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SYNCHRONOUS AND METACHRONOUS TUMORS OF THE BILIARY TREE.

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Introduction

Biliary tract cancers arise in the biliary tract epithelium and include intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, distal extrahepatic cholangiocarcinoma, and gallbladder cancer. These sites are anatomically contiguous and may appear related, but they are heterogeneous with distinct genetic and molecular signatures. Cholangiocarcinoma is the malignant tumor arising from the epithelium of the biliary tract, first histologically described by Durand-Fardel in 1840. Classification as originating from the intra- and extrahepatic biliary epithelium[1] is a common way of classifying these tumors as prognosis and behavior are different in both types. Extrahepatic cholangiocarcinomas are further separated like the Bismuth classification; into upper-third or perihilar (including the confluence of the right and left biliary ducts) tumors; middle-third tumors; and distal bile duct tumors. Performance of a margin-negative resection with regional lymphadenectomy remains the cornerstone of successful treatment of cholangipcarcinoma. Unfortunately, recurrence is common, even among patients with localized disease who undergo curative-intent resection. Around 50% of recurrences tend to be local within the biliary tree, and the remaining may be regional or distant. About 5% of cholangiocarcinomas may be multifocal[2]. The ultimate outcome is affected tumor histology, tumor locations, grade and stage and treatment technique. Multistep carcinogenesis of cholangiocarcinoma has been well highlighted by Nakanuma[3] . The wo types of precancerous lesions, biliary intraepithelial neoplasia (BilIN) and intraductal papillary neoplasm of the bile duct, may precede the development of many invasive cholangiocarcinomas. Slaughter et al [4] first proposed the concept of “field cancerization” to explain the multicentric

development of head and neck cancer. They proposed that exposure to carcinogens causes precancerous field changes which can progress to invasive cancers with multicentricity [5, 6, 7] .This process of field cancerization appears to be consistent with the multistep hypothesis of carcinogenesis of cancers of the biliary epithelium.

Synchronous gallbladder and malignancies of the bile duct would fall into the same category of cancers in the same epithelial field. Synchronous gall bladder cancer and cholangiocarcinoma are rare[8] ; however, there are increasing reports[9] of such incidences including a report of 7 cases by us. This probably suggests that they are more common than earlier reported, probably due to inadequate sampling of the gall bladder when performing a resection for extrahepatic bile duct malignancies. Their occurrence is seen to be approximately 5–7.4% [10, 11, 12] in Japan, where APBDJ seemed to be an important etiology [13, 14]. This clinical entity is often confused with metastasis from a primary elsewhere in the biliary tree.

Gertsch et al [15]. have suggested that the best way to differentiate these two entities is by applying the following criteria,

viz.:

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

These criteria, however, may not be sufficient to confirm synchronicity, especially in malignancies of the extrahepatic biliary tree. Kurosaki et al.[8] have in fact advised the mapping technique to confirm the distinctness of the two lesions.

PATHOGENESIS

Extrahepatic biliary cancers seemed to have a multifocal origin and so are labeled as synchronous cancers. Criteria for differentiating a synchronous primary cancer versus metastatic disease are still unclear and much progress needs to be done. Since early in the year 2000, the reasons for labeling extrahepatic biliary cancers as synchronous seemed to be based on a multifocal origin. Gallbladder cancer does not seem to follow the adenoma-carcinoma but rather the dysplasia in situ invasive carcinoma sequence.[16, 17] 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, or all other factors that the local biliary environment permits.

Intra-epithelial spread of cancer is known to occur and whether it contributes to multifocality is unproven. However, this has been demonstrated to occur in about 4% of papillary adenocarcinomas.[18] 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.

The etiopathogenesis of cholangiocarcinomas may in itself give an idea of the predisposition to field changes. 90% of patients diagnosed with cholangiocarcinoma in non-south east Asian countries do not have any risk factors. However, the remaining 10% of cases are associated with certain risk factors. Apart from factors related to chronic inflammation, both intra- and extrahepatic cholangiocarcinomas are common in primary sclerosing cholangitis . Other known risk factors include obesity, hepatolithiasis, bacterial infection, and/or bile stasis-related chronic cholangitis [19, 20 , 21] .

