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Surgery Section

Carcinoma of the Gall Bladder: A Prospective Study in a Tertiary Hospital of Bombay, India

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ABSTRACT

Introduction: Despite the pre-operative procedures, gall bladder carcinoma is commonly detected intraoperatively or on histopathological examination after cholecystectomy. The prevalence of gall bladder carcinoma is highly variable across the world and it remains the most common malignancy of the biliary tract worldwide. Very high incidence rates are found in northern India and Chile. Gall bladder cancer has been frequently referred as a lethal and incurable disease. Despite the advances in medical imaging, most of the cases (70-80%) of gall bladder cancer are only discovered incidentally on histopathological examination after cholecystectomy which is performed for presumed benign biliary disease. Therefore, the morphological studies have had a significant impact on the diagnosis of this cancer, thus lowering the number of cases that could be under diagnosed and guiding the extent of the surgical resection. Although the subject of gall bladder cancer has been well explored, there is relative paucity of clinicopathological studies on this topic.

Objective: To analyze the demographics, the clinical presentation and the diagnostic modalities in patients with gall bladder carcinoma and to assess the various treatment modalities which have been offered and their results.

Methods: This prospective study was carried out on patients with carcinoma of the gall bladder, who were admitted in a tertiary hospital, Bombay, between 2004 to 2007. After taking the informed consent of the patients, their detailed clinical history which was related to their demographics and their clinical manifestations was taken. Various diagnostic modalities and their TNM staging and treatment were analyzed. All the patients who presented with features which were suggestive of biliary diseases were evaluated by using abdominal ultrasonography and CT, but only those with a confirmatory diagnosis of carcinoma by CT or histopathology were included in the study.

Results: A total of 50 patients were included in the study, with a male:female ratio of 1:2.3. Their ages ranged from 25 to 80 years, with a mean of 54years. Many (34) patients were from the northern states. A lump in the right hypochondrium was seen in 28 patients (56%). It was also noted that 14 patients had presented with obstructive jaundice. Ultrasound and CT revealed a locally advanced disease status in a majority of the cases. Many (90%) cases had associated gall stones. A majority (92%) were in stage IV as was found by TNM staging. Two were identified as incidental findings following cholecystectomy. A majority of the cases were managed with palliative gastrojejunostomy, ERCP stenting and chemoradiotherapy. The cases of early cancer had a better 2 year survival, whereas many of the advanced cases had poor survival rates.

Conclusion: Early detection contributes to a higher survival rate. The prognosis of gall bladder cancer is thus poor, mainly because of the delayed presentation. Besides other factors, TNM staging remains the most imperative prognostic factor which affects the survival. It is desirable to search for any factor which can be linked to gall bladder cancer or which can help in the diagnosis of the disease in the early stages, thus making surgical intervention possible so that it can ultimately result in a good prognosis. Moreover, to positively affect the outcome of the patients in the advanced stage of the disease, newer cancer treatment strategies need to be adopted.

Key Words: Gall bladder, Carcinoma, Prognosis, TNM staging, Follow up

INTRODUCTION

Carcinoma of the gall bladder is rare and it is a common malignant tumour of the gall bladder mucosa [1-3]. It is the 5th most common tumour of the gastro-intestinal tract and it accounts for 3% of all the gastro-intestinal tumours. The Indian Council of Medical Research Cancer Registry has recorded an incidence of 4.5 and 10.1 per 100,000 males and females respectively in the northern parts of India, and that of 1.2 per 100,000 population in females in the southern parts of India. Although different associations have been described, gallstones are found to be associated in 70% to 90% of the cases of gall bladder cancer. Approximately 0.4% of all the patients who are affected with gallstones eventually develop carcinoma of the gall bladder. An autopsy study had shown that the overall incidence of carcinoma of the gall bladder is 1% to 3% in patients with cholelithiasis. The most common malignancy is adenocarcinoma, with a peak incidence in the 6th to 7th decades of life. The five year survival in most of the large series is less than 5%, with a median survival of less than six months [4-9]. The clinical pessimism which surrounds gall bladder carcinoma is due to its late presentation and its lack of effective therapy. Its clinical presentation is non-specific, with a vague symptomatology. The disease is advanced at presentation because the tumour directly involves the liver early and it also invades the adjacent organs. The disease clinically mimics the benign gall bladder diseases and it usually escapes detection until late in its course [3].

