REVIEW ARTICLE

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Basic Surgical Pathology of Perihilar Cholangiocarcinoma: Bridging Knowledge for Surgical Practice

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ABSTRACT

Perihilar cholangiocarcinoma (PCC) is a devastating disease with poor prognosis. Surgical resection remains a first-line therapy in patients with PCC, and the primary goal is to gain a tumor-free surgical margin. However, surgical margins are sometimes involved after curative intent surgery even now, which is plausibly explained by the fact that there is a potential gap between the extent of radiologic tumor staging and that of histologic cancer invasion. It is known that cancer cells of cholangiocarcinoma invade the surrounding area beyond the gross tumor border. The length is limited within 1 cm for invasive cancer and 2 cm for carcinoma in situ (CIS) in most cases of cholangiocarcinoma. Although this finding guides the ductal margin length, it is often difficult to obtain a satisfactory length, especially in the proximal direction for PCC. Therefore, pathological assessment with frozen sections of the ductal stump is widely used to confirm the ductal margin status. A positive ductal margin with CIS, unlike one with invasive cancer, is a mild prognostic factor, so it works negatively only in patients with an early-staged tumor who are expecting a prolonged survival. The present review article provides an overview on the growing knowledge about the surgical pathology of cholangiocarcinoma.

Key words: cholangiocarcinoma, perihilar cholangiocarcinoma, surgical pathology, and surgical margin

INTRODUCTION

Surgical resection remains a first-line therapy in patients with perihilar cholangiocarcinoma (PCC), and the primary goal is to gain tumor-free surgical margins (R0 resection). Although most HBP surgeons as well as radiologists assess the extent of biliary and vascular invasion to plan an optimal surgical procedure, the diagnostic accuracy is not satisfactory with the leading-edge imaging modalities (1-3). Unfortunately, some patients will have a positive surgical margin after curative-intent resection (4). One plausible explanation for this surgical failure is that there is a potential gap between the radiologic tumor staging and the actual extent of histologic cancer infiltration.

Since the first surgery for PCC was performed at our clinic in 1977, we have

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consistently researched surgical anatomy, technique, pathology, and oncology-specific findings related to cholangiocarcinoma. The findings gained throughout the studies have refined our daily practice for this complicated disease (4). To our best knowledge, there are no reviews focusing on surgical pathology for surgical application.

Clinical definition of PCC

Based on the Johns Hopkins classification for cholangiocarcinomas (5), PCCs are defined as cholangiocarcinomas that involve the hepatic duct bifurcation or require its resection. Because the boundary between the intrahepatic and extrahepatic bile ducts is often unclear, PCCs are potentially composed of two types of tumors. One is an "extra-hepatic" type, which arises from the large hilar bile duct, and the other is an "intrahepatic" type, which has a significant hepatic component and involves the bile duct of the hepatic hilum. These two types of tumor exhibit the same clinical presentation, demonstrate similar radiological features, require an identical surgical intervention, have comparable histological characteristics, and show similar survival rates (6). These two tumors overlap considerably, as previously suggested by Klatskin in 1969 (7). Therefore, clinically, both tumors should be treated as PCC (5, 6), and this definition has been adopted in the AJCC cancer staging manual (8). Thus, the perihilar tumor category is not a pathological entity, but rather is a practical disease entity that includes extrahepatic and intrahepatic cholangiocarcinomas.

Recently, a Japanese group (9) proposed a more specific definition. PCCs are defined as cholangiocarcinomas that involve the perihilar bile duct (the duct located topologically between the right side of the umbilical portion of the left portal vein and the left side of the origin of the right posterior portal vein); for tumors with a significant live mass, the center is located between the portal landmarks described above (*fig. 1*). This definition has a major characteristic in that the portal system is used as a referential landmark to determine tumor location. In other words, the definition does not require an estimation of the resectional procedure. Therefore, this feature enables radiological diagnosis in unresectable disease and facilitates application by physicians and radiologists in a multidisciplinary team.