The tissue adjacent to the malignancy has various morphological and genetic changes that probably compete with field cancerization in promoting cancerous changes in the adjacent epithelium. Molecular aberrations in normal tumor adjacent tissues are seen as compared to normal tissues. This is hypothesized to be caused by field cancerization or microenvironment alterations influenced by the tumor [22] . The regions immediately surrounding tumors have many morphologic and phenotypic distinctions from non-tumor-bearing healthy tissue, including pH levels [23], allelic imbalance and telomere length[24], stromal behavior, and transcriptomic and epigenetic aberrations [25].

The mutation rates of K-ras, p53, and p16 were found to be 20.0, 35.7, and 30.7%, respectively, in gall bladder cancers by Kim et al in 2001. However, no mutations were found in dysplasia or adenoma. [26] In patients with biliary cancer, accumulation of p53 protein was detected in 50%. K-ras mutations were detected in 33% by Ahrendt et al and the overall survival in patients

with p53-negative tumors was significantly longer than that in patients with p53-positive (mutant) tumors. Various genomic analyses of driver mutations or other molecular alterations (such as KRAS, IDH1/2, FGFR2 fusions, BRAF, and MSI) have been well described[27]. Not only have distinct genomic patterns been described for tumors of specific anatomic sites, but there is also substantial genomic heterogeneity within GBC and CCA, which increases the challenge of designing meaningful clinical trials. In cholangiocarcinomas, miR-21, miR-31, and miR-223 were found to be over-expressed, whereas miR-122, miR-145, miR-200c, miR-221, and miR-222 were down-regulated, but no correlation with clinicopathological features was found[28].

It is clear that we must understand the many different ways in which cancer cells interact with their immediate, local, and remote environments if we are to understand how tumors form and thrive. This is vital for effective treatment, especially surgical and loco-regional therapies, and prevention strategies. In the recent past, several researchers have investigated gene expression profiles of tumors' surroundings, but the biological significance of these findings remains poorly understood. Several cancer development theories can explain this widespread epithelial field pre-cancerous change predisposition. Cancer often arises in the context of prolonged inflammation. The "wound that never heals" theory[29], which implies that cellular and biochemical processes associated with wound healing are similar to those involved in the growth and development of tumor stroma, strongly coincide with the theory of tumor adjacent phenotypical and genotypical changes. Tumor and environment interaction may also produce changes that in the surrounding tissue to promote tumorigenesis, tumor propagation and metastasis. Tumor hypoxia, for example, may be responsible for the expression of many different factors that induce mucosal transformation and epithelial change, and neo-vessel formation. One such factor is HB-EGF, whose expression in tumors is associated with activation of changes in the tumor adjacent tissues[30] . Some researchers have suggested that secretion of this and other factors by the tumor activates a cascade of transcription factors and enzymes associated with the induction of TNF-α and TGF-β signaling pathways, which, in turn, are prominent inducers of tumorigenesis, and are strongly activated in the adjacent endothelium. The field cancerization theory, on the other hand, implies an evolutionary process that results in the phenotypical change in the epithelium prior to frank tumorigenesis.

CAUSES/ ETIOLOGY

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. Risk factors for the development of cholangiocarcinoma include:

- APBDJ – abnormal pancreato-biliary duct junc tion.
- parasitic infections,
- primary sclerosing cholangitis,
- choledochal cysts,
- hepatolithiasis, and
- toxins.[31]

Bile duct cancer develops often after hepatico-enterostomy. The development of cholangiocarcinoma can also occur after biliary enteric anastomoses. Tocchi et al. reported a rate of 5.5 %, where 55 out of 1000 cases developed cholangiocarcinoma after biliary enteric anastomoses for benign pathologies [32] . There have been 31 cases of cholangiocarcinoma occurring after resection of choledochal cyst reported in the literature.

