Pathological aspects of cholangiocarcinoma

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Abstract
Cholangiocarcinoma (CC) arises from the biliary epithelium and in most cases represents adenocarcinoma. Pathomorphological evaluation is of decisive impact for the prognosis and management of CC. Morphological subtyping (histotype; hilar vs peripheral type), TNM classification, lymphatic spread, and resection margin status are of prognostic relevance. Distinction from hepatic metastases may be aided by immunohistology and clinico-pathological correlation. There is convincing evidence of the development of CC via premalignant lesions, especially biliary intraepithelial neoplasia, although further knowledge about the biology and diagnostic definition of these lesions has to be accumulated. Currently, there are no established molecular markers of prognosis or therapeutic target structures to be evaluated at the tissue level. Future progress is needed and expected in novel differential diagnostic and predictive markers, in uniform definition of resection margin status and further understanding of molecular and morphological changes in the development of CC.

Key Words: Bile duct, bile duct cancer, cholangiocarcinoma, histopathology, resection margin

Introduction
Bile duct cancer (cholangiocarcinoma (CC)) accounts for about 3% of all gastrointestinal cancers with a dismal long-term survival of 3.5% [1]. It arises from the ductal epithelium of the biliary tree. Depending on its location, it is classified into intrahepatic (ICC) or extrahepatic (ECC) CC, the latter being subclassified into proximal, middle, and distal subgroups. A three-tiered classification system into intrahepatic, perihilar (defined as a tumor located in the extrahepatic biliary tree proximal to the origin of the cystic duct), and distal CC seems more appropriate, however, since it correlates with anatomical distribution, preferred surgical treatment, and resectability rates [2]. According to this classification, perihilar tumors occur most frequently, followed in order by the extrahepatic distal and intrahepatic types [3].

Macroscopically, CC is usually a firm to hard, white to tan-white mass without extensive necrosis. ICC can form a single mass with or without satellite nodules, in most cases not accompanied by cirrhosis. Less frequently, it consists of multiple nodules [4]. Japanese authors have distinguished two macroscopical growth patterns of ICC – “mass forming” and “periductal infiltrating” types [5] – which largely corresponds to ICC being classified into peripheral and hilar tumors, depending on their origin from small or large intrahepatic biliary ducts [6]. Both hilar and peripheral ICC have been related to different premalignant conditions, progression features, and prognoses [7]. ICC usually attains a larger size than perihilar and distal ECC, probably as a consequence of later onset of symptoms: in a large recently reported series of 564 patients, the median diameter of ICC was 5.5 cm versus 2.5 cm and 2 cm of perihilar and distal tumors, respectively [3]. Perihilar ECC can cause segmental atrophy of the liver, leading to radiological overestimation of the tumor size, which can affect resectability assessment. ECC usually displays a periductal infiltrating growth or appears as polypoid indurated masses [8]. Depending on its primary site of origin, ECC may extend to the liver, gallbladder, pancreas, ampulla, or duodenum. Since all these organs themselves may give rise to carcinomas with similar morphological features, identification of the exact origin relies on precise macroscopy but may be impossible in larger tumors, even after careful clinicopathologic correlation.

