

RESEARCH ARTICLE

Impact of Routine Histopathological Examination of Gall Bladder Specimens on Early Detection of Malignancy - A Study of 4,115 Cholecystectomy Specimens

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Abstract

Gall bladder carcinoma is the most common cancer of biliary tree, characterized by rapid progression and a very high mortality rate. Detection at an early stage, however, is indicative of a very good prognosis and prolonged survival. The practice of histopathological examination of gall bladder specimens removed for clinically benign conditions and its usefulness has been a subject of controversy. The present prospective study was carried out over a period of four years in order to find out the incidence of unsuspected gallbladder carcinoma in cholecystectomy specimens received in our histopathology laboratory and to analyze their clinico-pathological features. A total of 4,115 cases were examined. Incidentally detected cases comprised 0.44%, which accounted for 72% of all gall bladder carcinomas detected. The majority were in an early, surgically resectable stage. From the results of this study we recommend that in India and other countries with relatively high incidences of gall bladder carcinoma, all cholecystectomy specimens should be submitted to histopathology laboratory, as this is the only means by which malignancies can be detected at an early, potentially curable stage.

Keywords: Gall bladder carcinoma - early detection - incidental detection - routine histopathology

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Introduction

Gall bladder carcinoma is the most common cancer of biliary tree and the 5th most common gastrointestinal malignancy. (Bartlett, 2000; Lam et al., 2005; Shih et al., 2007). It is characterized by rapid progression and very high mortality rate. Early stages of gall bladder carcinoma are usually asymptomatic or symptoms are very similar to those of benign conditions, like chronic cholecystitis. Detection at early stage indicates a very good prognosis and prolonged survival.

The incidence of gall bladder cancer varies by geographic region and racial ethnic group. The highest incidences are reported in Indians, Pakistanis, Chileans, Bolivians, Central Europeans, Israelis, Native Americans and Americans of Mexican origin (Lazcano-Ponce et al., 2001; Randi et al., 2006). India is a highly populated country with a major fraction of population of lower socioeconomic status having less access to proper health facilities, a reason why early stage malignancy may escape detection leading to poor survival.

Necessity of histological examination of all gall bladder specimen removed for clinically and radiologically benign conditions is controversial. Some authors suggest that it should be selective (Darmas et al., 2007; Mittal et

al., 2010), however several studies have confirmed its importance for early detection of this highly aggressive cancer (Hamdani et al., 2012; Mazar et al., 2012). Wang et al. (2012) observed that early diagnosis and timely radical surgery are directly correlated to the prognosis of the patients. Incidental detection of gall bladder cancer in cholecystectomy specimen do has been reported in 0.3-2% of all cholecystectomy performed for benign conditions (Lam et al., 2005; Sun et al 2005; Misra et al., 2006).

With this background, we carried out this study with the following objectives: i) To find out the incidence of gall bladder carcinoma in cholecystectomy specimens received in histopathology laboratory. ii) Clinicopathological analysis of gall bladder carcinoma cases, especially incidentally detected cases.

Materials and Methods

This was a prospective study carried out over a period of four years from January 2009 to December 2012 in the Department of pathology, Hindu Rao Hospital, Delhi.

The surgically resected specimens were fixed in 10% neutral-buffered formalin and embedded in paraffin. For the cases without any gross abnormality, standard 3 sections including fundus, body and neck were taken.

In cases with any growth, irregular mucosa, thickened wall, calcification, necrosis etc more sections were taken. Apart from routine Hematoxylin and Eosin stain special stains like mucicarmine, PAS, Alcian blue and immunohistochemistry were used whenever needed. Gross and microscopic features of all incidentally detected cases were studied in details.

Results

Total 4115 gall bladder specimens were received during the period from January 2009 to December 2012. This included open cholecystectomy, laparoscopic cholecystectomy and partially resected specimens.