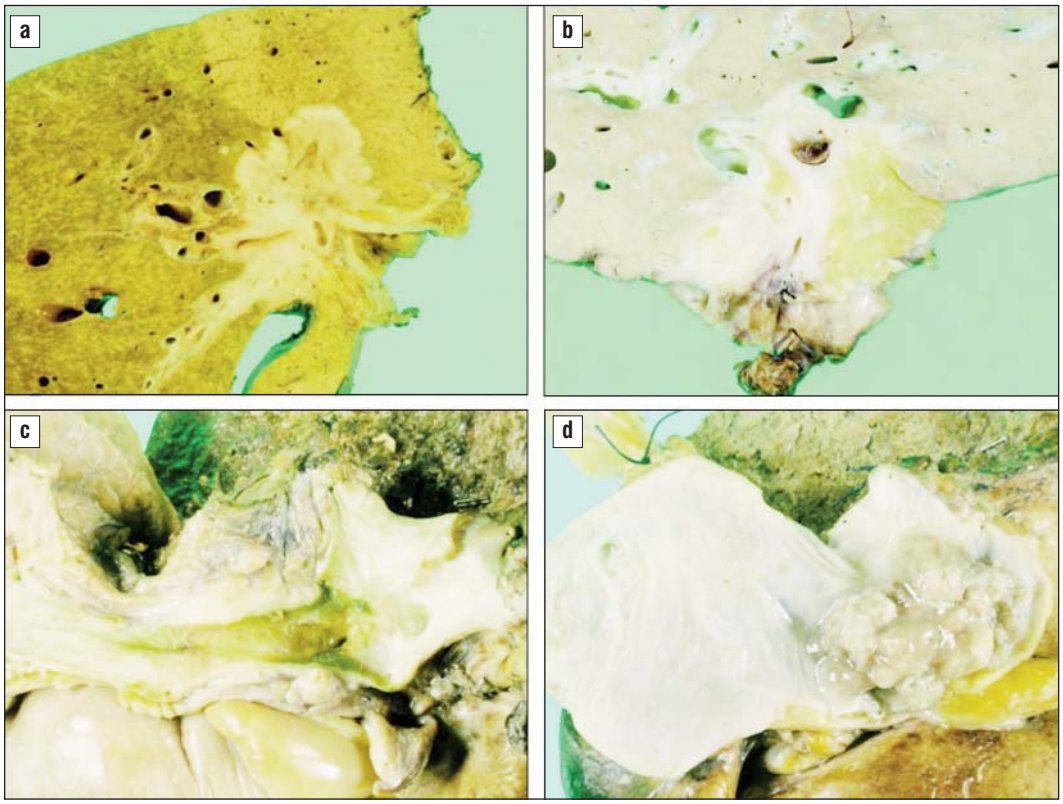

Figure 1 - Gross morphology of perihilar cholangiocarcinoma. All these tumors are classified in the perihilar category because the center of the stricture/mass is located adjacent to the hepatic hilus. Mass-forming tumor (a); periductal-infiltrating tumor (b); nodular - sclerosing tumor to nodular-sclerosing (c); papillary tumor (d)

Optimal surgical margin of the bile duct

The cancer cells of cholangiocarcinomas microscopically infiltrate the surrounding duct beyond the extent of a macroscopic tumor (10, 11), and such unexpected tumor extensions can be histologically classified into carcinoma in situ (CIS) and invasive cancer (*fig. 2*). This histological feature in cholangiocarcinoma often leads to failure in surgery, leaving a positive ductal margin at an incidence of 6% to 16% for CIS and 8% to 21% for invasive cancer (12-18). One pathologic study (10) treating 253 patients with cholangiocarcinoma demonstrated an inverse correlation between the length of the proximal ductal margin and margin positivity (*fig. 3*). The length of microscopic invasive cancer and CIS was limited to within 1 cm and 2 cm, respectively, from the gross tumor border in approximately 90% of cases of cholangiocarcinomas (10). This observation clearly guides the optimal resection line of the bile duct so that '1 cm and 2 cm tumor-free margins' are recommended for the eradication of unexpected invasive cancer and CIS, respectively.