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Microscopically, classic CCs are adenocarcinomas consisting of tubules, acini, solid nests, or trabeculae, usually embedded in a desmoplastic stroma. The tumor cells typically express cytokeratins 7 and 19, epithelial membrane antigen, BER-EP4, and display a cytoplasmic positivity for carcinoembryonic antigen (CEA). The absence of a membrane staining for polyclonal CEA and hepatocyte antigen (Hep Par 1) aids in distinguishing ICC from hepatocellular carcinoma (HCC) with pseudoglandular pattern [9]. Invasive papillary CCs show different morphological, immunohistological, and clinical/prognostic characteristics compared with classical CCs [10] and belong to the spectrum of biliary papillary tumors (see below). Histological variants of CC other than papillary adenocarcinomas are altogether rare (less than 10%) and include mucinous and signet ring cell carcinomas characterized by large amounts of extracellular mucus, adenosquamous carcinomas, squamous cell carcinomas, probably arising from metaplastic epithelium, and usually associated with solitary liver cysts [11], mucopidermoid carcinomas, glycogen-rich clear cell carcinomas, and spindle cell/undifferentiated carcinomas. The adenosquamous and spindle cell variants appear to have a worse prognosis than classical adenocarcinomas [12–14]. A rare type of ICC with a better prognosis than the classical type is the so-called hepatobiliary cystadenocarcinoma, a papillary adenocarcinoma usually arising in a multicystic cystadenoma or in a unilocular bile duct cyst [15]. In female patients, the stroma of cystadenocarcinomas and of their benign counterparts (hepatobiliary cystadenomas) is densely cellular (“ovarian-like”). This fact, together with the expression of hormone receptors in the stromal cells, has suggested an origin from ectopic Mullerian epithelium [16].

ICC should be distinguished from HCC with pseudoglandular pattern (discussed above) and metastatic adenocarcinoma. Organ-specific antigens (e.g. PSA, TTF-1, CDX-2, hormone receptors) may aid in some cases in the differentiation of ICC from metastatic adenocarcinoma, but distinction also relies on the clinical exclusion of an extrahepatic primary tumor. Combined HCC-CC is characterized by unequivocal cholangiolar (e.g. mucin production) and unequivocal hepatocellular differentiation and is considered a special subtype of HCC [4]. ECC has to be distinguished from reactive/inflammatory conditions, as in primary or secondary sclerosing cholangitis. This can be difficult and sometimes impossible in small biopsies of well-differentiated lesions. Preservation of the lobular arrangement of the glands, strong inflammatory background, less pronounced nuclear hyperchromatism and epithelial atypia favor a benign process, whereas the presence of perineural infiltration almost always indicates malignancy. p53 overexpression has been suggested as an additional criterion of malignancy in the differential diagnosis between ECC and reactive epithelial atypia, but is not thoroughly evaluated and currently not a standard diagnostic criterion [17].

Premalignant/preinvasive lesions of the biliary tree belong to two different subgroups: biliary intraepithelial (BilIN) and biliary intraductal papillary neoplasia (biliary IPN). BilINs are a group of flat, pseudopapillary, or micropapillary lesions classified by a recent international consensus into three categories (grades) based on the degree of atypia: BilIN-1, BilIN-2, and BilIN-3, this last-mentioned also including carcinoma in situ [18]. Since BilINs share morphology and expression patterns of mucin core proteins (MUC1 and MUC2) with pancreatic intraepithelial neoplasia (PanIN) [19], it has been suggested that they represent the counterpart of PanIN [18]. Biliary IPNs are grossly visible, non-invasive, intraductal papillary proliferations and resemble pancreatic intraductal papillary mucinous neoplasms (IPMN) [20]. Biliary IPNs, including biliary papillomatosis, show macroscopic mucinous hypersecretion in about 30% of cases and may display three different forms of differentiation: pancreaticobiliary, intestinal, and gastric. When invasive, they can display a tubular or mucinous pattern, the former bearing a worse prognosis [10]. Biliary papillary carcinomas have a more favorable prognosis than classical non-papillary adenocarcinomas, with a 5-year survival rate of 22% versus 8%, respectively [8].

