male population while 89.65 % comprised of female population.
- (5)* In IGBC population, 5 female patients presented with pain as the chief complain.
- (0)* In IGBC population, symptom of pain was absent in the male

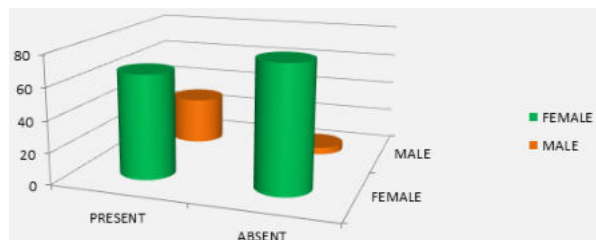
counterpart.



ANOREXIA CHART:

ANOREXIA	PRESENT	ABSENT	PERCENTAGE
MALE	30	30	50% of male population
FEMALE	66 (1)*	79	45.52% of female population
TOTAL	96	109	46.83% of total population

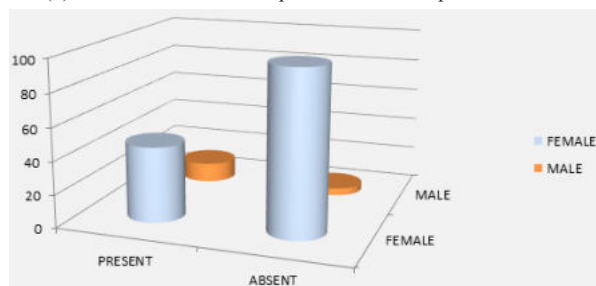
- 46.83 % of total study population presented with anorexia (96 cases out of 205).
- 50 % of male population and 45.52 % of female population presented with anorexia.
- Anorexia was more common in the female population (66 out of 96 cases).
- (1)* 1 female patient that came out to be IGBC presented with anorexia out of 5 female IGBC cases.



PRESENCE AND ABSENCE OF LUMP:

LUMP	PRESENT	ABSENT	PERCENTAGE
MALE	12 (1)*	48	20.0% of the male population
FEMALE	46 (4)*	99	31.72% of female population
TOTAL	58	147	28.29% of total population

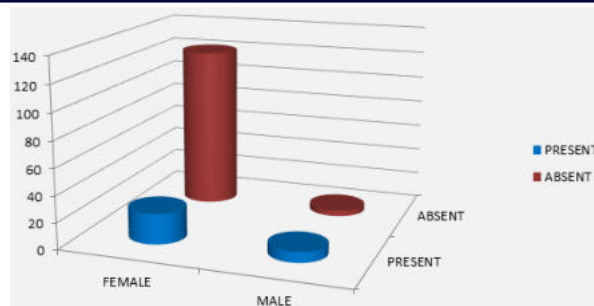
- 28.29 % of the total population presented with lump (58 out of 205 cases).
- 20.0% of male population and 31.72 % of female population had a palpable lump at the time of presentation. Lump was more prevalent in the female population (46 out of 58 cases).
- (1)* 1 male case of IGBC presented with lump.
- (4)* 4 female case of IGBC presented with lump.



PRESENCE AND ABSENCE OF VOMITING:

VOMITING	PRESENT	ABSENT	PERCENTAGE
MALE	8	52	13.33 % of male population
FEMALE	23	122	15.86 % of female population
TOTAL	31	174	15.12 % of total population

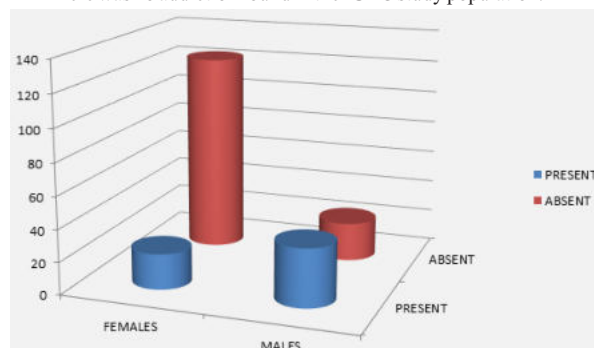
- 15.12 % of the total population presented with vomiting (31 out of 205 study population).
- 13.33 % of male study population and 15.86 % of female study population presented with vomiting.
- Vomiting was prevalent among the female study population.
- None of the IGBC cases presented with vomiting.



