

A prospective study of radical cholecystectomy for gallbladder carcinoma

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Abstract

Background: Gallbladder cancer tends to be an aggressive tumor that spreads early and leads to rapid death. The clinical pessimism surrounding gallbladder cancer is because of its late presentation and lack of effective therapy. Definitive resection for Gallbladder cancer depends on stage and location of the tumour as well as whether it is repeat resection after a previous simple cholecystectomy. Serious problems soon after surgery can include bile leakage into the abdomen, infections, and liver failure. **Material and Methods:** From the report of Hospital Based Cancer registry (HBCR) of CNCI information regarding all cancer cases were collected and analyzed to find the proportion of cancer in gall bladder cases. Patients for this study was selected from the patients who undergone radical cholecystectomy for gall bladder carcinoma. Morbidity and mortality of the patient were observed within 30 days of procedure. **Results:** Proportion gall bladder cancer cases for male and female was 3.7% and 8.94% respectively and overall proportion observed was 6.28%. The incidence of wound infection was higher in diabetics than non diabetics in patients undergoing CRS (15.4 vs. 11.0%, $P < 0.001$) and patients undergoing GS (5.3 vs. 3.1%, $P < 0.001$). Bile leakage is common with patients undergone common bile duct resection. Among 6 patients underwent CBD resection, 4 patients had <50ml bile leakage post operatively. Out of 30 patients, one hypertensive patient developed acute myocardial infarction. 10 % patient had suffered major bleeding and given 3units of blood. The mean number of post-operative blood transfusion of the patients was 1.83 ± 0.59 units with range 1-3 units. **Conclusion:** Proportion gall bladder cancer observed was 6.28%. As radical cholecystectomy is a major procedure, we encountered few post operative complications like bleeding, septicemia wound infection, bile leak etc.

Key words: Gall bladder Cancer, Radical cholecystectomy, Post operative complication

Introduction

Gallbladder cancer which is the most common malignant tumor of the biliary tract is comparatively rare in comparison to other GI malignancy. Moreover it is a highly aggressive malignancy but usually presents at an advanced, incurable stage [1,2]. It is a fact that gallbladder cancer almost always present with dismal prognosis, still surgical modalities only can offer cure or at least long term survival.

The incidence of gallbladder cancer varies by geographic region and racial-ethnic groups. The highest incidences are reported in Indians, Pakistanis, Chileans, Bolivians, Central Europeans, Israelis, American Indians, Mexican and Japanese [3,4]. It has been suggested that lower

socioeconomic status may lead to delayed access to cholecystectomy, which may increase gallbladder cancer rates [5]. Various studies showed chronic inflammation(gallstone disease, porcelain gallbladder), history of biliary problems, older age, and female sex, presence of anomalous pancreaticobiliary duct junction, typhoid carriers, obesity, Helicobacter pylori are the risk factors for the development of gallbladder cancer[6,7].

Gallbladder cancer is managed by combined modality of surgery, chemotherapy and radiation .Surgery in the form of radical cholecystectomy forms an important part of management. The procedure is technically challenging because of rarity, anatomical complexity in and around respective anatomical site as well as majority are done as redo cases after simple cholecystectomy. So studying morbidity and mortality profile becomes imperative for such procedure.

Manuscript Received: 04th March 2017
Reviewed: 12th March 2017
Author Corrected: 20th March 2017
Accepted for Publication: 30th March 2017

We have studied it because the incidence of operable gallbladder cancer is very low compared to others and to see the important cause of morbidity and mortality 30 days post operatively in patients who had undergone radical cholecystectomy so that we can throw light to prevent morbidity and mortality in future..

Aim and objectives

- To find out the proportion of gall bladder cancer among patients attending to CNCI surgical OPD.
- To find out 30days morbidity and mortality in patients who undergone radical cholecystectomy

Material and methods

Study design: Cross sectional study in which prospective observations were made.

Study site: Dept. of Surgical Oncology, Chittaranjan National Cancer Institute, Kolkata

Inclusion criteria

All operable patients with Gallbladder malignancy presented to CNCI surgical oncology OPD

Exclusion criteria

1. Patient not given consent for study
2. Patient had some other malignancy along with GB malignancy
3. Patients not fit for surgery medically
4. Patient having T1a/Tis gallbladder cancer detected incidentally after cholecystectomy with negative margins

Participants: Patients for this study was selected from the patients who undergone radical cholecystectomy for gall bladder carcinoma at Department of Surgical Oncology of Chittaranjan National Cancer Institute, Kolkata with the help of computer generated random numbers by the process of randomization. 30 patients with operable gall bladder participated in the study.