As expected, most of the specimens revealed benign pathology, which included chronic calculus cholecystitis (with mild to severe non specific inflammation) and with specific changes like eosinophilic cholecystitis, follicular cholecystitis, xanthogranulomatous cholecystitis, cholesterolosis, etc. Adenomatous hyperplasia, pyloric metaplasia and intestinal metaplasia were frequently noticed, but only one case of tubular adenoma was detected. Three cases of calcified gall bladder were diagnosed, all needed decalcification before processing.

Out of total 4115 cases, 25(0.6%) cases of carcinoma were diagnosed. Eighteen were clinically unsuspected, incidentally detected cases, comprising 0.44% of total clinically benign gall bladder specimens. Clinicopathological features of these cases are given in Table 1. As expected, female predominance (M: F ratio 0.87) was noted. The age of the patients ranged from 35-80 years (mean 54 years). The peak age of presentation was sixth decade followed by fourth decade of life. All were associated with gall stones (mostly multiple).

Among the 25 cases, detailed morphology could be studied only in cases where intact gall bladder specimens were available. Out of such 18 unsuspected carcinoma cases, on gross examination diffuse thickening of the wall was seen in 8 cases and localized growth in the form of nodule or focal thickening was found in 10 cases. Fundus was the most common location (8 cases) followed by body (2 cases).

Mucosal lesions thought to be premalignant (metaplasia, dysplasia) were detected in 8 cases out of 10 localized carcinoma specimens, in and around tumor area. Dysplasia (Figure 1A) was detected with or without metaplasia in 5 cases which ranged from low to high grade. Pyloric metaplasia (Figure 1B) was detected in 4 cases

and intestinal metaplasia (Figure 1C) was detected along with it in 2 cases.

Among all 25 cases, we found adenocarcinoma not otherwise specified (with well, moderate and poor differentiation) in 20 cases, mucin secreting adenocarcinoma in 2 cases, single cases of papillary adenocarcinoma, adenosquamous carcinoma and adenocarcinoma with areas of hepatoid differentiation. Distribution of different histological variants in unsuspected cases is given in Table 2.

On pathological staging, most of the incidentally detected cases were found to be in surgically resectable stages, T2 (10 cases, 56%) and T1b (7 cases, 39%) and Tis (1case, 5%). One case had a positive lymph node dissected from the gall bladder neck. Perineural invasion was seen in 2 cases.

Few cases were of diagnostic challenge, for example, one with marked necrosis, resembling ischemic necrosis (Figure 2A), and one case with marked fibrosis infiltrated by relatively smaller cells resembling inflammatory cells.

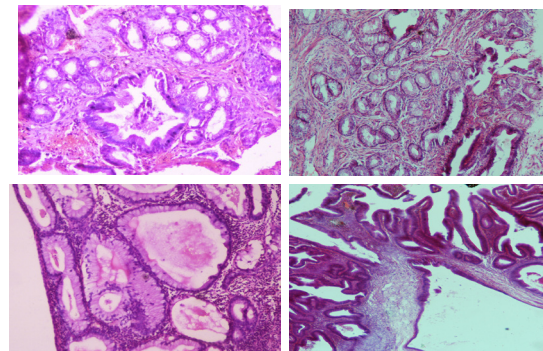


Figure 1. Mucosal Lesions with Malignant Potential. A) Dysplasia, B) Pyloric metaplasia, C) Intestinal metaplasia D) Tubular adenoma, (H&E, x100)

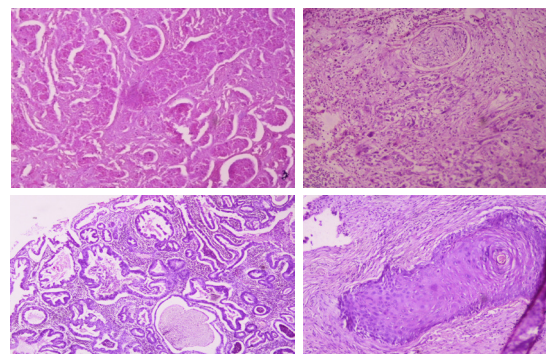


Figure 2. Carcinoma Cases with Diagnostic Challenge. A) Tumor necrosis mimicking ischemic necrosis, B) Small tumor cells resembling inflammatory cells (arrow), C) Adenocarcinoma in situ, exophytic growth and severe dysplasia and, D) Adenosquamous carcinoma showing area of squamous differentiation (H&E, x100)

