EDITORIAL

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Is genomic analysis possible in a tissue acquired via endoscopic ultrasound-guided fine-needle biopsy in cholangiocarcinoma?

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See "Clinical utility of endoscopic ultrasound-guided tissue acquisition for comprehensive genomic profiling of patients with biliary tract cancer, especially with intrahepatic cholangiocarcinoma" Takafumi Yanaidani, Kazuo Hara, Nozomi Okuno, et al., Clin Endosc 2024;57:384–392.

Cholangiocarcinoma (CCA) incidence is significantly higher in Asian countries (including Korea, China, and Thailand) than in other geographical regions, potentially attributed to parasitic infections, notably those related to *Clonorchis sinensis*. The poor CCA prognosis is mostly due to advanced-stage diagnosis and the limited effectiveness of available medical interventions, including targeted therapy and chemotherapeutics. The gemcitabine plus cisplatin (GP) regimen has been established as the first-line chemotherapy for CCA since the early 2000s. Despite high expectations, the addition of nab-paclitaxel to the GP regimen failed to demonstrate a significant extension in survival in a phase 3 study.[1,2] The recent National Comprehensive Cancer Network guidelines have included immune checkpoint inhibitors (e.g., durvalumab or pembrolizumab) to the GP regimen for CCA treatment. However, this approach is reportedly largely ineffective, since survival periods were extended by approximately one month only (D+GP vs. GP, 12.8 vs. 11.5 months; P+GP vs. GP, 12.7 vs. 10.9 months).[3,4] According to the location and growth patterns, CCA comprises intrahepatic, perihilar, and extrahepatic subtypes as well as intraductal, ductal, and mass-forming types, respectively. These classifications have been associated with distinct prognoses and genetic variants. Consequently, a better understanding of the unique characteristics of these subtypes, including genetic studies, would be warranted and would enable the pursuit of customized precision medicine therapeutics for individual patients, thereby potentially overcoming therapeutic challenges. Pathogenic variants of intrahepatic CCA include FGFR2, IDH1/2, EPHA2, BAP1, KRAS, SMAD4, ARID1A, GNAS, TP53, BRCA1/2, ERBB2, and PIK3CA. In addition, the genetic variants of PRKACA/B, ELF3, ARID1A/B, KRAS, SMAD4, GNAS, TP53, BRCA1/2, ERBB2, and PIK3CA have been implicated in extrahepatic CCA. Furthermore, gallbladder carcinoma (GBC) is associated with pathogenic EGFR, ERBB2/3, PTEN, ARID2, MLL2/3, TERT, TP53, BRCA1/2, and PIK3CA variants.[5] FGFR2 variants have been studied extensively in the context of intrahepatic CCA, and therapies targeting such genetic changes, including pemigatinib and futibatinib, demonstrated promising response rates of 35.5% and 42%, respectively, when used as second-line

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treatments.[6,7]

CCA diagnosis is predominantly confirmed via endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous liver biopsy in advanced stages. The diagnostic technique selection being influenced by the anatomical location of the tumor. The lower sensitivity of the ERCP biopsy led to a growing preference for fine-needle aspiration (FNA) and fine-needle biopsy (FNB), facilitated by endoscopic ultrasound (EUS). A recent meta-analysis revealed ERCP and EUS-FNA sensitivity, specificity, and diagnostic accuracy, in the context of malignant biliary strictures, as 49% and 75%, 96.3% and 100%, and 60.6% and 79%, respectively.[8] Comprehensive genomic profiling (CGP) requires higher tissue quantity than that routinely required for pathological diagnosis. Therefore, percutaneous liver biopsy or surgical biopsy are commonly employed to obtain sufficient CGP material. However, such procedures are more invasive and carry a higher complication risk than EUS-FNA or EUS-FNB. Therefore, the latter procedure could be considered a chosen diagnostic technique if an acceptable diagnostic rate and CGP adequacy could be irrefutably demonstrated. Several studies using CCA tissue for CGP harvested via EUS-FNB described pathogenic variant detection rates of 0% to 30%. However, the tissue quantity adequacy rates remained undocumented in these reports.[5] These studies were predominantly limited by patient selection, with most enrolled patients suffering from intrahepatic CCA or GBC and very few cases representing ductal infiltration and extrahepatic CCA. Notably, a study evaluating EUS-FNA efficacy in pancreatic cancer reported CGP adequacy rates of 72.5%, 53.5%, and 33.3% for 19-G-FNB, 22-G-FNB, and 22-G-FNA, respectively.[9] This result implies that EUS-FNA could lead to positive results with minimal complications compared to traditional laparoscopic biopsy in pancreatic cancer diagnosis. These findings imply that transitioning from percutaneous methods to EUS-FNA could be advantageous for CCA diagnosis, highlighting the potential benefits of this approach in obtaining tissue samples for genetic analysis with minimal complications.