Primary carcinoma of the gall bladder is an unexpected histopathological finding in 1–3% of the resected specimens of elective cholecystectomy which are performed for benign gall bladder diseases [4-8]. The overall prognosis has remained dismal, with a

5-year survival of 5-10% due to the late detection of the disease [4, 9-12]. Prior to the era of ultrasonography and CT scanning, the rate of the correct pre-operative diagnosis was only 8.6% [4], which has improved considerably to 75–88%, with the use of these newer imaging techniques [11-15]. Still, a pre-operative diagnosis of early carcinoma of the gall bladder is seldom made, where the 5-year survival is 91-100% [16,17]. Most of the available literature has been reported from developed countries which have a sociocultural and health setup, which is different from that of a developing country such as India. This study was aimed at defining the disease profile in the Indian population and at determining the effect of various prognostic parameters on the clinicopathological behaviour of the disease.

OBJECTIVES

To analyze the demographics, clinical presentation and the diagnostic modalities in patients with gall bladder carcinoma and to assess the various treatment modalities which have been offered and their results.

MATERIALS AND METHODS

This prospective study was carried out on patients with carcinoma of the gall bladder, who were admitted in a tertiary hospital, Bombay, India between 2004 to 2007. After taking the informed consent of the patients, a detailed clinical history which was related to their demographics and clinical manifestation was taken. Various diagnostic modalities and their TNM staging and treatment were analyzed. All the patients who presented with features which were suggestive of biliary diseases were evaluated by using abdominal ultrasonography and only those with a confirmatory diagnosis which was either by CT or by histopathology means were included in the present study. During this 3-year period, 50 patients with carcinoma of the gall bladder were treated. Haematological, biochemical, and radiological investigations followed a detailed clinical examination to define the extent of the disease and for the general assessment of the patient. The follow- up was carried out at monthly intervals for the first 6 months and thereafter at 3-month intervals.

RESULTS

A total of 50 patients were included in the study who consisted of 35 females and 15 males with a ratio of 2.3:1. Their ages ranged from 25 years to 80 years with a mean of 54years. Among these, 34 patients were from the northern Indian states.

Among these, 28 patients (56%) presented with a lump in the right hypochondrim. It was also noted that 14 patients presented with obstructive jaundice. The clinical findings are shown in [Table/Fig-1].

Laboratory Investigations

All the patients underwent routine haematological and biochemical investigations. Among these, 10 cases had anaemia and 6 patients had leucocytosis. The liver function tests were abnormal in 14 patients with obstructive jaundice, with a significant rise in the direct bilirubin and alkaline phosphatase levels.

Ultrasonography(USG) was done in all the patients. The findings are shown in [Table/Fig-2]. A majority had gall bladder fossa mass with liver extension. Gall stone was detected in 45 cases. A majority of them multiple gall stones.

A contrast enhanced computed tomography (CECT) was done in all the cases. The results are shown in [Table/Fig-3]. A majority had findings which were similar to that of the ultrasound findings.

The disease was staged by using TNM staging, based on the CECT findings. The TNM staging is shown in [Table/Fig-4]. A majority of the cases (92%) were found to be of stage IV by TNM staging.

The treatment which was offered is shown in [Table/Fig-5].

2 patients had a retrospective diagnosis of carcinoma of the gall bladder following cholecystectomy, which was done for suspected chronic cholecystitis. Histopathology revealed adenocarcinoma which was restricted to the submucosa, with no transmural invasion and with transmural invasion in one case each. Both these patients were observed.

Clinical features	No of patients (%)
Lump in Right hypochondrium	28 (56)
Obstructive jaundice	14 (28)
Calculous cholecystitis	6 (12)
Incidental	2 (4)

[Table/Fig-1]: Clinical findings of gall bladder carcinoma

USG findings	No. of patients (%)
Suspicious gall bladder wall thickening	5 (10)
Gall bladder fossa mass extension into liver	26 (52)
Mass in the gall bladder with dilated intrahepatic biliary radicals	14 (28)
Gall bladder fossa mass with non synchronous liver metastasis	3 (6)
Gall bladder with cholecystitis changes	2 (4)

[Table/Fig-2]: Ultrasonography finding in gall bladder carcinoma

CT scan findings	No of patients (%)
Mass lesion in gall bladder with invasion into liver	26 (52)
Mass lesion in gall bladder with invasion of porta hepatis and IHBR dilatation	14 (28)
Mass lesion in gall bladder with liver non synchronous metastasis	6 (12)
Gall bladder wall thickening suspicious of malignancy	2 (4)
Gall bladder with cholecystitis changes	2 (4)

