Synchronous Gall Bladder and Bile Duct Cancer: A Short Series of Seven Cases and a Brief Review of Literature

Harshal Rajekar

Centre for Liver and Pancreatic Diseases, Ruby Hall Clinic, Pune 411001, India

Background: Simultaneous presence of cancer in the gall bladder and in the biliary tree could be due to local spread, metastases, *de novo* multifocal origin, or as part of a field change. In the past, such an association has been described in patients with anomalous pancreatobiliary ductal junction. **Aims:** We studied seven consecutive patients with simultaneous gall bladder and bile duct malignancy with a view to identify the best way to treat them, and if possible to hypothesize the etiopathogenesis. **Methods:** Over a period of 24 months, there were seven cases, with synchronous gall bladder and extra-hepatic bile duct cancer. **Results:** None of our patients had anomalous pancreatobiliary ductal junction. Three patients were found to have inoperable disease, three other underwent curative resection, and one patient had a complete response to chemotherapy. Herein, we describe these patients and our lessons learnt from these patients with synchronous bile duct and gall bladder cancer. Of the seven patients, we were able to complete a curative resection in three patients, and the three patients were found to have inoperable disease. One patient had an excellent response to chemotherapy. **Conclusion:** Thus aggressive therapy in such patients with gall bladder cancer may be warranted in select cases. Also, the gall bladder specimens in patients undergoing surgery for cholangiocarcinoma should be analyzed in detail to identify foci of dysplasia or change in the epithelium. The pathogenesis may be due to a common field change in the biliary epithelium. (J CLIN EXP HEPATOL 2017;7:115–120)

Gall bladder cancer occurring at the same time along with cancer of the extra-hepatic bile ducts (cholangiocarcinoma) is a rare occurrence,¹ but increasing reports suggest that this may be more common than previously believed, probably due to inadequate sampling of the gall bladder specimen when resected along with extra-hepatic bile ducts for cholangiocarcinomas. The occurrence is believed to be approximately 5–7.4%^{2–4} in Japan, where abnormal pancreatobiliary ductal junction (APBDJ) is an important association.^{5,6} The possible explanations for such an occurrence could range from the rare synchronous malignancies to local peri-neural, lymphatic or vascular invasion, or to metastasis. This clinical entity may often be confused with metastatic spread from a primary elsewhere in the biliary tree.

Kurosaki et al. and Hori et al. suggested in 2006 that an APBDJ was not required in double cancers on the biliary tract.^{2,7} Extrahepatic biliary cancers are labeled as synchronous based on a multifocal origin. Criteria for defining synchronous primary cancer and differentiating from metastatic disease are still being developed. Gallbladder cancer does not usually follow the adenoma-carcinoma but rather the dysplasia in situ invasive carcinoma sequence.¹ Therefore, it may become possible for two different foci of malignancy to arise within the same dysplastic environment. The entire biliary epithelium is exposed to biliary carcinogens that may arise due to changes in the nature of bile. The theory of field cancerization was described in 1953 by Slaughter et al. for the aerodigestive tract.⁸ The same field cancerization may apply to biliary epithelium, especially in patients with APBDJ. In other patients with double cancers, the cause for a change in the mucosa and dysplasia will need to be investigated. Carcinomas of the pancreas, gallbladder, extrahepatic bile ducts, and ampulla have a common embryonic cellular origin, differentiation pattern, mucosal histology, and population-related tumor development indicating a field effect in those developing malignancy. Also, the genetic profile of these malignancies, p53 mutations, and K-ras mutations are common to gall bladder, biliary, ampullary, and pancreatic cancers. Gemcitabine and the pyrimidine analog 5-fluorouracil have also been shown to be associated with improvement, albeit marginal improvement, in survival in the biliopancreatic cancers. Thus these cancers behave in a similar way, occur

Keywords: gall bladder cancer, cholangiocarcinoma, synchronous, field cancerization, obstructive jaundice, metastasis

Received: 10.06.2016; **Accepted:** 21.10.2016; **Available online:** 21 November 2016

Address for correspondence: Dr. Harshal Rajekar, Consultant Hepatobiliary and Transplant Surgeon, Centre for Liver and Pancreatic Diseases, Ruby Hall Clinic, 1st Floor, Cancer Building, 40, Sassoon Road, Pune 411001, India.