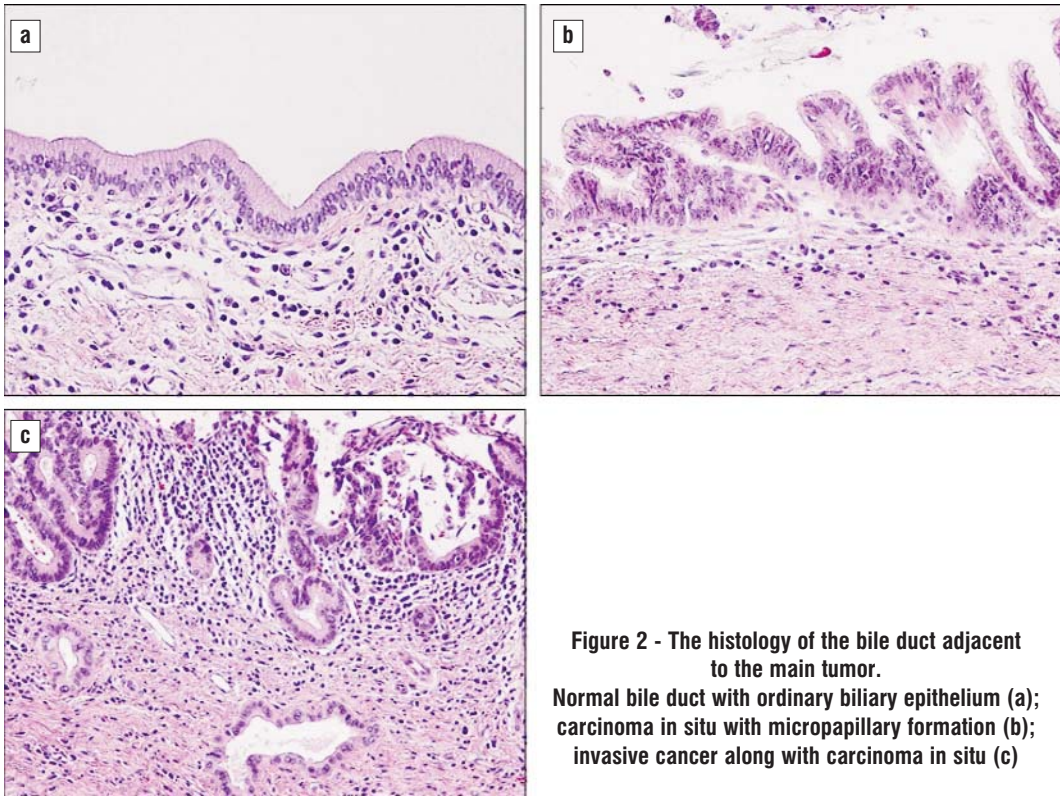

Figure 2 - The histology of the bile duct adjacent to the main tumor.
Normal bile duct with ordinary biliary epithelium (a); carcinoma in situ with micropapillary formation (b); invasive cancer along with carcinoma in situ (c)

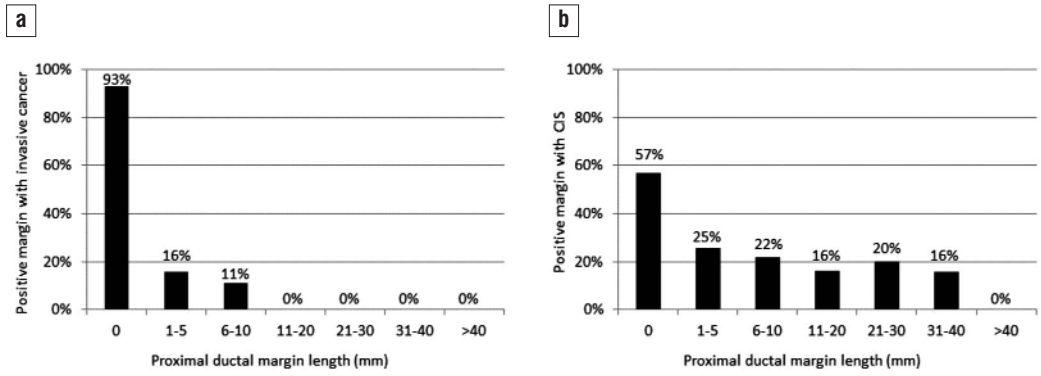

Figure 3 - Inverse correlation between ductal margin length and positive margin rate.
Narrow margin length carries a risk of a positive ductal margin (10).
Invasive cancer (a) and carcinoma in situ (CIS) (b)

In PCCs, however, it is often difficult to obtain a satisfactory margin length that meets the above requirement, especially in the proximal (hepatic) direction. Therefore, a proximal resection line of the bile duct should be set at the farthest proximal point that is technically possible, and pathological assessment with frozen sections of the ductal stump is recommended to confirm the ductal margin status.