The modes of spread of CC include perineural infiltration, described in 39% of patients with ICC [21] and in up to 75% of patients with ECC [22], as well as lymphatic permeation and venous invasion, seen in 61% and 64% of patients with ICC [21], in 50% and 38% of patients with upper bile duct cancer, and both in 73% of patients with lower bile duct cancer [22]. These factors have been associated with a worse prognosis of bile duct cancer, mostly at univariate analysis, in different surgical series [23,24]. Perihilar and distal CCs frequently spread by direct extension into the surrounding soft tissues and along the wall of the bile ducts. Lymph node metastases have been reported in 47% of resected CC. In this series of 564 patients, a larger proportion of distal cancers (60%) had positive locoregional lymph nodes compared with perihilar (28%) and intrahepatic (29%) cancers [3]. The most frequently involved lymph node stations in cases of distal CCs are the posterior-superior pancreatico-duodenal, the pericholedochal and those around the mesenteric artery [25]. Positive lymph nodes usually represent a prognostic relevant factor in univariate analyses [3,21,23,26]. Distant metastases have been described in up to 70% of patients; diffuse peritoneal seeding usually occurs late as a result of local recurrence [8].

According to the UICC (International Union Against Cancer) TNM rules, ICC (together with HCC) is classified as “liver tumor”, resulting in a different staging system compared to that used for
ECC [27]. The assessment of tumor differentiation (grading), however, has to follow the general four-tiered UICC or alternatively the three-tiered World Health Organization classification [28] for both ICC and ECC, since the specific UICC grading guideline for liver tumors is not applicable to ICC.

Obtaining negative margins (R0) at resection represents an important prognostic factor in all subgroups of CC, as shown in all large surgical series [2,3,26,29]. Perihilar CC has the lowest R0 rates compared to ICC or distal ECC, although the performance of a partial hepatic resection together with the bile duct resection seems to increase the number of curative resections [3,29]. Some studies have suggested that only invasive carcinoma and not carcinoma in situ at the bile duct resection margin significantly affects the survival of patients with hilar and/or distal ECC [26,30]. The relevance of the radial margin status in extrahepatic CC has been underscored by others [31]. However, the criteria for the definition of R1 resections are not univocal: for example, Japanese authors require a distance of 5 mm to define R0 resections [21,32], whereas in Western countries usually no recommendation is given, so that only the presence of a tumor at the resection margins is considered to define R1 (see, for example, the recommendations of the College of American Pathologists at www.cap.org). Moreover, examination of the resection margin – at least for hilar and distal ECC – is usually performed intraoperatively, with the lower quality of frozen sections surely impairing the evaluation of parameter, such as the presence of dysplasia/carcinoma in situ and their differentiation from reactive changes. Since a curative resection is one of the most robust prognostic factors for CC, larger studies are surely needed to obtain an international consensus for the pathological examination of surgical specimens with CC.

Consensus statements

- Cholangiocarcinoma (CC) arises from the epithelium of the biliary tract and in most cases represents adenocarcinoma. Morphological subtyping of CC is relevant for differential diagnosis and bears some prognostic impact.
- Subtyping of CC according to location is relevant in regard to prognosis and therapy and partly correlates to macroscopic and microscopic tumor morphology. It has not been performed in a uniform manner, but the majority of data favor a distinction of peripheral intrahepatic, (peri)hilar, and distal (extrahepatic) CC.
- Differential diagnosis of CC versus metastases or non-malignant conditions requires clinico-pathological correlation and is aided by immunohistology.
- TNM classification according to UICC differs for intra- and extrahepatic CC. For tumor grading, the general four-step UICC or the three-step WHO grading has to be applied.
- Assessment in operation specimen of (lympho-)glandular spread and resection margin status is of prognostic relevance, although the definition of the R-status has not been applied in a uniform manner worldwide.
- Convincing evidence exists for the stepwise development of CC via premalignant conditions. Most cases appear to arise from biliary intraepithelial neoplasia, while less frequently intraductal papillary neoplasia or hepatobiliary cystadenoma may represent alternative precursor lesions. The frequencies and time spans required for malignant transformation are unknown. A consensus for a three-tiered grading (BilIN 1-3) has been reached, although distinction of BilIN 2 is currently unsatisfactory.
- Relevant topics to be addressed in the future are:
  - More specific diagnostic and prognostic markers of CC.
  - Application of a uniform topographical classification.
  - Prospective evaluation of intraepithelial neoplasia.
  - Uniform definition of R-status and its evaluation.

References