E-mail: harshal_rajekar@yahoo.co.in

Abbreviations: APBDJ: abnormal pancreatobiliary ductal junction; CBD: common bile duct; CT: computerized tomography; PET: positron emission tomography

<http://dx.doi.org/10.1016/j.jceh.2016.10.003>

in the same environment that is exposed to bile, and may share the same genetic origins.

METHODS

Seven consecutive patients with synchronous malignancy of the gall bladder and the extra-hepatic bile ducts were included in this brief review. Five consecutive patients with synchronous gall bladder as well as bile duct malignancy treated at Post-graduate Institute of Medical Education and Research, Chandigarh, and one patient with similar presentation at B.J. Medical College and Sassoon General Hospital, Pune, and one patient treated at Jehangir Hospital, Pune were included in the analysis (Table 1).

Patient Characteristics

Of these seven patients, five were female and two male. Five patients had gall stones, but only two patients had a history of biliary colic. Five patients presented with obstructive jaundice, and two patients were operated without jaundice. Of the five patients with jaundice, one patient presented

as Mirizzi syndrome, and no tumor was detected on pre-op imaging. Four other patients had jaundice. Two patients were diagnosed on pre-operative imaging as cholangiocarcinoma in the common hepatic duct (hilar cholangiocarcinoma, Bismuth type 2 and 3); in whom, the gall bladder cancer was detected at surgery. All the patients underwent pre-operative evaluation with tri-phasic computerized tomography (CT) scan of the abdomen and pelvis, and had a chest X-ray. Positron emission tomography (PET)-scan was not done as a routine in these patients, though one patient had a PET scan done before she was referred to us. CT scan did not demonstrate vascular invasion in any of the patients who were offered primary surgery. One patient was diagnosed to have gall bladder cancer extending to the common hepatic duct, who had a second tumor in the common bile duct (CBD) at surgery. One patient presented with metastatic hilar cholangiocarcinoma with obstructive jaundice, who had a near complete response to chemo-radiation, and subsequently was found to have a T1a malignancy of the fundus of the gall bladder.

The two patients, who presented without jaundice, were a female who was referred for biliary colic, and was found

Table 1 Clinical Profile of all the Patients in the Study.

Sr. no.	Age/sex	Anatomy of double cancer	GSD	APBDJ	Jaundice	Surgery
1.	37 F	Hilar Cholangiocarcinoma + gall bladder lesion (6 mm, discontinuous, near the cystic duct)	—	—	+	Extended cholecystectomy with radical resection of extra-hepatic bile ducts + hepatico-jejunostomy
2.	61 F	Presented with Ca GB, and intra-op detection of 10 mm growth in supra-duodenal CBD (non-obstructing, encasing the portal vein and hepatic artery + celiac nodes)	+	—	—	Inoperable, hence bile duct stented, and referred for palliative chemotherapy
3.	43 M	Operated for Mirizzi syndrome; found to have a 13 mm growth in the GB fundus (pre-op imaging diagnosed at multiple GB calculi) as well as a discontinuous growth in the infra-cystic CBD (hepato-duodenal vessels involved + celiac and aortocaval nodes)	+	—	+	Inoperable. The obstructing stone was removed, and the CBD was stented (patient had a fatal cardiac event on post-op day 2)
4.	63 F	Klatskin tumor (Bismuth type 2) detected to have a discrete 8 mm growth in the fundus of the gall bladder	—	—	+	Extended cholecystectomy with radical resection of the extra-hepatic bile ducts + hepaticojejunostomy.
5.	51 F	Operated for Ca GB, found to have non-obstructing growth in the retro-duodenal CBD, with aortocaval nodes, and celiac nodes	+	—	—	Inoperable, CBD was stented and referred for palliative chemotherapy
6.	55 M	Operated for Ca GB causing obstructive jaundice, found to have a second growth in the retro-duodenal CBD involving the duodenum and pancreatic head	—	—	+	Extended cholecystectomy + pancreato-duodenectomy (Whipple's operation) [fatal cardiac event on post-op day 4]
7.	41 F	Stg 4 cholangio Ca with retroperitoneal nodes. Stent + chemo + radiation—complete radiological response to CT + RT	—	—	+	Cholecystectomy—after CT + RT no residual disease found at Ex-lap. Histology shows T1b cancer at fundus of GB

Clinical details of the patients included in the study. The eventual outcomes and surgery performed are mentioned in the last column.