Sample size with justification: A total of 30 cases of gallbladder cancer were selected. It had been observed that on an average 5 out of every 17 patients radical cholecystectomy for gallbladder carcinoma were

Results

Total cancer cases detected in 2 years were 8236.out of which 518 cases are gall bladder cancer. For male and female proportion were 3.67% and 8.94% respectively during the study period whereas 6.28% was the overall proportion of gallbladder. (Table-1).

performed. Thus proportion of radical cholecystectomy among the patients having gall bladder carcinoma was 29.4% ~ 29.0% (i.e. p=0.29) in this institute. The number of subjects required for this study was 29.65 ~ 30 with power 43%. The formula used for sample size calculation was as follows:-

$$n = \frac{4pq}{L^2}$$

Where

n= Required sample size

p= Proportion of radical cholecystectomy among the patients having gall bladder carcinoma

q = 1 - p

L = Loss %

Time frame to address the study: From June 2014-May 2016

Methodology

Patient was examined, detail history including chief complaints, any associated illness, habits, addiction was duly noted down. Clinical examination of neck nodes, general condition, abdomen, chest, was done systematically. Investigations in the form of USG abdomen, CT scan of abdomen and pelvis, CA 19.9.

Intra-operative assessment ,Operative time, Units of blood transfusion, Days of ICU stay, time of start of enteral and oral feed, time of drain removal, any complication in postoperative phase, date of discharge and complication like wound infection, postoperative hemorrhage, biliary leakage are noted.

Statistical Methods- Descriptive statistical analysis was performed to calculate the means with corresponding standard deviations (S.D.).

Test of proportion was used to find the Standard Normal Deviate (Z) to compare the difference proportions and chi-square (χ^2) test was performed to find the associations. Corrected chi-square (χ^2) test was used where any one of the cell frequencies was less than zero. p value <0.05 was taken to be statistically significant.

Table-1: Proportion of cancer in gall bladder cases according to the gender

| Gender | Number of Ca GB | Total cancer cases | Respective proportions % |
|--------------|-----------------|--------------------|--------------------------|
| Male | 152 | 4144 | 3.67% |
| Female | 366 | 4092 | 8.94% |
| Total | 518 | 8236 | 6.28% |

The mean age (mean \pm s.d.) of the patients was 54.10 \pm 12.55 years with range 28-80 years and the median age was 55.0 years. Test of proportion showed that the proportion of the patients with age \geq 50 years (70.0%) were significantly higher than other age group ($Z=5.65$; $p<0.0001$). Only 10.0% were with age $<$ 40 years and 26.7% of the patients were with age \geq 60 years.

Test of proportion showed that proportion of females (73.3%) was significantly higher than that of males (26.7%) ($Z=6.59$; $p<0.0001$). Thus Ca-GB was more prevalent among females than males.

The sex ratio was found as Male: Female = 1:2.75

Chi-square (χ^2) test showed that there was no significant association between age groups and gender of the patients ($p=0.07$). The mean age (mean \pm s.d.) of males was 48.62 \pm 7.30 years with range 35-59 years and the median age was 49.0 years. The mean age (mean \pm s.d.) of females was 56.09 \pm 13.57 years with range 28-80 years and the median age was 56.0 years. The t-test showed that there was no significant difference in mean ages of males and females ($t_{28}=1.47$; $p=0.15$). Most of the patients had no addiction (73.3%) which was significantly higher than addiction (26.7%) ($Z=6.59$; $p<0.00001$). Out of the all addictions smoking (13.3%) was more prevalent than drinking of alcohol with smoking (6.7%) and use of chewing gutkha (6.7%).

30% of the patients had no co-morbidity. Out of the all co-morbidities hypertension (46.60%) and diabetes (36.6%) were more prevalent.

Most of the patients had raised CA19.9 (66.7%) which was significantly higher than normal (33.3%) ($Z=4.72$; $p<0.0001$).

Most of the patients had raised alkaline phosphatase (50.1%) which was significantly higher than that of raised conjugated bilirubin ($Z=6.20$; $p<0.0001$). 40.0% of them had normal LFT.ss

Most of the patients had pre-operative gall bladder stone as per USG findings (86.7%) which was significantly higher ($Z=10.39$; $p<0.0001$). 4(13.3%) did not have pre-operative gall bladder stone.

Most of the patients had not undergone previous surgery for gall bladder (66.7%) which was significantly higher ($Z=7.15$; $p<0.0001$). Rest of the 10 patients 5(16.7%) were underwent Laproscopic Cholecystectomy and 5(16.7%) were underwent Open Cholecystectomy.

4(13.3%) had gross adhesion during surgery. 6(20.0%) had CBD resection. 2(6.7%) had colon resection. Most of the patients (63.3%) presented with T3N1M0 Staging. 4 patients died within 30 days postoperatively.