Table 1. Clinicopathological Features of Incidentally Detected Carcinoma

Clinico-pathological features	Number of cases
Incidence in unsuspected cases	18/4108 (0.44%)
Incidence in total malignancy	18/25 (72%)
Male : female ratio	0.87
Mean age	54 years
Associated with gall stones	18/18 (100%)
Localised growth on gross	10/18 (55.55%)
Fundus as the site of growth	8/10 (80%)
Pre-cancerous lesion	8/10 (80%)

Table 2. Histological Variants of Incidentally Detected Carcinoma

Histological type of carcinoma	Number of cases
Adenocarcinoma NOS type	15/18 (83.3%)
Papillary adenocarcinoma	1/18 (5.5%)
Adenosquamous carcinoma	1/18 (5.5%)
Adenocarcinoma with hepatoid differentiation	1/18 (5.5%)

Table 3. Incidence of Unsuspected Carcinoma in Different Studies

Study	Incidence	Number of cases studied
Tantia et al., 2009	0.59%	3205
Shreshtha et al., 2010	3.30%	668
Mitrovic et al., 2010	0.69%	3007
Mittal et al., 2010	1.00%	1312
Ghimire et al., 2011	1.28%	783
Yi X et al., 2013	0.18%	14073
Our study, 2013	0.44%	4115

(Figure 2B), the case of in situ carcinoma (Figure 2C), and the case of adenosquamous carcinoma with predominance of well differentiated squamous component (Figure 2D). Extensive sampling was needed for confirmation of malignancy.

Discussion

Gall bladder carcinoma has a high mortality rate because of its late presentation, high propensity to metastasize and lack of effective therapy. In the United states, it continues to be a rare cancer and it is thought to be disease of elderly. The scenario is, however, different in India. Here, cancer of gallbladder shows varying geographic distribution. In Delhi, it ranks among the first five common cancers in females (Tyagi et al., 2008).

Many previous studies have shown that incidence of gall bladder carcinoma steadily increases with age, reaching its maximum in 7th decade of life. In our study, mean age was 54 years, with peak (32%) in sixth decade and a significant number (28%) in fourth decade. Similar results were observed in other studies from India (Pandey et al., 2001; Kapoor et al., 2003). Increasing detection rate at early age may be due to increasing awareness and accessibility to health care facilities.

Early stage gall bladder cancer is difficult to detect clinically and radiologically. On ultrasonography (USG) examination, 40-60% cases can be detected only when there is a solid intraluminal mass (Levy et al., 2001). Diffuse wall thickening is a non specific finding as it is seen in chronic inflammatory condition as well. In this study we observed that approximately half of the carcinoma cases had diffusely thickened wall, histologically showing infiltration by malignant cell involving entire gall bladder.

Most of the incidentally detected carcinoma are surgically resectable, with a good survival rate (Mitrovik et al., 2010; Mazer et al., 2012, Yi et al., 2013). This study revealed most of them in pathological T1b and T2 stage. Though simple cholecystectomy is said to be sufficient in stages Tis and T1a carcinomas, radical resection is strongly recommended in stages beyond that. Yi et al. (2013) suggested that the reoperation should be performed as soon as possible, preferably within 10 days after the initial operation. This reflects the importance of histopathological study of all cholecystectomy specimens, irrespective of clinical impression. .