GSD, gall stone disease; APBDJ, anomalous pancreatobiliary ductal junction; CaGB, carcinoma gall bladder; CT, chemotherapy; RT, radiotherapy; GB, gall bladder; CBD, common bile duct.

to have a polypoidal growth in the neck of the gall bladder. And another woman was diagnosed with a growth in the gall bladder on routine investigational ultrasound for abdominal pain.

Intra-operatively, the first patient was found to have a growth in the supra-duodenal common bile duct with involvement of the hepatic artery, portal vein, and mild dilatation of the proximal biliary tree with partial obstruction of the bile duct. The celiac lymph nodes were involved, the lesion was deemed unresectable, and the bile duct was stented. The other patient with no jaundice was found to have marginally dilated biliary radicles on biliary imaging, and intra-operatively, she was found to have a mass in the supra-duodenal bile duct with invasion into the duodenum. The celiac and superior mesenteric nodes were enlarged and pathologically involved with metastatic cancer. Hence the cancer was unresectable, the bile duct was stented, and the patient was advised palliative chemotherapy.

In three patients, the gall bladder cancer was diagnosed on frozen section, done for suspicious lesion in the gall bladder. Of these, one was the patient with Mirizzi syndrome, who was also found to have a lesion in the distal bile duct encasing the hepatic artery and involving the celiac lymph nodes. The remaining two patients underwent curative resection of the extra-hepatic biliary tree along with an extended cholecystectomy.

One patient had a mass in the gall bladder extending into the liver with peri-hilar lymphadenopathy on pre-operative imaging. The patient was stented pre-operatively to relieve his obstructive jaundice. On exploration, a mass was also palpable in the lower end of the bile duct which on FNAC (Fine needle aspiration cytology) was suggestive of adenocarcinoma. Portal vein, hepatic artery, and celiac nodes were not involved. Thus a combined Whipples with extended cholecystectomy was done for this patient.

Two patients succumbed to post-operative cardiac events on day 2 and day 4, respectively. All other patients had uneventful recovery and were discharged. Mean hospital stay 6.5 days (3–12 days).

There was one female, who was diagnosed with metastatic cholangiocarcinoma, with involvement of celiac, caval, and superior mesenteric nodes on PET-scan. She underwent palliative metal stenting, chemotherapy (gemcitabine and oxaliplatin) and radiation to the hepatic hilum. The seemed to be a complete radiological response with no growth or lymph nodes evident on CT, PET or magnetic resonance imaging scan. Given the rarity of the response to chemotherapy, the patient was explored for residual disease, and no disease was found. All nodes and hepatic hilum were free, and the CBD had no lesion. The gall bladder was removed, which showed a T1a lesion in the fundus of the gall bladder that was away from the cystic duct margin, which was free of tumor. This could be considered a double lesion, though a histology of the cholangiocarcinoma is unavailable.

Thus three patients underwent curative resection. One patient among these died on post-op day-2 due to cardiac event (acute myocardial infarction). Two patients who underwent curative resection are doing well at 18 and 28 months after surgery. Both patients received adjuvant gemcitabine-based chemotherapy. The patient, who received primary chemotherapy and had a complete response, is free of disease at 21 months from diagnosis. One patient, who was stented intra-operatively, refused chemotherapy and is presently asymptomatic with metastatic disease at 18 months after surgery.

DISCUSSION

Synchronously occurring double cancers in the biliary-pancreatic system are rare. Double cancers were thought to be associated with pancreato-biliary mal-junction APBDJ owing to the action of the same carcinogen on the mucosa of the entire extrahepatic biliary tree.^{9,10} In patients without APBDJ, the presence of double tumors poses the question whether differentiation between independent primary cancers has occurred or different cancer foci have metastasized from a single tumor. Two competing hypotheses may be able to explain the pathogenesis of double cancers of the biliary tract: independent primary lesions (multicentric/synchronous) or metastasis of the original cancer. Fujii et al.¹¹ reported that 62.5% of synchronous double cancers of biliary tract and 100% of metachronous double cancers of biliary tract are because of APBDJ. Biliary cancer cases with APBDJ are thought to develop multicentrically, in part owing to the influence of pancreatic juice reflux on the mucosa of the entire biliary tract.^{5,9} Furthermore, Fahim et al.¹² found that biliary tract carcinomas had intraductal spread in only about 4%. The findings of these previous authors suggest that double carcinomas of the biliary tract tend to derive from different primary lesions.