ADDICTION CHART:

ADDICTION	PRESENT	ABSENT
MALES	36	24
FEMALES	22	123

- 36 males were addicted to alcohol and smoking. 60% of the male population were found to be addicted.
- 22 females were addicted to tobacco chewing comprising of about 15.17% of the female study population.
- There was no addiction found in the IGBC study population.

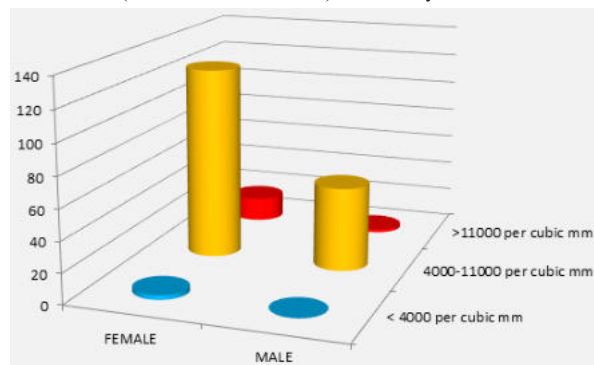


ADDICTION CHART

LAB STATISTICS :

TOTAL LEUCOCYTE COUNT (per cubic millimeter)	< 4000	4000-11000	>11000
MALE	0	55	5
FEMALE	3	126	16

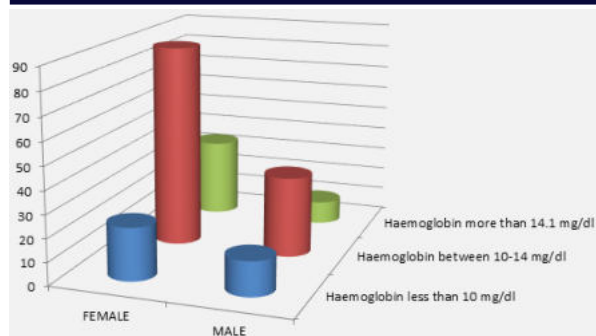
- 181 cases (55 males and 126 females) had total leucocyte count in the normal range of 4000-11000 per cubic millimeter of blood comprising about 88.29% of the total population.
- 3 female patients suffered from leucopenia.
- 21 cases (5 males and 16 females) had leucocytosis.



HAEMOGLOBIN CHART:

HAEMOGLOBIN	< 10 mg/dl	10-14 mg/dl	>14.1 mg/dl
FEMALE	23	88	34
MALE	15	35	10

- 23 female cases and 15 male cases had haemoglobin less than 10 mg/dl.
- 88 female cases and 35 male cases had haemoglobin in the range of 10-14 mg/dl.
- 34 female cases and 10 male cases had haemoglobin more than 14.1 mg/dl.

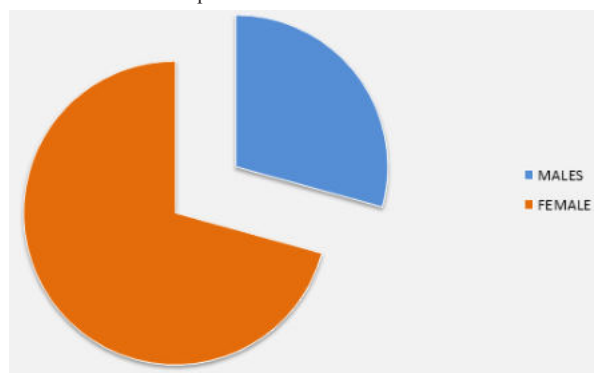


HAEMOGLOBIN CHART

RENAL FUNCTION CHART:

RENAL FUNCTION TEST	NORMAL	ABNORMAL
MALE	60	0
FEMALE	145	0

- All study population had normal renal function test parameters.
- Out of 205 study population, 60 males and 145 females had normal renal function test parameters.