Impact of positive ductal margin

Although the ductal margin status is generally dichotomized into a negative or positive margin (8), the latter can be further divided into a positive margin with CIS and that with invasive cancer. Wakai et al (12), followed by several Japanese investigators, (13-18) studied the relation between the ductal margin status and survival. They observed that the survival rate for patients with a positive ductal margin with CIS was comparable to that for patients with a negative ductal margin. Residual CIS, unlike invasive cancer, does not have a significant negative impact on survival. However, we sometimes experience that CIS residue steadily and insidiously progresses to an anastomotic tumor mass over time (12, 14, 19), suggesting that it has a slow-growing nature. Tsukahara et al (20) first demonstrated the nature of the residual CIS at the margin in early-staged (pT0-2pN0) cholangiocarcinomas. The cumulative incidence of local recurrence in this setting was 33% at 5 years, which was higher than that of 4% after R0 resection. Survival for patients with CIS residue was worse than for those without: 35% vs 79% at 5 years (P=0.005). CIS residue was the single independent predictor of survival by multivariate analysis. Thus, a positive ductal margin with CIS is a less severe prognostic factor so that it works negatively only in patients with an early-staged tumor who are expected to have a prolonged survival.

When the ductal margin is positive by intraoperative frozen section diagnosis, surgeons should consider the histology of the involved cancer cells, namely, invasive cancer or CIS. The following should be considered when making a subsequent decision during surgery. First, nodal metastasis, poor histological grade, major vascular invasion, and positive surgical margins with invasive cancer (6, 9, 21-23) had a greater prognostic impact than CIS residue. Among the strong predictors, nodal involvement is observed most frequently (~50% of patients) (13, 21, 23). Therefore, nodal status should be confirmed during surgery by extensive sampling of lymph nodes. Second, additional resection of >5 mm of the proximal duct is practically difficult after maximal or near-maximal resection of the duct. Such limited resection of a margin-positive proximal duct does not improve survival, even when a negative margin can be achieved after additional resection (24). The clinical value of additional resection of the proximal duct in PCC might be limited.

Specific types of cholangiocarcinoma that are difficult to treat surgically

There are two specific tumor types that are difficult to manage (*fig. 4*). One is 'superficial spreading cholangiocarcinoma' (11, 13, 25), which is defined as cholangiocarcinoma with a CIS extension longer than 2 cm. The length of the superficial spread averages 54 mm (13), suggesting that this tumor often requires extensive resection to obtain a negative ductal margin. Superficial spreading-type tumors are also characterized by a papillary or expansile tumor configuration, a papillary or well-differentiated histology, and less advanced pT and pN classifications, which lead to a favorable prognosis (13, 25-27). In such patients, complete eradication of the superficial spreading lesion is necessary.

The other is 'diffusely infiltrating cholangiocarcinoma', which is defined as a cholangiocarcinoma with an extensive infiltration from the hilar bile duct down to the lower bile duct. A cholangiogram of this type shows a wide range of irregular biliary strictures and often mimics a benign inflammatory disease; therefore, the entire extrahepatic biliary system should be removed for curative intent. Overall, patients with these two specific tumors are good candidates for the most challenging procedure, hepato-pancreatoduodenectomy (HPD), provided that they have a good hepatic functional reserve (28-30).

Synchronous and metachronous biliary cancer

Multiple synchronous biliary tumors are more common than previously thought; the incidence of multiple tumors ranges from 5% to 9% (10, 31-33). Thus, multiplicity seems to be a characteristic feature of biliary neoplasms. Gertsch et al. (31) proposed three criteria for multiplicity: no direct continuity between the two tumors, a growth pattern typical of a primary tumor, and clear histologic differences between the two tumors. However, it is often difficult to distinguish a genuine synchronous from a metastatic foci of the biliary cancer elsewhere. Interestingly, most of the second tumors are incidental early-stage gallbladder cancers (31, 33), which are not identified by the pre-

