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Perspective

Diagnostic Challenges in Combined Hepatocellular-Cholangiocarcinoma

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DESCRIPTION

Combined hepatocellular-cholangiocarcinoma represents a rare primary liver malignancy that exhibits both hepatocellular and biliary differentiation within a single tumor. This dual lineage poses significant diagnostic challenges due to overlapping clinical, radiological, and histopathological features with conventional hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Accurate diagnosis is essential, as combined hepatocellular-cholangiocarcinoma demonstrates a more aggressive clinical course, distinct therapeutic considerations, and poorer prognosis compared with either component alone. Despite advances in imaging, histology, and molecular techniques, distinguishing combined hepatocellular-cholangiocarcinoma from other primary or metastatic liver tumors remains complex and requires a comprehensive approach integrating multiple diagnostic modalities.

Clinically, patients with combined hepatocellular-cholangiocarcinoma often present with nonspecific symptoms, including abdominal pain, weight loss, fatigue, or jaundice. Laboratory investigations may reveal elevated serum alpha-fetoprotein, carbohydrate antigen 19-9, or liver function test abnormalities, reflecting contributions from hepatocellular and biliary components. However, these markers lack specificity and may not reliably differentiate combined tumors from solitary hepatocellular carcinoma or cholangiocarcinoma. The absence of pathognomonic clinical features necessitates a high index of suspicion, particularly in patients with chronic liver disease, viral hepatitis, or cirrhosis, who are at risk for hepatocellular carcinoma but may also develop tumors with mixed differentiation.

Radiological evaluation, including ultrasound, computed tomography, and magnetic resonance imaging, provides important information on tumor location, size, vascularity, and patterns of enhancement, yet may be insufficient for definitive diagnosis. Hepatocellular carcinoma typically demonstrates arterial phase hyperenhancement with rapid washout, whereas cholangiocarcinoma often presents as a hypovascular mass with delayed enhancement and biliary ductal involvement. Combined hepatocellular-cholangiocarcinoma may exhibit features of both tumor types, including heterogeneous enhancement, areas of necrosis, and irregular margins, leading to misclassification as either hepatocellular carcinoma with atypical features or cholangiocarcinoma. Furthermore, small or heterogeneous tumors may escape detection on imaging or mimic benign lesions, complicating preoperative assessment and treatment planning.

Histopathological examination remains the gold standard for diagnosis but is complicated by tumor heterogeneity and sampling limitations. Combined hepatocellular-cholangiocarcinoma contains regions of hepatocellular differentiation, often with trabecular, pseudoglandular, or solid growth patterns, and areas of biliary differentiation characterized by glandular structures, desmoplastic stroma, and mucin production. Transitional zones between these components may be subtle, and small biopsies may sample only one lineage, resulting in misdiagnosis as either hepatocellular carcinoma or cholangiocarcinoma. Accurate diagnosis therefore depends on obtaining adequate tissue, thorough sampling, and careful evaluation of architectural and cytological features, as well as recognition of mixed growth patterns within the tumor.

Immunohistochemistry is critical for confirming the dual differentiation of combined hepatocellular-cholangiocarcinoma. Co-expression of hepatocellular and biliary markers within the same tumor or in adjacent regions supports the diagnosis of combined hepatocellular-cholangiocarcinoma. Nevertheless, variability in marker expression, focal positivity, and overlap with other liver tumors can complicate interpretation, emphasizing the need for comprehensive panels and correlation with morphology.

Molecular profiling may aid in distinguishing combined tumors from collision tumors, which represent separate hepatocellular carcinoma and cholangiocarcinoma masses in the same liver, as true combined tumors often share clonal origins. However, the requirement for specialized laboratory techniques, cost, and interpretation of complex results limits widespread clinical application, and molecular data are usually complementary rather than primary diagnostic tools.Surgical resection is the preferred treatment for combined hepatocellular-cholangiocarcinoma when feasible, but preoperative misdiagnosis may affect operative planning and prognosis.

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Inaccurate identification of the tumor type may lead to inappropriate surgical approaches, insufficient margins, or delayed adjuvant therapy. Similarly, systemic therapies used for hepatocellular carcinoma, including kinase inhibitors and immunotherapy, or chemotherapeutic regimens for cholangiocarcinoma, may have limited efficacy in combined tumors due to their mixed biology. Accurate preoperative and postoperative diagnosis is therefore crucial to guide optimal management, select appropriate therapies, and provide accurate prognostic counseling.

Diagnostic challenges in hepatocellular-combined cholangiocarcinoma underscore importance ofthe multidisciplinary collaboration. Radiologists, pathologists, hepatologists, and surgeons must integrate clinical, radiological, morphological, immunohistochemical, and molecular information to arrive at an accurate diagnosis. Careful attention to tumor heterogeneity, comprehensive tissue sampling, and judicious use of immunohistochemical panels improve diagnostic accuracy, minimize misclassification, and enhance patient management. Education and awareness of the unique features of combined hepatocellular-cholangiocarcinoma are essential for pathologists and clinicians to recognize this rare entity and implement appropriate therapeutic strategies.

CONCLUSION

Combined hepatocellular-cholangiocarcinoma presents a unique diagnostic challenge due to its dual lineage, heterogeneous morphology, and overlapping clinical and radiological features with other liver tumors. Accurate diagnosis requires careful integration of imaging, histopathology, immunohistochemistry, and, when available, molecular profiling. Recognition of mixed differentiation and the use of lineage-specific markers are critical to distinguish combined hepatocellular-cholangiocarcinoma from hepatocellular carcinoma, cholangiocarcinoma, or collision tumors. Diagnostic precision is essential for guiding surgical and systemic therapies, predicting prognosis, and optimizing patient outcomes.