[Table/Fig-3]: CT finding in gall bladder carcinoma

Staging	TNM	No of patients
Stage I	T1N0M0	2
Stage II	T2N0M0	1
Stage III	T3N0MO	1
Stage IV		46

[Table/Fig-4]: TNM staging in gall bladder carcinoma

Treatment	No of patients
Curative surgery Cholecystectomy Extended cholecystectomy	4 2 2
Palliative surgery Gastrojejunostomy Segment III bypass	6 5 1
Palliative bypass stenting ERCP stenting PTBD stenting	8 5 3
Palliative chemo radiotherapy	10

[Table/Fig-5]: Treatment done for gall bladder carcinoma

Two patients underwent extended cholecystectomy for localized gall bladder carcinoma. Both the patients underwent intraoperative frozen section examination to confirm malignancy before proceeding with the resection.

All the 14 patients with obstructed jaundice had advanced disease on imaging. In addition, two patients had gastric outlet obstruction due to invasion of the duodenum. One of these patients underwent palliative gastrojejunostomy (GJ) and segment III bypass. The other patients underwent palliative ERCP stenting and operative GJ. Of the remaining 12 patients, 4 refused any form of therapy and they were discharged. The remaining 8 patients underwent ERCP. ERCP stenting was possible in 5 patients. The remaining 3 patients underwent PTBD (Percutaneous transhepatic biliary drainage) and stenting.

Out of 46 patients with advanced disease, 10 underwent palliative radio chemotherapy and 4 had gastric outlet obstruction, who underwent palliative GJ. Four patients (young patients of < 40years of age) underwent FNAC to prove the diagnosis. 32 patients were symptomatically palliated (narcotic analgesics/ nutritional support).

FOLLOW-UP

The follow up was obtained through OPD visits and letters which were sent to the patients.

Both the patients with incidental carcinoma were asymptomatic at 2 years of follow up.

Of the two patients who underwent extended cholecystectomy, 1 patient developed local recurrence 6 months after the surgery and succumbed to the disease 3 months later. The other patient is asymptomatic at 2 years of follow up.

Of the 46 patients with advanced disease, 14 were lost from follow up and 32 succumbed to death within 6 months of the diagnosis.

Of the 5 patients who underwent ERCP stenting, 2 developed stent blockage and they underwent repeat ERCP and stent change. Of the 3 patients in whom the PTBD stenting was done, only one was internalized and he was asymptomatic at the end of 6months of follow up. The remaining 2 were discharged with external stents. Two of the 8 patients who were stented are alive at the end of 1year of follow up.

DISCUSSION

Carcinoma of the gall bladder is a rare malignancy which arises from the gall bladder mucosa. It is the 5th most common tumour of the gastro-intestinal tract and it accounts for 3% of all the G.I tract malignancies [1,3,6]. Its clinical presentation is non-specific, with a vague symptomatology. The disease is advanced at presentation because the tumour directly involves the liver early and it also invades the contiguous organs [1,10-16]. Because of the advanced stage at presentation, there is no role for curative resection [1,2,6].

In our study, 50 patients were followed up for over a period of 2 years. The age group of the patients was 25-80years with a maximum incidence in the sixth decade of life, which compared well to the worldwide peak incidence which was reported in the sixth or seventh decades of life [7,8,10].

The reported female to male ratio worldwide is 4:1 and we found a ratio of 2.3:1. The disease was found to be more common in the northern states of India. The various risk factors included age, sex, gall stones, diet and chronic inflammation [1,4]. The geographical variations may reflect cultural, dietary or genetic differences in the population. The incidence of gall bladder carcinoma was found to be more in females than in males because the incidence of gall stones and bladder diseases was more common in females. There was an increased incidence of gall bladder carcinoma in north India because of the increased incidence in gall stones there [1,4,9,16]. Physical trauma which was produced by the stones might have resulted in epithelial dysplasia and ultimately in the progression to carcinoma. In our study, 90% of the patients had associated gall stones. Similar results were noted by Khan et al, in 96.15% of the cases [9].