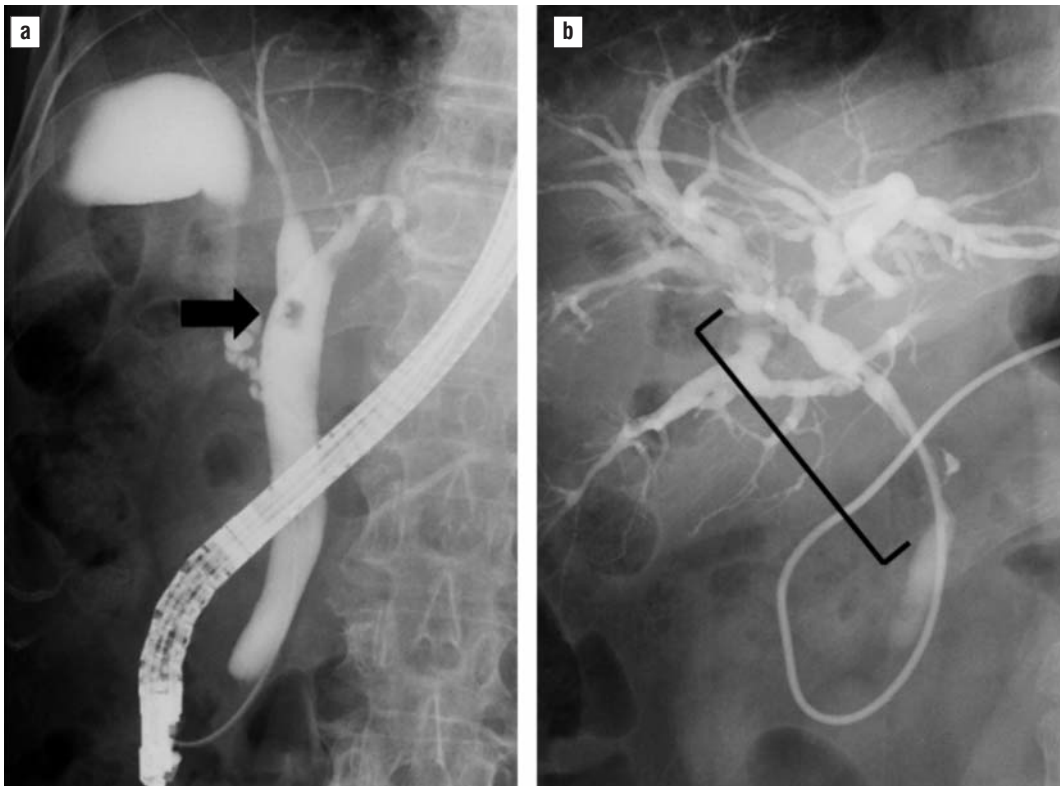

Figure 4 - Choangiograms of two specific types of cholangiocarcinoma.
(a) Superficial spreading cholangiocarcinoma. Frozen section examination revealed that carcinoma in situ was extensively present around the small papillary tumor (arrow), although the surrounding bile duct looked seemingly naove to naive. (b) Diffusely infiltrating cholangiocarcinoma. The extrahepatic biliary tree was widely involved (bracket). Hepatopancreatoduodenectomy is the sole surgical approach to eradicate the cancerous stricture.

operative work-up. This indicates a need for intra-operative surveillance, meticulous inspection of the specimen immediately after resection, and appropriate sampling of tissues for pathology.

Recently, Shinohara et al (34) reported that metachronous distal cholangiocarcinoma developed in 6 of 480 patients who had undergone initial surgery for PCC. All tumors were detected as a tumor mass in the intrapancreatic bile duct by follow-up CT with a median interval of 42 months and were resected by pancreato-duodenectomy. Extensive immunohistochemical and genetic analysis supports a field cancerization concept in this biliary carcinogenesis, although there are a limited number of samples. Taking these findings into account, close and long-term surveillance after resection is needed for early detection ofa second metachronous tumor as well as to identify disease relapse (35).

CONCLUSION

In conclusion, when surgeons design or chose a definitive resectional procedure for perihilar cholangio-carcinoma, they should understand the mode of tumor extension, paying a close attention to the potential gap between the radiologic tumor staging and the actual pathologic one. The present article specifically outlines the surgical pathology for surgeons by surgeons, providing a basis to answer surgical issues on perihilar cholangiocarcinoma that are often faced in daily practice.

Conflicts of interest and funding

The authors declare that there are no conflicts of interest, and no funding was received in support of this work.

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