RENAL FUNCTION CHART

LIVER FUNCTION STUDY:

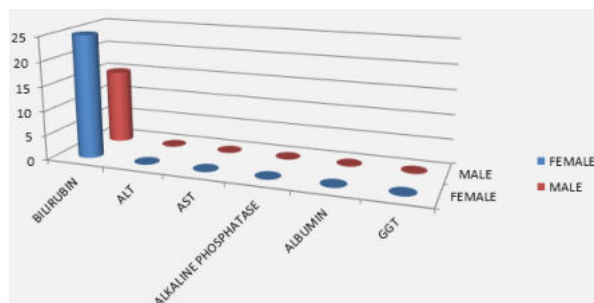
LIVER FUNCTION TEST	MALE	FEMALE
BILIRUBIN (TOTAL)	Raised in 15 cases	Raised in 25 cases
ALT	Normal in all	Normal in all
AST	Normal in all	Normal in all
ALKALINE PHOSPHATASE	Normal in all	Normal in all
ALBUMIN	Normal in all	Normal in all
PROTHROMBIN TIME	Normal in all	Normal in all
GGT	Normal in all	Normal in all

ALT → Alanine Transaminase

AST → Aspartate Aminotransferase

GGT → Gamma Glutamyl Transferase

- In the liver function tests, 15 male cases and 25 female cases were found to have elevated bilirubin levels, but bilirubin level did not exceed 5 mg/dl in any of the jaundiced subjects.
- Rest all other liver function test parameters were within the normal limits.



LIVER FUNCTION CHART

ALT : Alanine Transaminase

AST : Aspartate Aminotransferase

GGT : Gamma Glutamyl Transferase

INTRAOPERATIVE STATISTICS:

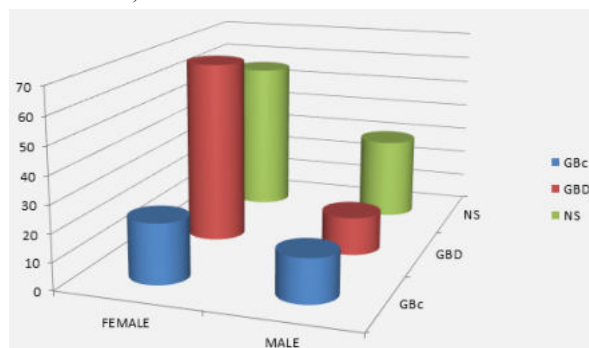
INTRA-OP FINDINGS	GBc	GBD	NS
MALE	16	14	30
FEMALE	22	67	56
TOTAL	38	81	86

Gbc → Gall Bladder Contracted

GBD → Gall Bladder Distended

NS → Normal Study (Gall Bladder neither distended nor contracted)

- 26.6% of male population and 15.17% of female population have contracted gall bladder.
- 23.33% of male population and 46.21% of female population have distended gall bladder.
- 50% of male population and 38.62% of female population had a normal gall bladder (gall bladder was neither distended nor contracted).



INTRA-OPERATIVE FINDINGS

Gbc : Gall Bladder Contracted

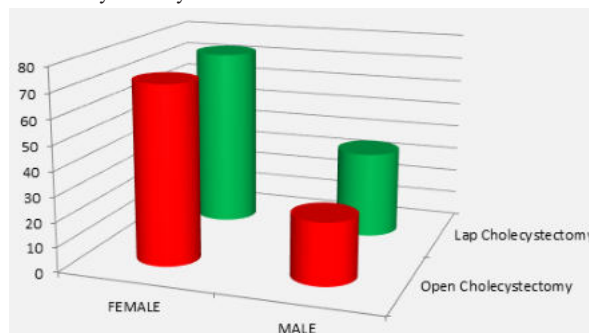
GBD : Gall Bladder Distended

NS : Normal Study (Gall Bladder neither distended nor contracted)

MANAGEMENT STATISTICS:

Management	Open Cholecystectomy	Lap Cholecystectomy
MALE	25	35
FEMALE	72	73

- 41.67% of male population and 49.66% of female population underwent open cholecystectomy (of which 1 male case and 1 female case had to undergo **Extended Cholecystectomy**).
- 58.33% of male study population and 50.34% of female study population underwent laparoscopic cholecystectomy.
- In the study population none of the patient had to undergo conversion of laparoscopic cholecystectomy to open cholecystectomy.