The risk and side effect of surgery depend on how much tissue is removed and patient's general health before the surgery. All surgery carries some risk, including the possibility of bleeding, blood clots, infections, complications from anaesthesia, and pneumonia. Liver resection usually cause blood loss. To replenish we transfused blood post operatively. For liver resection we used CUSA(cavitron ultrasonic surgical aspirator).only 3 patients suffered post operative blood loss for which they were stabilized with 3 units each of blood.

Blood sugar level is directly proportional to the post operative complications like wound infection. 54.09% of diabetic patient suffered wound infection post operatively.

The incidence of wound infection was higher in diabetics than nondiabetics in patients undergoing CRS (15.4 vs. 11.0%, $P < 0.001$) and patients undergoing GS (5.3 vs. 3.1%, $P < 0.001$).

Bile leakage is common with patients undergone common bile duct resection. Among 6 patients underwent CBD resection, 4 patients had <50ml bile leakage post operatively all of them were treated conservatively.

A number of patients with septicemia developed respiratory tract infection at first. Most of them had a history of diabetes. Out of 30 patients, one hypertensive patient developed acute myocardial infarction. (Table-2).

Table-2: Post-operative complications

| Complications | Yes | No |
|-----------------------------|-----------|-------------|
| Wound infection | 13(43.3%) | 17 (56.7%) |
| Bile leakage | 4 (13.3%) | 26 (86.7%) |
| Septicaemia | 3 (10%) | 27 (90%) |
| Acute myocardial infarction | 1 (3.33%) | 29 (96.67%) |
| Respiratory tract infection | 6 (20%) | 24 (80%) |
| Bleeding | 3 (10%) | 27 (90%) |

Most of the patients had wound infection (43.3%) followed by respiratory tract infection (20%) ($Z=6.23; p<0.0001$). Only 3.33% had acute myocardial infarction.

10 % patient had suffered major bleeding and given 3units of blood .(Table-3).

Table-3: Post-operative blood transfusion

| Post-operative blood transfusion | Number | % |
|----------------------------------|-----------|---------------|
| 1 | 8 | 26.7% |
| 2 | 19 | 63.3% |
| 3 | 3 | 10.0% |
| Total | 30 | 100.0% |

The mean number of post-operative blood transfusion (mean± s.d.) of the patients was 1.83 ± 0.59 units with range 1-3 units and the median was 2 units.

Discussion

Gallbladder cancer which is the most common malignant tumour of the biliary tract is a highly aggressive malignancy that usually presents at an advanced, incurable stage [1]. It is fifth most common malignancy of GI tract.

Risk factors for developing gallbladder cancer- There are several risk factors identified to cause cancer of the gallbladder. These include various physiological and genetic factors. Obesity, gender, age group, infection of hepatobiliary tract, various chemicals which are proven as carcinogens, geographical distribution including age and ethnicity all are somewhat related to gallbladder cancer. Above all gall stone disease is identified as the most influential factor to develop gall bladder cancer.

Pathophysiology- Most common form of gall bladder carcinoma is adenocarcinoma. There are three histological varieties of adenocarcinoma of gall bladder, i.e infiltrative, nodular and papillary forms. Among these infiltrative one is common type and papillary form has good prognosis. Other forms of gall bladder carcinoma carry poor prognosis.

Gall bladder carcinomas progress from metaplasia to dysplasia to carcinoma in situ to invasive carcinoma. Chronic inflammation may play a role in development of premalignant lesions [12]. Progression from dysplasia to invasive carcinoma can take about 15 years [13]. Several mutations most notably P53, Kras are common in gall bladder cancer[14]. The lack of a well defined muscularis leads to early entry of carcinoma in to perimuscular connective tissue, lymphatics, neural and hematogenous invasions occur earlier with Gall bladder cancer than with other cancers of gut. They can spread through the wall of the gall bladder, adjacent liver or any other organs. They have a high propensity to seed and grow in the peritoneal cavity along the tract of needle biopsy and as laparoscopic port sites. Hematogenous metastasis leads to hepatic metastasis in segment iv and v of the liver. Isolated lung metastasis in absence of advanced locoregional disease is rare. Intraabdominal

recurrences are very common in comparison to distant metastasis which occurs late after resection. Survival for advanced disease is very poor.

