Editorial Commentary

The evolving landscape of biliary tract cancers: comparing French and US National Comprehensive Cancer Network guidelines

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Biliary tract cancers (BTCs) constitute a heterogeneous group of hepatobiliary malignancies originating along the biliary tree. Approximately up to 20% of primary hepatobiliary tumors consist of BTCs (1). The primary risk factors include cholelithiasis, chronic inflammatory diseases of the bile ducts, non-alcoholic steatohepatitis (NASH), liver cirrhosis, tobacco use, and chronic viral hepatitis B and C infections (2). Well-known subtypes of BTCs are intrahepatic cholangiocarcinoma (iCCA), perihilar cholangiocarcinoma (pCCA), distal cholangiocarcinoma (dCCA), and gallbladder carcinoma (GBC). Recently, Roth *et al.* published French National Clinical Practice guidelines for patients with BTCs (3). Recommendations were graded based on the level of scientific evidence, ranging from 'high' to 'very low', in accordance with the guidelines of the French Health Authority. Compared to the United States National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, version 2.2024, updated in April 2024, the recently published French clinical practice guidelines exhibit significant similarities with only minor but important differences (4).

The guidelines have no major differences regarding imaging modalities for diagnosing and staging BTCs. The French guidelines emphasize using advanced imaging techniques such as enhanced computed tomography (CT) and magnetic resonance imaging (MRI) for accurate diagnosis and staging (5). Similarly, the NCCN guidelines recommend high-quality cross-sectional imaging (CT or MRI) for initial diagnosis and staging. For the French guidelines, fluorodeoxyglucose (FDG)-positron emission tomography (PET) is not routinely recommended for extension work-up but may be considered for differential diagnosis. Likewise, the NCCN guidelines do not routinely recommend FDG-PET. Although PET/CT has limited sensitivity, it possesses high specificity and may be considered when there is an equivocal finding or on a case-by-case basis (6). The routine use of PET/CT in the preoperative setting has not been established in prospective trials.

Pathological diagnosis with ultrasound-guided biopsy is recommended for iCCA in both the French and NCCN guidelines. For pCCA or dCCA, the NCCN guidelines advise evaluating whether the patient is a candidate for resection or transplantation before performing a biopsy. If

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the patient is a potential transplant candidate, a referral to a transplant center should be considered prior to biopsy. On the other hand, the French guidelines suggest considering fine-needle aspiration (FNA) of the primary tumor but recommend discussing it on a case-by-case basis. If a lymph node appears suspicious, both guidelines agree that a biopsy is appropriate for any suspicious lymph node.

Regarding the treatment of localized BTC, both the French and NCCN guidelines recommend upfront surgery as the cornerstone of treatment. No neoadjuvant treatment has been validated to date. The French guidelines advise against its use (grade C) except within clinical trials. The NCCN guidelines similarly recommend against routine neoadjuvant therapy, with some consideration for gallbladder cancer, emphasizing that the decision should be individualized in a multidisciplinary team. Given limited clinical trial data, no standard regimen has been defined, and participation in clinical trials is encouraged (7). The French guidelines suggest adjuvant capecitabine as grade B for adjuvant therapy, while the NCCN recommends it as a category 1. The NCCN recommends a multidisciplinary evaluation for patients with GBC or dCCA with resected positive margins (R1), gross residual local disease (R2), or iCCA with residual local disease (R2). Systemic therapy and clinical trials are preferred for R1 margins or positive regional nodes, and fluoropyrimidine-based chemoradiation is a potential, though not primary option. In contrast, the French guidelines explicitly advocate adjuvant chemoradiotherapy (CRT) with capecitabine following 4 to 6 months of adjuvant capecitabine for R1 resection cases of pCCA, dCCA, or GBC as an expert opinion. The French approach delineates a more defined sequence of capecitabine followed by CRT. At the same time, the NCCN guidelines provide a broader range of options without establishing a single optimal strategy for R1 or positive node scenarios. In advanced disease, for the first-line systemic treatment, gemcitabine and cisplatin combined with durvalumab or pembrolizumab is category 1 in the NCCN guidelines and grade A in the French guidelines, based on the results of the TOPAZ-1 and KEYNOTE-966 trials (8,9). Both guidelines recommend comprehensive molecular profiling for patients with unresectable or metastatic BTC who are candidates for systemic therapy.