MANAGEMENT STATISTICS

BIOPSY REPORT STATISTICS:

BIOPSY REPORT	CHRONIC CHOLECYSTITIS	GBC
MALE	59	1
FEMALE	140	5

- 98.33% of male study population and 96.55% of female study population biopsy report suggested features of chronic cholecystitis.
- 1.67% of male study population and 3.45% of female study population biopsy report came out to be gall bladder cancer. This

- population constituted the incidental gall bladder cancer group. (6 cases out of 205 population under study).
- Incidence of incidental gall bladder cancer came out to be 2.93%

INCIDENTAL GALL BLADDER CANCER :

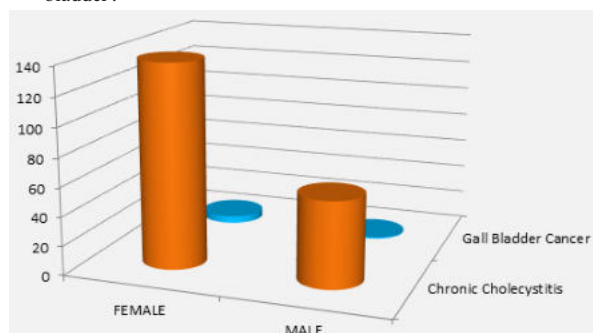
S.No	Name	Age	Sex	Chief Complaint	CECT	Intra-Op	Management	Biopsy
1.	DK	38	F	P,L	Cholelithiasis	Ascites + Omental seedings + multiple gall stones	OC	Mucinous Adenocarcinoma of gall bladder
2.	BP	45	F	P,L	Thickened GB Wall + Loss of fat planes + multiple periportal lymphadenopathy	GB Distended + Adhesions present + multiple gall stones	EC	Well Differentiated Adenocarcinoma of GB
3.	MK	48	F	P,L	Thickened GB Wall + Gall Bladder Polyp	GB Distended + Adhesions present + Gall Bladder Polyp	OC	Well Differentiated Adenocarcinoma of GB
4.	BK	55	M	J,L	Thickened GB Wall + GB Distended + Multiple Gall Stones	GB Distended + Adhesions present + Multiple Gall Stones + GB Wall Thickened	EC	Well Differentiated Adenocarcinoma of GB
5.	SD	34	F	P,An	Thickened GB Wall + Multiple Gall Stones	Gall Bladder Contracted + Multiple Gall Stones	OC	Well Differentiated Adenocarcinoma of GB
6.	BD	60	F	P,L	Thickened GB Wall + Cholelithiasis	Gall Bladder Contracted + GB Wall Thickened + Cholesterosis	LC	Well Differentiated Adenocarcinoma of GB

OC : Open Cholecystectomy

EC : Extended Cholecystectomy

LC : Laparoscopic Cholecystectomy

- Among the IGBC study population, 5 cases were female while 1 case was male. Thus 16.67% of IGBC population was male and 83.33% of IGBC population was female.
- All of the IGBC population were above 30 years of age.
- The chief complaints comprised of pain and lump constituting 66.67 % of IGBC population. Only 1 case presented with jaundice.
- Thickened GB wall in the fundal region was a consistent feature in CECT in most of the IGBC cases.
- Open cholecystectomy were performed in 5 cases(in which 2 cases had to undergo extended cholecystectomy) and 1 case was operated via the laparoscopic technique.
- Intra- operatively multiple gall stones were found in 4 cases , 1 case had GB polyp and 1 cases had features of cholesterosis.
- Biopsy report suggested well differentiated adenocarcinoma of the gall bladder in 5 cases and mucinous adenocarcinoma of the gall bladder in 1 case. Thus well differentiated adenocarcinoma constituted 83.33 % of the IGBC study population and 16.67% of the case comprised of mucinous adenocarcinoma of the gall bladder.

**BIOPSY REPORT CHART****DISCUSSION**

This was a prospective observational study. It was done to know the predictors of incidental gall bladder carcinoma amongst the patients who presented with benign gall bladder disease. We have analysed data from Jan 2018 to September 2019. Incidental Gall Bladder Carcinoma was analysed and studied to determine any specific epidemiological,

clinical, biochemical parameter that might prove predictors of gall bladder cancer in general population from chronic cholecystitis.

The cases were subjected to a structured interview in indoor & out-patient department of surgery. The analysis was then performed under the direct supervision of the General Surgeon and Pathologist. Subsequently all information recorded in the proforma were verified. The results were compared with data obtained from different geographical region. A total of 205 patients who satisfied the inclusion criteria were incorporated in the study group.

Inapparent (also called occult or incidental) GBC is defined as GBC unrecognized before or at operation and detected for the first time on histopathological examination of the gallbladder which has been removed for presumed gallstone disease.¹⁵⁶

DEMOGRAPHIC PROFILE:

205 patients were included in study population.