The differentiation between these mechanisms is important since these two mechanistic origins imply different stages of disease, and therefore, a change in treatments and prognoses.

Warren and Gates¹³ and Gertsch et al. have attempted to define synchronous cancers of the biliary tree. Gertsch et al.¹⁴ suggested that the best way to differentiate between synchronous malignancy versus metastatic spread is by applying the following criteria, viz.:

1. No direct continuity between the two tumors,
2. Growth pattern typical of a primary tumor, and...
3. Clear histologic differences between the two tumors.

These criteria, however, may be inadequate to confirm synchronicity, especially, in malignancies of the extra-hepatic biliary tree. Kurosaki et al.² have in fact advised the mapping technique to confirm the distinctness of the two lesions. Over a period of time, the reasons for labeling extra-hepatic biliary cancers as synchronous have been

based on multifocality, that is, the same tumor being multi-focal or arising at many locations and are monoclonal. Whereas a trulysynchronous lesion will have two tumors in the same epithelial milieu with different clonality, i.e. two totally heterogenous tumors (Figure 1).

The reported incidence of p53 mutation is 31–92% in gallbladder carcinoma and 33–73% in bile duct carcinoma.^{15,16} In general, there is a tendency for higher grade carcinomas to express more p53 protein. A statistically significant difference is found for the incidence of p53

Figure 1 Diagrammatic representation to indicate the location of the two tumors ($n = 7$).

protein expression between extrahepatic bile duct carcinomas from the distal portion and those from the lower mid-region. This tendency is the same as that for K-ras mutations, and the effect of APBDJ may override the effect of p53 gene mutations. The p53 gene mutations have been closely associated with determination of clonality. Allelic loss or deletions at the TP53 locus (17p13) reported ranging from 58% to 92% in gallbladder cancer have been noted at histologically, normally appearing epithelium near gallbladder cancer.¹⁷ Pre-neoplastic lesions were identified in 60% of gall bladder cancers with LOH at one or more of the seven genes/loci examined. In all of cases, LOH (Loss of Heterozygosity) was present in the corresponding invasive carcinoma. p53 protein over expression was also detected in the corresponding invasive carcinoma along with corresponding normal mucosa as well as the pre-neoplastic lesions. Thus, in all instances, in which an abnormality was detected in non-neoplastic epithelium, the same abnormality was present in the corresponding normal mucosa.¹⁷

Adenocarcinomas of gallbladder generally arise from a foregut cell lineage via a metaplasia–dysplasia–carcinoma sequence. A background of chronic inflammation increases the frequency of expression of an intestinal goblet-cell phenotype and p53 in the cancers.¹⁸ Intra-epithelial spread may also contribute to multifocality. Though this is known to occur and has been demonstrated pathologically, this has been demonstrated to occur in only 4% of persons with papillary adenocarcinomas.¹²

The biliary tree is exposed to a high volume of concentrated bile, bile salts, and bile acids. Hence, there has to be an effect of the bile on the lining epithelium of the biliary tree and, consequently, on carcinogenesis, since prolonged exposure to bile, especially in higher concentrations, has been shown to have carcinogenic potential.^{19,20} In patients with APBDJ, activated bile and bile salts may be responsible due to mixing with pancreatic juice.⁹ Further evidence of the effect of bile chemistry and the idea of field cancerization has been the detection of high levels of secondary bile acids (with accompanying raised biliary deoxycholates).^{21,22} Though these findings have not been proven beyond doubt, there are factors in the bile that need to be studied further to understand the pathogenesis of gallbladder and biliary cancer.

In the case of field cancerization, the phenotype is a result of a molecular event affecting multiple cells separately and independently of each other, or a single molecular event in a single clonal progenitor that leads to widespread clonal expansion or an alternative means of undergoing lateral spread across the mucosa.