While a histopathological diagnosis is crucial for the discovery of incidental carcinoma (which was diagnosed in two patients in our study and was operated), it is only supportive otherwise, as CT scan is highly sensitive and specific but it also correlates well with the final staging of the disease [9-15]. In other studies, the incidence of occult carcinoma of the gall bladder varied from 1% to 2.5% [9]. The staging and the pattern of the spread are clearly defined by the presence or absence of the direct invasion of the adjacent organs, this being the important prognostic factor [1,4,17,18]. Abdominal ultrasound is a valuable screening method for the early detection of the carcinoma, as it is seen as a polypoidal mass or a thickened wall. However, it will detect carcinoma only in 30-50% of the cases. Abdominal CT is a sensitive method and it shows the thickened wall and the contrast enhancement of the gall bladder. Recently, endoscopic ultrasound was found to be valuable in the early detection and staging of the gall bladder carcinoma [6,10,12]. Despite the advances in hepatobiliary imaging, a precise pre-operative staging for gall bladder carcinoma is still difficult to establish. The overall accuracy of the image-T is 52.6%; however, image-T was a significant predictor of the lymph node metastasis and the patient outcome.

In our study, 50 patients underwent CT scan, which proved to be diagnostic; the recent advances in radiology have increased the diagnostic yield [1,4,10-15]. Despite the advances in medical imaging it is still difficult to diagnose gall bladder cancer pre-operatively. A gall bladder carcinoma is suspected pre-operatively in only 20%-30% of all the patients; the other 70%-80% of all the cases are detected intra operatively, or are incidentally discovered by the pathologist [1].

Pre-operative FNAC was sought in patients of the younger stage groups where a radiological suspicion of malignancy existed. The tissue confirmation of adenocarcinoma was available in our study in 12% of the patients. The early stage disease is rarely picked up since the clinical presentation is uncertain [1,4,10,16-18]. In our study, only 3 patients were in stages I and II. The rest (94%) had advanced disease (stages III and IV) at the time of diagnosis.

The key finding was the lymphatic spread of the gall bladder cancer: the cystic, pericholedochal, and the posterosuperior peri-pancreatic nodes. By integrating the image-T factor and the data from the intraoperative examination of the frozen sections of the key lymph nodes, the most accurate staging before the resection may be possible. Based on this staging, the algorithms for the surgical treatment of the gall bladder carcinoma can be planned. These algorithms are useful in patients with up to stage IVa disease. An extended lymph node dissection plus or minus an extended liver resection should be performed in some patients with more advanced disease. However, there was no survival advantage to the more radical procedures, including bile duct resection or pancreaticoduodenectomy [1,8].

Owing to the strong association of gallstones with the disease, attempts should be made to convince the patients regarding the risks which are involved, to ensure an early cholecystectomy, more

so in patients with stones which are larger than 3 cm, who reside in a high-incidence area. A routine histopathological examination of all the cholecystectomy specimens is a must. The decision as to which therapeutic option should be used, depends on whether the carcinoma has been diagnosed pre-operatively, per-operatively or post-operatively, as well as on the stage of the disease – that is, whether it is localized resectable, localized unresectable or advanced disease. Any detection of unsuspected carcinoma in stage I following cholecystectomy needs only a meticulous follow-up. If the disease is detected in stage II, a radical cholecystectomy is required, and beyond this stage, an adjuvant therapy in the form of radiotherapy or chemotherapy or both is required, even though its role is not well elucidated [2,18,19].

The recommended surgical management of the stage I disease is simple cholecystectomy. We had two such patients in our study. Incidental carcinoma was detected in these patients following surgery for chronic cholecystitis by histopathology. The growth was restricted to the mucosa and the submucosa without involvement of the muscle layer. Hence, a simple cholecystectomy in these patients was curative. There was no need for re-exploration for an extended resection and a completion cholecystectomy. Two patients underwent an extended cholecystectomy with liver wedge resection. In the presence of ascites with or without liver metastasis, even the palliation of obstructive jaundice may not be possible [10-18].

The 5 year survival correlates with the staging of the disease at the time of presentation. The survival rates of the disease in stages II, III and IV are approximately 25%, 12%, and 1-2% respectively [10-16]. Among these, 32 patients succumbed to the disease within 6 months. The best prognosis was noted in patients with incidental carcinoma. Overall, the prognosis of the disease remained grim.

It is desirable to search for any factor which can be linked to the gall bladder cancer or that which can help in the diagnosis of the disease in its early stages, thus making a surgical intervention possible and ultimately resulting in a good prognosis. Moreover, to positively affect the outcome of the patients in the advanced stage of the disease, newer cancer treatment strategies need to be adopted.

CONCLUSION

We should accept the fact that gall bladder cancer is a disease with low numbers of patients who are amenable to surgery. Thus, instead of retrospectively analyzing the individual institutional data, high volume institutions with the necessary expertise for treating gall bladder cancer should collaborate with a view to generating a strong evidence to support the different surgical strategies – a move that may provide us with the evidence-based surgical guidelines which we are looking for, to enable us better to tackle this dreadful disease.

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