The minimum age was 6 years maximum age was 78 years with the mean age of 42 years. The mean age of study population was 44.46 years. This finding is going parallel with previous studies. Shukla et al (1985)³⁶ reported mean age of the CAGB patients to be 50 years (Range 40-60 years.), the mean age of 1,728 patients from 29 series, reported upon since 1960 was 65.2 years with incidence of carcinoma of the gallbladder of 0.1; 1.5; 8.9; 19.6; 37.0 and 32.0 % in third, fourth fifth, sixth, seventh and eighth decades respectively.⁴²

Among 199 chronic cholecystitis patients 29.64 % are males and 70.35 % are females. The seemingly greater number of female could be explained by the fact that cholecystitis is most common in female. Thus in a hospital-based study, women patients form a majority of the study population.

Piehlher JM and Crichlow RW showed that "Carcinoma of the gallbladder is predominantly a disease of elderly females of 2,998 patients from 51 series reported over last 20 years, there were 2,292 females (75%) and 706 males (25%), a female to male ratio of 3.2:1⁴². In the study by IARC under SEARCH program gallbladder cancer was found to be commonest among women (56%) with cancer of the ampulla of the Vater coming second with 30 percent".

According to our study GBC is common in female population because of chronic cholecystitis being more prevalent in the female population. Also in our study the female to male ratio came out to be 2.4:1 (145 females and 60 males).

Among 205 patients 68.5% are from rural area & 31.5% are from urban area. This only indicates Geographical distribution of population.

Shukla et al (1985)³⁶ reported an incidence of 4.4% of all malignancies and 0.03 % of total hospital admissions from Varanasi, India. Chao and Greager (1991)¹⁰ reported an incidence of 2.5/100,000 population and found carcinoma of the gallbladder in 1-3 percent of cholecystectomy specimens. In our study the incidence of incidental CaGB is 2.9%.

STUDIES	No of IGBC	Total Cholecystectomy	Incidence Rate%
Daphna ¹⁸¹ et al	6	1697	0.3
Tantia ¹⁸² et al	19	3205	0.6
Mittal ¹⁸³ et al	13	1305	0.9
Morera ¹⁸⁴ et al	4	372	1.1
Amanullah ¹⁸⁵ et al	8	428	1.9
Shigeki ¹⁸⁶ et al	4	84	4.7
Current Study	6	205	2.9

Clinical features of patients in this study were as follows:

Among 205 patients 88.78% of the total study population had upper abdominal pain. 86.67 % of male population and 89.65% of female population had pain at the time of presentation. In this population 19.51% had jaundice, 15.12% patient had vomiting, Fever was not present in any of patients, 28.29% patient c/o palpable lump, 43.83% had anorexia, 0% patients had hepatomegaly.

In comparison, data regarding presentation of Ca Gall bladder is presented in table below.

Clinical symptoms of gallbladder cancer

Series	Pain	Anorexia	Jaundice	Weight loss	Nausea / vomiting
Piehlner and Crichtlow ¹¹¹	76%	34%	38%	39%	32%
Shieh et al ¹¹²	60.4%	43.7%	35.4%	33.3%	35.4%
Al-Hadeedi et al ¹¹³	47.3%	39.4%	36.4%	39.4% ^a	10.5%
Shukla et al ¹¹⁴	85%	40%	60.3%	14.9%	24.7%
Klamer and Max ¹¹⁵	70%	-	40%	40%	30%
Silk et al ¹¹⁶	78.5%	35.6%	28.5%	45.7% ^b	35.6%
Perpetuo et al ¹¹⁷	97%	-	44%	77%	64%
Kelly and Chamberlain ¹¹⁸	74%	-	32%	48%	51% ^c
Chao et al ¹¹⁹	81.1% ^d	4.1%	32.4%	1.4%	16.2%
White et al ¹²⁰	83%	-	47%	70%	-
Chao and Greager ¹²¹	54.1%	18.9%	45%	28.4%	18.9%

a – did not differentiate between anorexia and weight loss;

b – reported nausea / vomiting separately;

c – nausea alone;

d – 50% right quadrant and 35% epigastric

Pain was present in 47-97% of patients. This is comparable to the data (88.78%) in our study. Similarly, anorexia, jaundice and vomiting were comparable in this study and jaundice is a feature of advanced Ca GB. This shows that there are no clinical features that would be suggestive of gall bladder cancer in a patient who presents with symptoms of chronic cholecystitis.

