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Emerging Role of Circulating Tumor DNA for Early Detection of Recurrence in Biliary Tract Cancers

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Editorial

Emerging role of circulating tumor DNA for early detection of recurrence in biliary tract cancers

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Cholangiocarcinoma (CCA) is the second most common primary liver cancer and accounts for 3% of all gastrointestinal (GI) malignancies (1). Surgical resection is the mainstay of treatment and only curative option, although only 20–30% of patients are candidates (2). After upfront curative resection, the standard of care involves adjuvant capecitabine for a total of 6 months based on the BILCAP study, providing an overall survival (OS) benefit in the prespecified sensitivity and per-protocol analyses, although not in the intention-to-treat population (3). It is included in the National Comprehensive Cancer Network (NCCN) guidelines as an appropriate adjuvant therapy (4).

Despite this multi-modality treatment approach to early-stage resectable CCA, approximately 60–70% of patients have recurrent disease with subsequent poor outcomes (3). There are therefore opportunities for improving treatment paradigms for the majority of patients who will ultimately recur.

In the past few years, circulating tumor DNA (ctDNA) has increasingly been investigated as a minimally invasive biomarker for tumor recurrence, among other uses. In the surveillance setting, it may predate radiographic recurrence by months and has so far been applied as an adjunct to standard of care imaging modalities (5). The presence of ctDNA after curative intent therapy has demonstrated a worse disease-free survival (DFS) in a variety of GI malignancies (5-7). While residual ctDNA leads to worse outcomes, ongoing research has also aimed to prospectively identify patients who may benefit from additional escalation of therapy or to guide treatment de-escalation in the adjuvant setting, such as in the CIRCULATE-NORTH AMERICA trial for colorectal cancer (CRC) (8).

Among GI malignancies, CRC studies (namely the GALAXY, BESPOKE, and DYNAMIC trials) provide the real-world data to support the highly prognostic value of ctDNA in the adjuvant or post-curative intent setting. For example, the detection of ctDNA after curative intent surgery (in the GALAXY and BESPOKE trials) and ctDNA dynamics in response to adjuvant chemotherapy (in the GALAXY trial) were highly prognostic of DFS in resected CRC patients (9,10). In the GALAXY study, having undetectable ctDNA at multiple time points post-surgery is associated with a dramatically higher 18-month DFS as compared to persistently positive ctDNA at multiple time points (92.1% *vs.* 22.9%, respectively) (9). It is possible

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with longer study follow-up, all patients with persistently positive ctDNA after surgery may eventually have clinical recurrences, although it should be noted, there appears to be a small subset of patients who also clear ctDNA without systemic therapy, possibly by immune surveillance mechanisms (9).

In resected CCA, there is comparatively less data for its utility. A sub-analysis of the phase II STAMP trial in CCA looked at the feasibility of ctDNA to predict recurrence risk in the adjuvant setting. The trial compared adjuvant capecitabine to adjuvant gemcitabine and cisplatin and showed no difference in recurrence-free survival (RFS) or OS. ctDNA was analyzed at three different time points: pre-adjuvant chemotherapy, after five cycles of adjuvant chemotherapy, and after eight cycles of adjuvant chemotherapy, using a tumor-informed ctDNA assay [Signatera, bespoke multiplex PCR-next-generation sequencing (NGS) assay]. Patients with positive ctDNA pre-adjuvant chemotherapy demonstrated a trend towards shorter RFS [hazard ratio (HR) =1.7, 95% confidence interval (CI): 0.98–2.8, P=0.069] compared to negative ctDNA. In addition, all patients with persistent positive ctDNA during adjuvant chemotherapy recurred clinically with a significantly shorter RFS (11).

In the paper by Yu *et al.*, the authors use ctDNA in CCA to identify the presence of microscopic CCA before evidence of radiographical recurrence and ahead of a rise in cancer antigen 19-9 (CA-19-9) tumor marker. The patient had positive ctDNA with increasing titer while on adjuvant capecitabine. Despite an overall lack of data to guide early treatment intervention in this scenario, with shared patient decision making, a relatively low-risk intervention with the immune checkpoint inhibitor (ICI), pembrolizumab, was initiated based on microsatellite instability-high (MSI-H) and tumor mutational burden high (TMB-H) status of the tumor. With pembrolizumab, there was clearance of ctDNA and the patient remains without radiographical evidence of disease in the 2 years following initial surgery. He continues on surveillance with ctDNA and standard of care imaging (12).