In the current issue of *Clinical Endoscopy*, the clinical utility of EUS tissue acquisition for CGP in patients with biliary tract cancer, especially those with intrahepatic CCA,[10] is highlighted by including a larger cohort of 94 patients, surpassing the number of participants in previous articles with similar objectives. Factors positively associated with sample adequacy included the use of a larger needle gauge (19-G vs. 22-G, 93.1% vs. 54.5%; p=0.013), FNB needle type choice (FNA vs. FNB, 37.5% vs. 83.7%; p=0.013), primary lesion presence instead of metastasis (p=0.015), target size >30 mm (p<0.001), and performing >3 punctures (p=0.016).

This study describes the genomic analysis of tissue samples obtained via EUS-FNB to evaluate eight critical therapeutic molecular markers as follows: IDH1 variants (involved in metabolic pathways)[11]; FGFR2 fusions (keys to cell growth and angiogenesis)[12]; neurotrophic receptor tyrosine kinase (NTRK) fusions (important for neural development and function)[13]; BRAF V600E variants (keys to the MAPK signaling pathway)[14]; receptor tyrosine-protein kinase erbB-2 (ERBB2) amplifications (associated with cell proliferation and survival)[15]; rearrangements during transfection (RET) fusions (impacting cell growth and differentiation)[16]; microsatellite instability-high status (indicative of a defective DNA mismatch repair system)[17]; and tumor mutational burden (TMB, reflecting the number of mutations carried by tumor cells).[18] FGFR2 fusions were detected in 12.9% of intrahepatic CCA, making it the most prevalent variant. IDH1 variants were the second most common genetic cause of intrahepatic CCA (9.7%). While GBC frequently (21.4%) exhibited ERBB2 amplification as the primary alteration, TMB-high status (17.9%) was the second most common variation. Furthermore, the pathogenic variant detection rate in intrahepatic CCA and GBC was approximately 30%, being notably lower than that in extrahepatic CCA (0%). KRAS and TP53 status evaluations in intrahepatic CCA (32.3% vs.32.3%), extrahepatic CCA (35.7% vs.71.4%), and GBC (7.1% vs.53.6%) revealed significant differences with a particularly lower KRAS variant detection rate in GBC compared to that in CCA (7% vs. 33%, p=0.011).

This study was limited by the fact that most of the enrolled patients displayed intrahepatic CCA and GBC. In addition, only four patients underwent targeted assessment of the bile duct using EUS-FNA/B, with adequate tissue collection in 50% of these cases. Consequently, this study might not have fully captured the specificity of ductal infiltration types and extrahepatic CCA within the CCA category. In contrast, this study highlights successful CGP performance in intrahepatic and mass-forming CCA using EUS-FNA/B. Furthermore, large-scale studies assessing CGP feasibility in patients with ductal infiltration types undergoing EUS-FNA/B are crucial for developing diagnostic strategies to combat CCA.

Conflicts of Interest

The authors have no potential conflicts of interest.

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Author Contributions

Conceptualization: SYH; Data curation: JL; Formal analysis: JL; Funding acquisition: SYH; Investigation: JL; Methodology: JL; Project administration: SYH; Resources: JL; Software: JL; Supervision: SYH; Validation: JL; Visualization: JL; Writing–original draft: SYH; Writing–review & editing: all authors.

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