However in the IGBC group in our study shows a consistent feature of thickness of the gall bladder wall in the fundal region in CECT that might help in arising a strong suspicion towards the potential of GBC.

No suggestive single clinical parameter of incidental gall bladder cancer could be obtained from this comparison. Other parameters were also compared but no result obtained. Taking into consideration 2 clinical parameters together might help in assessing IGBC. In our IGBC study population pain and lump were promising factors. But based on clinical parameters alone one should never suspect any case to be a malignancy. These clinical parameters along with the imaging modalities might help in raising a strong suspicion towards malignancy.

Only intraoperative findings are suggestive of IGBC in a few cases. These findings include adhesions, thickening, irregularity of gall bladder wall and abnormal mucosa of the gall bladder.

Open cholecystectomy were performed in 5 cases(in which 2 cases

had to undergo extended cholecystectomy) and 1 case was operated via the laparoscopic technique.

The following parameters of incidental gall bladder carcinoma were compared with chronic cholecystitis patients:

Among IGBC patients mean age was 46.67 years. Minimum age was 34 yrs and maximum age was 60 years. Among incidental GB cancer cases (n=6), male patients were 16.67% & female patients were 83.33%. Among incidental GB cancer patients 33.33% were living in urban area 66.67% were living in rural area. Among incidental Ca GB patients 83.33% had pain abdomen and 16.67% had no pain ; 0% patient had vomiting ; 83.33% had lump ; 16.67% had jaundice and anorexia. USG was normal (i.e: only suggestive of chronic cholecystitis) in 100% of incidental Ca GB cases.

No clinical, biochemical or radiological parameters were found as preoperative predictor of Ca GB in patients who underwent cholecystectomy for chronic cholecystitis.

There are no characteristic clinical features of EGBC (Early Gall Bladder Carcinoma). Unfortunately it becomes clinically apparent only when it is locally advanced, the symptoms being due to invasion of neighboring organs. In two series, both from areas with a high incidence of GBC, where the index of suspicion was high, none of the EGBC was diagnosed clinically and almost half of these were first diagnosed on histopathological examination of resected specimen, thereby highlighting the elusive nature of EGBC.

All patients diagnosed with IGBC were subsequently undergone staging work up with CECT abdomen, tumour markers like Ca 19-9 and CEA. They were managed by second operation like Completion Cholecystectomy, or Chemotherapy, Chemo-radiotherapy, palliative biliary drainage by ERCP, or best supportive care at home.

SUMMARY

- 1) In this study the incidence of incidental gall bladder cancer was 2.9% of 205 patients who presented with benign disease of the GB and underwent surgical intervention at Rajendra Institute of Medical Sciences, Ranchi.
- 2) Incidental gall bladder cancer was predominantly a disease of elderly female patients. The mean age was 46.67 years (minimum age was 34 years and maximum age was 60 years) and 83.33% of incidental GB cancer cases were female.
- 3) No clinical, biochemical or radiological parameters was suggestive or predictive of incidental Ca GB. It was detected for the first time on post cholecystectomy settings on histological examination of gall bladder, termed as Incidental Carcinoma, or inapparent carcinoma, or occult carcinoma Gall Bladder. However the IGBC group shows a consistent feature of thickness of the gall bladder wall in the fundal region in CECT that might help in arising a strong suspicion towards the potential of GBC.
- 4) Among the incidental Ca GB patients, one patients had laparoscopic cholecystectomy. Rest 5 cases underwent open cholecystectomy (2 extended cholecystectomy included).
- 5) If benign disease of GB is occurring in 3rd to 5th decade of life with thickened GB wall in CECT abdomen has high incidence oo incidental gall bladder carcinoma. In our study it was 83.33%.

CONCLUSION

In this study 205 patients of benign gall bladder disease were analyzed. In the process 6 patients were diagnosed with incidental GB cancer after cholecystectomy for chronic cholecystitis. In our study the incidence of incidental Ca GB was 2.9%.

Unfortunately no clinical, biochemical or radiological parameter was suggestive or predictive of GB cancer in patients who underwent cholecystectomy for benign disease.