CONCLUSION

Prognosis in such conditions depends on whether the simultaneous lesion is a metastasis or a synchronous one. Metastatic disease, lymph node extension, peri-neural

invasion, and involvement of cystic duct have been shown to be associated with poor prognosis,^{23,24} whereas in the case of synchronous lesions, a fairly good prognosis has been reported if a complete surgical resection of the disease is possible.^{2,10} Taking into consideration the limitations of the present-day options of adjuvant therapy, it is essential that complete removal of the tumor should be the goal in patients capable of withstanding a major resection.

A thorough sampling of the gall bladder may be important in detecting early lesions in patients being operated for extra-hepatic cholangiocarcinomas. We may suggest that all gall bladders resected along with the bile ducts for cholangiocarcinoma should be thoroughly inspected at surgery, and if suspicious lesions are found those should be subject to frozen section examination. If a gall bladder cancer is detected at surgery itself, surgical resection may be tailored accordingly to achieve tumor clearance and curative resection. Gall bladder cancers often present with obstructive jaundice. The presence of biliary obstruction in patients with gallbladder cancer is generally viewed as an indicator of advanced disease, inoperability and poor prognosis.^{25,26} In such cases, the possibility of a double lesion should be kept in mind. If each of the two lesions is resectable, then the patient would benefit from an aggressive surgical approach, and would have a much better prognosis than a gall bladder cancer with obstructive jaundice. It may be useful to have a detailed evaluation of the anatomy of the biliary obstruction as well as the gall bladder lesion. After resection of all gall bladder cancers, as well as surgery for cholangiocarcinomas, the resected gall bladder specimen should be analyzed in detail for the existence of dysplasia, carcinoma in situ and frank micro- macro-invasive cancer. A systematic examination of all gall bladder specimens as described by the College of American Pathologists,²⁷ may be useful to standardize the histological examination of high risk resected gall bladders.

The finding of double cancers more frequently than previously believed may lead one to re-visit the necessity for excision of the extra-hepatic bile ducts along with the gall bladder in patients with gall bladder cancer. One may suggest that all patients with gall bladder cancer should have the specimen examined by frozen section. If peri-neural or lymphatic or vascular emboli are seen, then the patient may benefit from a resection of the extra-hepatic biliary tree. Also patients with a positive cystic duct margin on frozen section, patients with choledochal cysts and patients with APBDJ may benefit from resection of the biliary tree as part of extended cholecystectomy.

CONFLICTS OF INTEREST

The author has none to declare.