APBDJ

Anomalous pancreaticobiliary ductal junction (APBDJ) junction without congenital choledochal cyst is a risk factor for hepatobiliary malignancies and is defined as the abnormal junction of the pancreatic duct and common bile duct that occurs outside the duodenal wall to form a long common channel (>15 mm). Kimura et al. has proposed a classification system for APBDJ where type 1 is defined as the pancreatic duct joined to the common bile duct (as the main duct) and type 2 is defined as the common bile duct joined to the pan-creatic duct (as the main duct) [33]. While synchronous gallbladder and biliary tree cancers have been reported between 5 and 7.4 % of cases, occurrence of metachronous cancers has been rarely reported for extrahepatic bile duct cancers[34]. Double cancers were

thought to be associated with APBDJ owing to the action of the same carcinogen on the mucosa of the entire extrahepatic biliary tree[35] 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. 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[36]. Furthermore, Fahim et al[37]. 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 biliary tree is almost exclusively exposed to 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. This has been noted in patients with APBDJ. Findings that further strengthen the opinion of bile chemistry and the idea of field cancerization have been the detection of high levels of secondary bile acids (with accompanying raised biliary deoxycholates)[38] and heavy metals as contaminants (metallothionein)[39] in the bile of patients with gallbladder cancer. While it may be argued that these findings, especially the former, have not stood the test of time, there are factors in the bile that need to be studied further if we are to understand the pathogenesis of gallbladder and biliary cancer. With APBDJ and with bilio-enteric anastomoses, some have postulated that carcinogenesis is caused by repeated damage of the biliary epithelium by reflux of pancreatic enzymes, early activation of pancreatic enzymes, activity of bile itself, secondary bile salts as well as bacterial contamination which leads to mucosal metaplasia [40].

PARASITIC INFESTATIONS

Two parasites are commonly incriminated as predisposing to cholangiocarcinomas. One is Opisthorchis verrini, which is found in Southeast Asian countries, including Thailand, Lao People's Democratic Republic, Vietnam, and Cambodia. The other is Clonorchis sinensis, which is common in rural areas of Korea and China.

Mechanical injury from the activities of feeding and migrating flukes contributes to biliary damage in the human host. Both oral and ventral suckers of the fluke hook onto the biliary epithelium, resulting in tissue damage even early in infection[41]. As the parasite matures, the lesion becomes more pronounced and ulcerates. Fluke eggs become entrapped in the periductal tissue through the ulcer and induce granulomatous inflammation around the eggs. The granulomata are generally readily visualized in experimental animal infections and occasionally in human cases with bile duct obstruction. The liver fluke secretes or excretes metabolic products, some of which are highly immunogenic, from the tegument and excretory openings into the bile or culture medium in vitro[42],[43]. Apart from inducing host immune responses, the metabolic products themselves may be toxic to or interact with the biliary epithelium. There have been studies that clearly indicate that metabolic products of Opisthorchis contain mitogen-like activity and can induce cell proliferation. This is in agreement with earlier findings of hyperplasia of biliary epithelial cells in opisthorchiasis[44]. Biliary cell damage induced by O. viverrini likely also stems from the actions of oxygen derived free radicals such as nitric oxide (NO) released from effector cells activated by inflammatory cytokines[45,46]. These radicals can induce oxidative DNA damage to the infected biliary epithelium. Moreover, excess NO and other reactive oxygen intermediates produced by inflammatory cells during infection might exert direct cytotoxic and mutagenic effects and cause increased cell proliferation. Marked infiltration of inflammatory cells at the periportal areas of infected hamster liver was associated with the presence of parasite antigens in the bile duct epithelium as detected by immunohistochemistry. Small bile ducts, the first-order ducts (where flukes do not reside because the diameter of the ducts is too small), were also positive for O. viverrini antigens and were markedly inflamed[44]. Opisthorchis antigens were also observed in macrophages, epithelioid cells, and giant cells of the granuloma. NO not only induces DNA damage but has been reported to mediate DNA repair inhibition[47]. Moreover, NO has also been demonstrated to inhibit apoptosis downstream of cytochrome c[48]. All of these manifestations facilitate carcinogenesis. During liver

fluke infection, inflammation, periductal fibrosis, and proliferative responses, including epithelial hyperplasia, goblet cell metaplasia, and adenomatous hyperplasia, may represent predisposing lesions that enhance susceptibility of DNA to carcinogens. Since the entire biliary epithelium is affected, synchronous or metachronous foci of dysplasia re seen which may predispose to multiple primary cancers. However, the risk of developing malignant neoplasia is definitely reduced after successful medical therapy.