In view of the findings from this study it may be concluded that chronic cholecystitis remains a significant surgical entity in our population. However the suspicion of incidental GB cancer should be borne in mind. This is important as laparoscopic cholecystectomy is being increasingly used as a treatment modality for benign diseases such as gall stones. Also if there is preoperative spillage of biliary contents there are possibilities for the very early disease becoming a disseminated disease. However as the incidence of incidental Ca GB is 2.9% in the study and no significant parameters could be found that can detect the condition except thickened GB wall in the fundal region

which was consistent feature in CECT abdomen in most of the IGBC cases. The operating surgeon should have high index of suspicion regarding this not so uncommon and uniformly fatal disease.

REFERENCES

1. Lazcano-Ponce EC, Miquel JF, Muñoz N, et al. Epidemiology and molecular pathology of gallbladder cancer. *CA: Cancer J Clin* 2001; 51(6):349–364.
2. Kapoor VK: Incidental gallbladder cancer. *Am J Gastroenterol* 96: 627-29-2001
3. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. *Int J Cancer*. 2006;118(7):1591–1602.
4. Kumar S. Infection as a risk factor for gallbladder cancer. *J Surg Oncol*. 2006;93(8):633–639.
5. Gonzalez-Escobedo G, Marshall JM. Chronic and acute infection of the gall bladder by *Salmonella Typhi*: understanding the carrier state. *Nature Reviews: Microbiology*. 2011 Jan;9(1):9–14.
6. Stephen AE, Berger DL. Carcinoma in the porcelain gallbladder: a relationship revisited. *Surgery*. 2001;129(6):699–703.
7. Cunningham SC, Alexander HR. Porcelain gallbladder and cancer: ethnicity explains a discrepant literature? *Am J Med*. 2007;120(4):e17–e18.
8. Zatonski WA, Lowenfels AB, Boyle P, et al. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. *J Natl Cancer Inst*. 1997;89(15):1132–1138.
9. Mitsugi Shimoda, Tsunehiko Maruyama, Kiyotaka Nishida, Kazuomi Suzuki, Tomoya Tago, Jiro Shimazaki, Shuji Suzuki. What are Preoperative Predictors for Incidental Gallbladder Cancer after Routine Cholecystectomy. *Surg. Gastroenterol. Oncol*. 2018;23(1):51-55 DOI: 10.21614/sgo-23-1-51
10. Agarwal AK, Kalayarasan R, Javed A, Gupta N, Nag HH. The role of staging laparoscopy in primary gall bladder cancer--an analysis of 409 patients: a prospective study to evaluate the role of staging laparoscopy in the management of gallbladder cancer. *Ann Surg* 2013;258(2):318-23. doi: 10.1097/SLA.0b013e318271497e
11. Shih SP, Schulick RD, Cameron JL, Lillemoe KD, Pitt HA, Choti MA, et al. Gallbladder cancer: the role of laparoscopy and radical resection. *Ann Surg*. 2007;245(6):893-901.
12. Tian YH, Ji X, Liu B, Yang GY, Meng XF, Xia HT, et al. Surgical treatment of incidental gallbladder cancer discovered during or following laparoscopic cholecystectomy. *World J Surg*. 2015;39(3):746-52. doi: 10.1007/s00268-014-2864-9.
13. Yamamoto H, Hayakawa N, Kitagawa Y, Katohno Y, Sasaya T, Takara D, et al. Unsuspected gallbladder carcinoma after laparoscopic cholecystectomy. *J Hepatobiliary Pancreat Surg*. 2005;12(5):391-8.
14. Kwon AH, Imamura A, Kitade H, Kamiyama Y. Unsuspected gallbladder cancer diagnosed during or after laparoscopic cholecystectomy. *J Surg Oncol* 2008;97(3):241-5. doi: 10.1002/jso.20944.
15. Pitt SC, Jin LX, Hall BL, Strasberg SM, Pitt HA. Incidental gallbladder cancer at cholecystectomy: when should the surgeon be suspicious? *Ann Surg* 2014;260(1):128-33.
16. Muszynska C, Lundgren L, Lindell G, Andersson R, Nilsson J, Sandström P, et al. Predictors of incidental gallbladder cancer in patients undergoing cholecystectomy for benign gallbladder disease: Results from a population-based gallstone surgery registry. *Surgery*. 2017;162(2):256-263. doi: 10.1016/j.surg.2017.02.009. Epub 2017 Apr 8.