It has been known for some time that MSI-H or deficient mismatch repair (dMMR) tumors may be predictive of clinical responses to ICIs, such as pembrolizumab, a monoclonal antibody to programmed cell death 1 (PD-1). TMB-H tumors are also associated with improved survival in patients receiving ICIs across a variety of tumor types (13). Based on the KEYNOTE-158 trial from 2017, pembrolizumab received accelerated approval for patients with MSI-H/dMMR advanced solid tumors after standard chemotherapy (14). In the 22 patients with CCA/biliary tract cancers with MSI/dMMR tumors receiving pembrolizumab in the refractory setting in KEYNOTE-158, the objective response rate was excellent at 40.9% (95% CI: 20.7% to 63.6%), with median OS of 19.4 months (95% CI: 6.5 months to not reached) and a median duration of response of 30.6 months (95% CI: 6.2 to 40.5+ months) (15). Subsequently, a number of case reports of CCA have also shown good and durable responses to pembrolizumab in the metastatic setting for this unique population of CCA with positive biomarkers (16,17). Additionally, another study with single agent nivolumab (another monoclonal antibody targeting PD-1) in CCA, found that all responders had MSI-H tumors (18). Response to ICIs in CCA (regardless of MSI-H/dMMR status) are further highlighted by the TOPAZ-1 and KEYNOTE-966 studies, which showed combining durvalumab or pembrolizumab respectively, with gemcitabine and cisplatin showed improved OS, becoming the new standard of care in the first-line metastatic setting (19,20).

MSI-H and TMB-H status are two well recognized distinct molecular subtypes within a variety of solid tumor malignancies, including CCA. The prevalence of MSI-H or TMB-H in CCA varies depending upon the study, although it is considered an overall relatively rare occurrence. For instance, in 352 biliary tract cancers, 2.0% of tumors (7/352) were MSI-H using next generation sequencing and 4.0% (14/352) were considered TMB-H, having greater than or equal to 17 mutations per megabase (21). In intrahepatic CCA, rates were similar at 2.5% MSI-H (n=5/198) and 3.5% TMB-H (n=7/198) (21). Rates of MSI-H in biliary tract cancers in other studies have been similar in the 1–3% range (22,23).

Whether or not an early intervention to target detectable ctDNA has an impact on OS such as in this patient (for example, instead of waiting for radiographic recurrence and then employing standard of care first-line systemic therapy for metastatic disease or single-agent pembrolizumab for MSI-H/dMMR) is unknown. However, it should be noted this patient had prolonged DFS (over 2 years) while maintaining good quality of life given lack of any symptomatic disease. Whether this patient might have been in the small subset of patients who spontaneously cleared ctDNA is also unknown, however titers of ctDNA were rising which make this possibility less likely. In the event the patient did not have a durable response to pembrolizumab, it also raises the question whether subsequent use of ICI,

as part of initial standard of care regimen with gemcitabine and cisplatin in the first-line metastatic setting, might influence response to treatment. Additionally, should this patient have had a targetable mutation (e.g., *FGFR2* fusion or *IDH1* mutation), as opposed to MSI-H status, the question also arises whether targetable intervention based on a biomarker approach could provide similar outcome (again, not part of the standard of care). It is plausible that in the future, ctDNA may play a role in CCA to potentially escalate adjuvant treatment if able to better predict the 60–70% of patients who may ultimately recur, presenting one area for further investigation. Studies are currently looking to improve upon the current standard of care in the adjuvant setting with capecitabine, such as the use of adjuvant capecitabine combined with an ICI to prevent recurrence (24).

When detection of ctDNA becomes highly prognostic of an eventual radiographic recurrence, in a setting where there are no potential treatment strategies for early intervention (or patients would not be interested in intervention given sparsity of data), this approach is generally discouraged, as it is unlikely to change management and may contribute to patient anxiety. In cases of ctDNA detection, there is however potential for more frequent surveillance imaging (or targeted imaging to particular areas of recurrence, such as the liver or lymph nodes), however there is no data to suggest this approach has benefit on outcomes. This approach was taken in a reported case by Monroe *et al.* in which after ctDNA positivity in resected CCA, a positron emission tomography (PET)-computed tomography (CT) detected disease recurrence at the hepatectomy margin (notably, a CT chest abdomen and pelvis 2 months earlier was negative for evidence of malignancy). The patient was subsequently treated with gemcitabine and capecitabine for four cycles, followed by concurrent capecitabine and radiation therapy with good outcome (25).

In conclusion, the management of resected CCA remains an area with need for improved treatment strategies. The emergence of ctDNA as a biomarker for early detection of recurrence holds promise for improving outcomes in this population. Particularly in CRC as well as other GI malignancies, ctDNA in the post-curative resection and adjuvant setting is highly prognostic. The case by Yu *et al.* highlights a potential early intervention guided by ctDNA analysis, in this instance use of pembrolizumab for an MSI-H, TMB-H CCA. Further research is needed to determine the impact of early intervention based on ctDNA detection, including in CCA. Use of ctDNA holds substantial promise for advancing management of resected CCA and improving outcomes.

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