PRIMARY SCLEROSING CHOLANGITIS

Cholangiocarcinoma is the most common malignancy in patients with primary sclerosing cholangitis (PSC) and carries a high rate of mortality. Although the pathogenesis of bile duct cancer in PSC is largely unknown, inflammation-driven carcinogenesis concomitant with various genetic and epigenetic abnormalities are underlying factors. The majority of malignancies develop from a dominant stricture, which is defined as a stricture with a diameter < 1.5 mm in the common bile duct or < 1.0 mm in the hepatic duct. In PSC patients this often presents as an abrupt aggravation of jaundice, pain, fatigue, pruritus, weight loss, or worsening liver biochemistries. The risk of cholangiocarcinoma in PSC is approximately 160- to 400-fold greater than in the general population.[49 , 50]

Development of cholangiocarcinoma in PSC is considered to develop through a multistep process involving preneoplastic multifocal lesions, where a sequence of inflammatory epithelial damage and biliary metaplasia, low-grade dysplasia and high-grade dysplasia eventually leads to development of cancer.[51] In a study evaluating 100 formalin-fixed PSC liver explants (including 30 with PSC and cholangiocarcinoma), livers harboring cholangiocarcinoma more frequently showed the presence of biliary dysplasia of any grade (83% vs 36%, P < 0.0001) and high grade dysplasia (60% vs 11%, P < 0.0001) than PSC livers without cancer, supporting an association between the presence of biliary dysplasia and the development of cancer in PSC. In the same study, presence of both biliary metaplasia, presence of dysplasia significantly predicted bile duct cancer, suggesting that PSC-cholangiocarcinoma develops through a sequence of gradually accentuating biliary dysplasia. Although there have been reports of a dysplasia-carcinoma sequence in PSC, the characteristics of pre-malignant lesions and prevalence of biliary dysplasia in PSC is incompletely understood[52, 53 ,54]. These facts result in several different questions for the clinician caring for the PSC patient. Chronic inflammation facilitates oncogenesis via induction of DNA damage, promotion of cellular proliferation, and inhibition of apoptosis. For example, inflammatory cytokines activate inducible nitric oxide (iNOS) with excess production of nitric oxide (NO) and consequent nitrosative stress[55]. iNOS is not present in normal biliary epithelia but its expression has been demonstrated in PSC as well as in cholangiocarcinoma. NO inhibits 8-oxodeoxyguanine base excision DNA repair processes with resultant accumulation of this oxidative lesion in PSC. The failure to repair 8-oxodeoxyguanine is mutagenic and fosters cancer development and progression. Thus, NO has an integral role in mediating DNA damage in biliary tract inflammation and carcinogenesis[56] .

Cholestasis occurring in the setting of PSC also confers an enhanced risk of the development of malignancy. Bile acids activate receptor tyrosine kinases such as epidermal growth factor receptor (EGFR). Sustained activation of EGFR in cholangiocarcinoma mediates proliferation and induces expression of cyclooxygenase-2 (COX-2) via a mitogen-activated protein kinase (MAPK)-dependent mechanism[57,58]. Stabilization of COX-2 expression by oxysterols has been implicated in the genesis and promotion of biliary cancer. Oxysterols also serve as activators of the hedgehog signaling pathway, a developmental pathway implicated in CCA development[59].

Biliary transduction of constitutively active Akt and yes-associated protein (YAP) coupled with lobar bile duct ligation and systemic interleukin (IL)-33 administration probably results in the development of malignancy in the biliary tree [60].

Li et al found that IL-33 promotes downstream activation of IL-6 signaling. IL-33, an IL-1 family member, is a known biliary mitogen, which promotes inflammation and fibrosis in the biliary tract[61].