17. Ahn Y, Park CS, Hwang S, Jang HJ, Choi KM, Lee SG. Incidental gallbladder cancer after routine cholecystectomy: when should we suspect it preoperatively and what are predictors of patient survival? *Ann Surg Treat Res* 2016;90(3):131-8. doi: 10.4174/astr.2016.90.3.131.
18. Glenn F, Hays DM. The scope of radical surgery in the treatment of malignant tumors of the extrahepatic biliary tract. *Surg Gynecol Obstet* 1954;99:529-41.
19. Pack GT, Miller TR, Brasfield RD. Total right hepatic lobectomy for cancer of the gall bladder; report of three cases. *Ann Surg* 1955;142:6-16.
20. Fahim RB, McDonald JR, Richards JC, Ferris DO. Carcinoma of the gallbladder: a study of its modes of spread. *Ann Surg* 1962;156:114-24.
21. James MC. Liver and biliary tract. In: Kumar V, Abul KA, Nelson F, editors. *Robins and Cotran Pathologic basis of Disease* (7th ed.). Philadelphia: Elsevier; 2004. 935.
22. Russel RCG. The gall bladder and bile ducts. In: Russel R.C.G, Williams N.S, Bulstrode C.J.K, editors. *Bailey and Love's short practice of Surgery* (24th ed.). London: Hodder Arnold Publication; 2004. 1095-1113.
23. Z'graggen K, Birrer S, Maurer CA, Wehrli H, Klaiber C, Baer HU. Incidence of port site recurrence after laparoscopic cholecystectomy for preoperatively unsuspected gallbladder carcinoma. *Surgery* 1998;124:831-8.
24. Lundberg O. Port site metastases after laparoscopic cholecystectomy. *Eur J Surg Suppl* 2000;(585):27-30.
25. Ouchi K, Mikuni J, Kakugawa Y; Organizing Committee, The 30th Annual Congress of the Japanese Society of Biliary Surgery. Laparoscopic cholecystectomy for gallbladder carcinoma: results of a Japanese survey of 498 patients. *J Hepatobiliary Pancreat Surg* 2002;9:256-60.
26. Suzuki K, Kimura T, Ogawa H. Is laparoscopic cholecystectomy hazardous for gallbladder cancer? *Surgery* 1998;123:311-4.
27. Yamaguchi K, Chijiwa K, Ichimiya H, Sada M, Kawakami K, Nishikata F, et al. Gallbladder carcinoma in the era of laparoscopic cholecystectomy. *Arch Surg* 1996; 131:981-4.
28. Bitar Geramizadeh, Ali Kashkooe. Incidental Gall Bladder Adenocarcinoma in Cholecystectomy Specimens; A Single Center Experience and Review of the Literature. DOI: 10.15171/mejdd.2018.118.
29. ST Weiland, DM Mahvi, JE Niederhuber, DM Heisey, DS Chicks, LF Rikkers, Should suspected early gallbladder cancer be treated laparoscopically?, *J Gastrointest Surg* 6 (2002) 50–57, PMID: 11986018.
30. C Wullstein, G Woeste, S Barkhausen, E Gross, UT Hopt, Do complications related to laparoscopic cholecystectomy influence the prognosis of gallbladder cancer?, *Surg Endosc* 16 (2002) 828–832, PMID: 11997831.
31. L Sarli, S Contini, G Sansebastiano, S Gobbi, R Costi, L Roncoroni, Does laparoscopic cholecystectomy worsen the prognosis of unsuspected gallbladder cancer?, *Arch Surg* 135 (2000) 1340–1344, PMID: 11074893.
32. Rashid A, Ueki T, Gao YT, et al. K-ras mutation, p53 overexpression, and microsatellite instability in biliary tract cancers: a population-based study in China. *Clin Cancer Res*. 2002;8(10):3156–3163.
33. Saetta AA. K-ras, p53 Mutations, and Microsatellite Instability (MSI) in Gallbladder Cancer. *J Surg Oncol*. 2006 Jun 15;93(8):644–649.
34. Levy AD, Murakata LA, Rohrmann CA., Jr Gallbladder carcinoma: radiologic-pathologic correlation. *Radiographics*. 2001;21(2):295–314. questionnaire, 549–555.
35. Roa I, de Aretxabala X, Morgan R, Molina R, Araya JC, Roa J, et al. Clinicopathological features of gallbladder polyps and adenomas. *Revista Medica de Chile*. 2004 Jun;132(6):673–679.