Second-line and beyond treatment options for BTCs are less clear and primarily oriented towards targetable tumor molecular alterations. The absence of standard treatments for patients without specific molecular targets highlights the complexity and variability in managing advanced BTCs. The FOLFOX (5-fluorouracil and oxaliplatin) chemotherapy is validated as the only second-line standard in the absence of molecular targets (10). However, the identification of targetable mutations, such as *IDH-1*, *FGFR2*, *HER2*, *BRAFV600E*, microsatellite instability (MSI)/mismatch repair deficiency (dMMR), *KRASG12C*, *NTRK*, and *RET* gene fusions, has led to the development of tailored therapies. These personalized treatments, though promising, are often constrained by issues of accessibility and limited clinical trial data, underscoring the need for ongoing research and the adaptation of guidelines to incorporate new evidence and improve patient outcomes. Among targetable options, ivosidenib for *IDH-1* mutation is the only grade A recommendation in the French guidelines and is listed as category 1 in the NCCN guidelines. For *FGFR2* fusion/rearrangement, the French guidelines list pemigatinib (reimbursed) and futibatinib (no access) as grade B options, while the NCCN guidelines categorize both as 2A options. Regarding *HER2* amplification/overexpression, the French guidelines mention several drugs, including zanidatamab (CAP), and combinations like trastuzumab with pertuzumab, trastuzumab with tucatinib, and FOLFOX with trastuzumab. However, access is limited, and there is a lack of expert consensus for the latter three. The NCCN guidelines recommend fam-trastuzumab deruxtecan-nxki for immunohistochemistry (IHC) 3+ cases and suggest trastuzumab with pertuzumab and tucatinib with trastuzumab (category 2A). The primary difference is the French guidelines' emphasis on limited access and lack of expert consensus, while the NCCN provides specific recommended treatments with a clear preference for fam-trastuzumab deruxtecan-nxki in certain cases. For *BRAFV600E* mutation, both the French and NCCN guidelines recommend dabrafenib combined with trametinib, though the French guidelines note this combination is not accessible. For MSI/dMMR cancers, the French guidelines recommend pembrolizumab (not accessible) if no anti-PD1/PD-L1 therapy has been used in the first line, classifying it as grade B. The NCCN guidelines list pembrolizumab as a category 2A treatment option and include dostarlimab-gxly as a category 2B option, with the primary difference being the inclusion of dostarlimab-gxly in the NCCN guidelines. For tumors with high tumor mutational burden (TMB-H), the NCCN recommends nivolumab combined with ipilimumab or pembrolizumab as a single agent, whereas the French guidelines do not mention these options.

Both guidelines recommend adagrasib for the

KRASG12C mutation. The French guidelines classify it as grade C and note its inaccessibility, while the NCCN lists it as a category 2A treatment option. For *NTRK* fusion, the French guidelines recommend larotrectinib (not accessible) and classify it as grade B, while the NCCN recommends both entrectinib and larotrectinib (category 2A). For *RET* gene fusion-positive cancers, the NCCN recommends selpercatinib and praseltinib, whereas the French guidelines do not list these options but note their European Medicines Agency (EMA) approval is restricted to *RET* fusion-positive advanced non-small cell lung cancer (NSCLC) and thyroid cancer, including medullary thyroid cancer for selpercatinib. The primary difference is that the NCCN guidelines actively recommend these drugs, while the French guidelines only note their restricted approval status without broader recommendations.

Conclusions

While both the French National Clinical Practice Guidelines and the NCCN guidelines share many fundamental principles in managing BTCs, there are nuanced differences in specific recommendations, particularly regarding adjuvant therapies and molecular profiling. Both guidelines provide a robust framework for managing BTC, reflecting regional practices and the latest evidence. However, ongoing updates and research will continue to shape these recommendations, ensuring they remain aligned with emerging scientific advancements and clinical insights.

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