HEPATOLITHIASIS

Hepatolithiasis is characterized by the presence of stones within the intrahepatic bile ducts proximal to the right and left hepatic ducts. Hepatolithiasis is rare in Western countries, and the incidence is higher in East Asia and south east Asian countries[62,63]. Parasitic infestation has often been thought to be a major cause of hepatolithiasis and infestation, as parasites have been detected in up to 30% of patients with

hepatolithiasis. In Eastern countries, the persistent prevalence of hepatolithiasis in Korea and the relatively high prevalence in Taiwan may be due to cultural trends of ingesting raw freshwater fish infected with Clonorchis sinensis[64]. The association between hepatolithiasis and cholangiocarcinoma has been well-documented, and many studies on the development of caner in hepatolithiasis have been published[65] .

Shoda et al have found that enhanced inflammatory cytokine-induced phospholipase A2, cyclooxygenase-2 (COX-2) and COX-2-derived prostaglandin E2 (PGE2) synthesis in the bile ducts are related to the initiation and propagation of inflammatory changes in hepatolithiasis[66] .

In terms of the biliary mucin molecules, an increase in acidic mucins, such as sulfomucins and sialomucins, in hepatolithiasis reduces pH in the bile and leads to precipitation of calcium bilirubinate in the bile ducts[67] . Recurrent cholangitis, biliary stricture, bile stasis, and chronic bacterial infection are common problems in hepatolithiasis patients, even after multimodal treatment. These recurrent or chronic inflammatory events cause prolonged inflammation of the bile duct epithelium and can lead to the development of cholangiocarcinoma[68]. The main morphologic feature of stone-containing bile ducts in hepatolithiasis is chronic proliferative cholangitis and peribiliary glands proliferation, in which the epithelial lining becomes hyperplastic. Chronic in-flammation can cause epithelial cell proliferation, and this may increase the rate of cellular DNA synthesis and the subsequent production of mutagens coupled with a compromised cellular repair function[69 70]. If these processes are sustained for a long period of time, they may cause the multiple molecular changes necessary to trigger the development of malignancy. During histologic exam by choledochoscopy using percutaneous transhepatic cholangioscopic lithotripsy (PTCSL), atypical epithelial hyperplasia and dysplasia are frequently recognized[71]. Chen et al reported that intraductal papillary neoplasia was found in 30% of patients with hepatolithiasis and displayed a histologic spectrum from papillary growth with dysplasia to carcinoma[72].

CHOLEDOCHAL CYST

Choledochal cysts are biliary cystic dilatations, which may occur at a single site in different particular sites in the bile duct or affecting multiple sites throughout the bile ducts. Many researchers have proposed different theories to explain the development of malignancy in choledochal cysts.

Bile-duct cysts are thought to develop from an abnormal pancreatico-biliary junction (APBDJ), in which the pancreatic and biliary ducts join outside the duodenum and are typically associated with a long common channel (>10 mm). This results in pancreatic enzymes refluxing into the biliary system with subsequent increased intraductal pressure and inflammation, leading to ductal dilatation[73] It has been postulated that the reflux of pancreatic enzymes, bile stasis, and increased concentration of intraductal bile acids contribute to chronic inflammation and hyperplastic change, contributing to the formation of malignant cells in patients with bile-duct cysts[74]. Probably the same etio-pathological process contributes to the development of malignancy in choledochal cysts; as is postulated in patients with APBDJ.

DISCUSSION

As above, all causes pre-disposing to the development of bile duct cancer, result in anatomical or physiological changes in the area of the biliary epithelium. Changes in the environment affecting the whole field, will probably result in widespread changes in the biliary epithelium and probably also gall bladder epithelium. Many, if not most cancers develop from a precancerous lesion through the accumulation of various genetic errors[75,76,77]. The TP53 tumor suppressor gene is a common target of genetic alteration, accounting for more than half of known human tumors [78] . TP53 is involved in central cellular processes, including gene transcription, DNA repair, cell cycling, genomic stability, apoptosis, and chromosomal segregation[79].However, the frequency of TP53 alterations are significantly different in different types of human cancers. TP53 mutant allele is frequently detected in pancreatic, colorectal, and breast cancers as well as in bone and soft-tissue sarcomas, whereas it is very uncommon in leukemia and gastric cancer[80,81]. In bile duct cancer, the prevalence of immunohistochemical detection of p53 has been reported to range from
19-86% [82] . Many factors may contribute to this broad range, such as different carcinogens within different cancer pandemic areas, antibodies used, and criteria applied. Such mutations may arise from chronic inflammation, epithelial hyperplasia and subsequent metaplasia and dysplasia. Since the factors causing a predisposition to cholangiocarcinoma affect the entire