Treatment protocol of gall bladder carcinoma- Surgery in the form of radical cholecystectomy [8,9] is the only curative option for gall bladder carcinoma. Absolute contraindication to surgery includes distant metastases, vascular involvement, nodal spread beyond hepatoduodenal ligament. Role of surgery including hepatic lobectomy when proximal hepatic ducts are involved is not much studied so considered inoperable at present situation..Again Tis and T1 lesions where tumour has not penetrated muscularis mucosa with negative margins simple cholecystectomy is sufficient. Post surgery adjuvant 5-FU based chemoradiotherapy has been found to enhance both local controls as well as survival [10].The results are much impressive in case of R0 resection. Some have advocated gemcitabine plus cisplatin in adjuvant setting. For inoperable and metastatic gallbladder carcinoma the 1 yr survival is <5%.So depending on the performance and physiological status chemotherapy along with palliative measures is the standard of care. Recently regional therapy in the form of intraarterial mitomycin-c has shown a response rate 48% and prolongation of median survival from 5 to 14 months compared with historical controls [11].

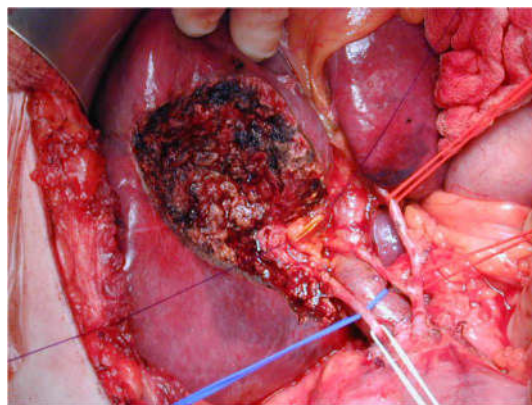
Surgical management of gall bladder carcinoma [8, 9]- Radical cholecystectomy for gall bladder cancer is used interchangeably with extended cholecystectomy. An extended cholecystectomy is a well defined surgical procedure which includes an en bloc resection of gallbladder with a 2 cm non anatomical wedge of the liver along with regional lymphadenectomy involving clearance of lymphatic tissue along the hepato- duodenal ligament, anterior and posterior to head of the pancreas and the hepatic artery up to its origin at celiac plexus.

A radical cholecystectomy on the other hand, is an oncologically radical procedure, the extent of which may vary depending upon the location of the tumour and adjacent organ involvement.

Extra hepatic bile duct excision: Many hepatobiliary surgeons routinely excise cystic duct stump and subject to frozen section examination so as to ensure negative cystic duct margin. We performed extra biliary duct excision for only those patient's where invasion of common bile duct was suspected.

Lymphadenectomy which included dissection of lymph nodes along the length of the hepatic artery (celiac axis to level of its bifurcation into the right and left hepatic arteries), retropancreatic lymphnodes, pericholedochal and periportal lymph nodes. Circumferential dissection of hepatoduodenal ligament was completed and the entire lymph nodal tissue is excised en bloc.

Para aortic , aorto-caval lymph node involvement is a sign of a very advanced disease.



Intra operative picture of radical cholecystectomy

Radical re-resection: In patients, diagnosed with gall bladder cancer based on histopathological examination of specimen of simple cholecystectomy, performed for calculous cholecystitis, there was a need to perform completion surgery, also referred to as radical re-resection.

In radical re-resection, wedge resection of gall bladder base, revision of cystic duct margin when indicated, lymph nodal dissection as described above was performed in this study for incidental gallbladder cancer.

Among the patients with an incidental finding of gall bladder cancer on pathological review (laparoscopic cholecystectomy performed in these patients), port site resection was not performed as many studies showed it did not give any survival benefit.

There is no ideal timing for radical re resection following primary surgery.

In our study we have found 8236 cancer cases in two years .among that 518 cases are gallbladder cancer which is mere 6.3% of solid cancers reported. Among these only 127(24.51% of total gallbladder cancer cases) were found operable. Among these few operable cases only 30 patients were considered for study others either denied for surgery or were found medically unfit for surgery or did not require surgery (T1a,Tis tumours if margins are negative).

In an epidemiological study conducted by Dutta U et al also found out that the mean age of the 121 patients studied was 55+/- 11.7 (SD) years. There were 51 (42%) patients aged less than 50 years [15].

The highest incidence of gallbladder cancer is observed in South America and Asia, and the lowest incidence is in Africa. More than half of gallbladder cancer cases occur in less developed countries [16].

Conclusion

There was no significant difference in mean ages of males and females. We found out that addiction has no role in development of carcinoma gall bladder. Diabetic patients are mostly affected by gall stone disease thus carcinoma gall bladder. These patients were also suffered post operative complication. Cases with poor nutritional status faced more morbidities post operatively but it is not associated with stages of gall bladder cancer.CA 19.9 was raised in most of the patients with gall bladder cancer.

Conflict of interest: None declared.

Funding: Nil, **Permission from IRB:** Yes

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How to cite this article?

Chejara S, Sahu S K, Giri R. A prospective study of radical cholecystectomy for gallbladder carcinoma. *Int J surg Orthopedics.* 2017;3(1):12-18. doi:10.17511/ijoso.2017.i01.03.

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