REFERENCES

- Shukla PJ, Barreto SG, Shrikhande SV, et al. Simultaneous gallbladder and bile duct cancers: revisiting the pathological possibilities. *HPB (Oxford)*. 2008;10(1):48–53.
- Kurosaki I, Watanabe H, Tsukada K, Hatakeyama K. Synchronous primary tumors of the extrahepatic bile duct and gallbladder. *J Surg Oncol*. 1997;65(August (4)):258–262.
- Kozuka S, Tsubone M, Hachisuka K. Evolution of carcinoma in the extrahepatic bile ducts. *Cancer*. 1984;54(July (1)):65–72.
- Chijiwa K. Synchronous carcinoma of the gallbladder in patients with bile duct carcinoma. *Aust N Z J Surg*. 1993;63(September (9)):690–692.
- Takayashiki T, Miyazaki M, Kato A, et al. Double cancer of gallbladder and bile duct associated with anomalous junction of the pancreaticobiliary ductal system. *Hepatogastroenterology*. 2002;49(January–February (43)):109–112.
- Kasuya K, Nagakawa Y, Matsudo T, et al. p53 gene mutation and p53 protein overexpression in a patient with simultaneous double cancer of the gallbladder and bile duct associated with pancreaticobiliary maljunction. *J Hepatobiliary Pancreat Surg*. 2009;16(3):376–381.
- Hori H, Ajiki T, Fujita T, et al. Double cancer of gall bladder and bile duct not associated with anomalous junction of the pancreaticobiliary duct system. *Jpn J Clin Oncol*. 2006;36(October (10)):638–642.
- Ha PK, Califano JA. The molecular biology of mucosal field cancerization of the head and neck. *Crit Rev Oral Biol Med*. 2003;14:363–369.
- Todani T, Tabuchi K, Watanabe Y, Kobayashi T. Carcinoma arising in the wall of congenital bile duct cysts. *Cancer*. 1979;44:1134–1141.
- Ikoma A, Nakamura N, Miyazaki T, Maeda M. Double cancer of the gallbladder and common bile duct associated with anomalous junction of pancreaticobiliary ductal system. *Surgery*. 1992;111:595–600.
- Fujii T, Kaneko T, Sugimoto H, et al. Metachronous double cancer of the gallbladder and common bile duct. *J Hepatobiliary Pancreat Surg*. 2004;11:280–285.
- Fahim RB, McDonald JR, Richards JC, Ferris DO. Carcinoma of the gallbladder: a study of its modes of spread. *Ann Surg*. 1962;156:114–124.
- Warren S, Gates O. Multiple primary malignant tumors: a survey of the literature and a statistical study. *Am J Cancer*. 1981;16:1358–1414.
- Gertsch P, Thomas P, Baer H, Lerut J, Zimmermann A, Blumgart LH. Multiple tumors of the biliary tract. *Am J Surg*. 1990;159:386–388.
- Shrestha ML, Miyake H, Kikutsuji T, Tashiro S. Prognostic significance of Ki-67 and p53 antigen expression in carcinomas of bile duct and gallbladder. *J Med Invest*. 1998;45(1–4):95–102.
- Rijken AM, Offerhaus GJ, Polak MM, Gouma DJ, van Gulik TM. p53 expression as a prognostic determinant in resected distal bile duct carcinoma. *Eur J Surg Oncol*. 1999;25(3):297–301.
- Wistuba II, Sugio K, Hung J, et al. Allele-specific mutations involved in the pathogenesis of endemic gallbladder carcinoma in Chile. *Cancer Res*. 1995;55(June (12)):2511–2515.
- Hughes NR, Bhathal PS. Adenocarcinoma of gallbladder: an immunohistochemical profile and comparison with cholangiocarcinoma. *J Clin Pathol*. 2013;66(March (3)):212–217.
- Bernstein H, Bernstein C, Payne CM, Dvorakova K, Garewal H. Bile acids as carcinogens in human gastrointestinal cancers. *Mutat Res*. 2005;589(January (1)):47–65.
- Komichi D, Tazuma S, Nishioka T, Hyogo H, Chayama K. Glycochenodeoxycholate plays a carcinogenic role in immortalized mouse cholangiocytes via oxidative DNA damage. *Free Radic Biol Med*. 2005;39(December (11)):1418–1427.
- Shimada K, Chijiwa K, Yanagisawa J, Nakayama F. Biliary bile acids in the gallbladder and the common bile duct of patients with anomalous pancreaticobiliary ductal junction. *J Gastroenterol Hepatol*. 1993;8(March–April (2)):138–141.
- Sugiyama Y, Kobori H, Hakamada K, Seito D, Sasaki M. Altered bile composition in the gallbladder and common bile duct of patients with anomalous pancreaticobiliary ductal junction. *World J Surg*. 2000;24(January (1)):17–20.
- Patel SH, Kooby DA, Staley 3rd CA, Sarmiento JM, Maithel SK. The prognostic importance of lymphovascular invasion in cholangiocarcinoma above the cystic duct: a new selection criterion for adjuvant therapy? *HPB (Oxford)*. 2011;13(September (9)):605–611.
- Kondo S, Takada T, Miyazaki M, et al. Guidelines for the management of biliary tract and ampullary carcinomas: surgical treatment. *J Hepatobiliary Pancreat Surg*. 2008;15(1):41–54.
- Agarwal AK, Mandal S, Singh S, Bhojwani R, Sakhuja P, Uppal R. Biliary obstruction in gall bladder cancer is not sine qua non of inoperability. *Ann Surg Oncol*. 2007;14(October (10)):2831–2837.
- Hawkins WG, DeMatteo RP, Jarnagin WR, Ben-Porat L, Blumgart LH, Fong Y. Jaundice predicts advanced disease and early mortality in patients with gallbladder cancer. *Ann Surg Oncol*. 2004;11(March (3)):310–315.
- Henson DE, Albores-Saavedra J, Compton CC. Protocol for the examination of specimens from patients with carcinomas of the gallbladder, including those showing focal endocrine differentiation: a basis for checklists. Cancer Committee of the College of American Pathologists. *Arch Pathol Lab Med*. 2000;124(January (1)):37–40.