During gross examination of gall bladder, one should look into minute details of the specimen, preferably with magnifying glass and select suspicious areas besides

routine sampling. As we observed in this study, a malignant lesion may present as easily detectable diffuse thickening, nodule or polypoid growth, or sometimes as focal thickening or mild mucosal irregularity which may not be obvious even on gross examination. Wakai et al. (2012) observed that two thirds of early gall bladder carcinoma are superficial, which were subdivided into elevated, flat or depressed macroscopically and majority were detected incidentally. Gall bladder specimen is one of the most frequently received specimens in the histopathology laboratory of any general hospital, so there is always a chance to miss a clinically unsuspected case if one does not pay individualized attention to them.

Histological examination of the tumors revealed findings similar to other studies (Hamdani et al., 2012). Adenocarcinoma not otherwise specified, was found to be most common histological type. Adenosquamous carcinoma and mixed adeno and hepatoid carcinoma were two rare variants also detected as incidental carcinoma in our study.

Underdiagnosis and overdiagnosis –both are not uncommon in gall bladder cancer (Giang et al., 2012). Marked necrosis, extensive fibrosis with few tumor cells, limited invasion with dysplastic glands- are some difficult situations which we encountered especially in unsuspected cases. Such cases are prone to be missed by less experienced observers.

There are two important carcinogenesis models known: the metaplasia-dysplasia-carcinoma sequence and the adenoma-carcinoma sequence. Several studies have reported association between pyloric metaplasia and dysplasia, pyloric metaplasia and cancer and an association between intestinal metaplasia and pyloric metaplasia, dysplasia and cancer (Yamagiwa et al., 1986; Meirelles-costa, 2010). In this study, we observed these changes in and around tumor area, supporting the first hypothesis. Gall bladder adenomas are relatively rare, few studies are available regarding their carcinogenic potential (Lee et al., 2010). In our study, we reported single case of adenoma (Figure 1D) and a case of adenocarcinoma in situ, which appeared to arise from a preexisting adenoma.

Chronic inflammation, infection and gall stones –are currently believed to be the factors leading to malignant transformation of gall bladder epithelium (Hamdani et al., 2012; Wang et al., 2012). Our study also supports association between gall stone and malignancy. Calcification of gall bladder (porcelain gall bladder) is said to be associated 10-25% cases of carcinoma in the literature. In our study, however, we could not find this association, as neither any carcinomatous gall bladder showed calcification and nor the calcified gall bladders showed carcinoma. Stephen et al. (2001) reported that a calcified gallbladder is associated with an increased risk of gallbladder cancer, but at a much lower rate than previously estimated.

The practice of histopathological examination of gall bladder specimens removed for clinically benign condition is subjected to controversy. There is widespread variation in the practice of general surgeons regarding intra operative examination as well as submission of specimens for histopathology, in India and other developing countries

(Samad et al., 2009). There are conflicting reports regarding usefulness of this practice, as the number of incidentally detected carcinoma is not very high (Table 3). In this study, although overall incidence of incidental carcinoma was found to be only 0.44%, they comprised 72% of total gall bladder carcinoma cases, and all of them were in surgically resectable stage. There is no screening method for early detection of gall bladder carcinoma, as routine clinical and radiological examination often fails to detect them. On histopathological examination also, as we have seen, there may be only subtle changes which may be missed by inexperienced and casual observer. Some authors have suggested selective histopathological examination of the cholecystectomy specimens in order to reduce cost, taking account of some parameters like clinical presentation, intraoperative finding etc, but no detailed study has been conducted regarding these parameters so far (Dix et al., 2003; Darmas et al., 2007; Chin et al., 2010; De Zoysa et al., 2010). In our experience, these parameters are not sufficient to differentiate malignant from benign ones.

To conclude, we recommend that in India and other countries with relatively higher incidence of gall bladder carcinoma, all cholecystectomy specimens should be submitted to histopathology laboratory, as gall bladder cancer can be detected at an early, potentially curable stage, only by histopathological examination. Careful and detailed gross as well as microscopic examination of every gall bladder specimen irrespective of clinical impression is required, so that we can detect and nip this highly aggressive tumor in its budding stage.

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