biliary epithelium, we can expect the entire field of biliary epithelium to be exposed to the same risk of developing cancer. So the theory of field cancerization holds true and the development of double cancers, synchronous or metachronous is not surprising.

TREATMENT

Clinicopathological analysis has revealed that multicentric adenocarcinomas of the biliary tract have distinct features compared with other single cancers. Pathologically, multicentric adenocarcinomas were more likely to be papillary adenocarcinomas and early cancers and were less likely to have lymph node metastasis than single cancers. Because the bile duct is a narrow passage, any tumor is likely to cause obstruction and therefore most patients may develop early symptoms. However, due to the rich lymphatics and blood supply, lymph node metastasis tends to occur early. The presence of double tumors increases the likelihood of the tumor being detected early, and so each tumor may be detected at an earlier stage.

It is also noteworthy that most of the multicentric cancers are usually associated with superficial epithelial tumor spread and extensive dysplastic epithelium around the tumor[83]. Rougemont et al. reported a case of multifocal early intrahepatic cholangiocarcinoma in extensive biliary dysplasia[84]. Extensive dysplasia in the background biliary epithelium suggests that multicentric adenocarcinomas might arise from the carcinogenetic background epithelial dysplasia. These multicentric cancer cases were consistent with the proposition that cholangiocarcinomas develop with a multistep progression from low-grade biliary intraepithelial dysplasia to high-grade dysplasia and carcino-ma in situ[85,78]. Long-term outcomes of multicentric cancers were also very unique. Long-term survival can be expected after surgery in patients with multicentric biliary adenocarcinoma. Surgical indications for even metachronous lesions can be the same as for single lesions because multicentric cancers are likely to be early cancers without lymph node metastasis. Previous reports have demonstrated initial experiences of safety after aggressive repeated resection for metachronous cancer of the biliary tract. Repeated resection for metachronous lesions might improve survival of those patients[86,87,88,89]. Careful perioperative management is essential for reoperations. Further case accumulation is necessary to clarify the safety and efficacy of repeated resection for metachronous cancer. Further observation is necessary to draw a firm conclusion, especially regarding the safety and effectiveness of aggressive resection of synchronous cancers, and for repeated resection for metachronous lesions of the remnant bile duct. Multicentric adenocarcinomas can develop remnant bile duct recurrence (or tertiary cancer) despite R0 resection. Close and longterm follow-up of patients with multicentric cancer and early papillary cancer is very important for early detection of metachronous lesions. Since multicentric cancer is likely to be early cancer without lymph node metastasis, aggressive repeated resection of the metachronous lesions might improve survival of patients with multicentric adenocarcinoma of the biliary tract. Careful perioperative management is essential for reoperations. Most of these operations involve a pancreatico-duodenectomy, or a liver resection or both. Long-term survival can be expected after surgery in patients with multicentric biliary adenocarcinoma. Considering recurrence, remnant bile duct recurrence has been reported in a patient with synchronous multicentric cancer despite R0 resection [84]. This recurrence might be considered to be metachronous tertiary cancer even though it developed within 2 years after the prior surgery.

Surgical indications for metachronous lesions can be the same as for single lesions because multicentric cancers are likely to be early cancers without lymph node metastasis. Previous reports have demonstrated initial experiences of safety after aggressive and repeat resection for metachronous cancer of the biliary tract[87,89,90]. Repeated resection for metachronous lesions might improve survival of those patients. However, reoperation is technically demanding because initial surgery is likely to be pancreaticoduodenectomy or major hepatectomy with biliary reconstruction.

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