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EDITORIAL – HEPATOBILIARY TUMORS

Circulating Tumor Cells are an Independent Risk Factor for Poor Prognosis in Gallbladder Adenocarcinoma Patients

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We congratulate Yan et al. for this interesting paper, investigating the correlation of circulating tumor cells (CTC) and survival in locally advanced/metastatic gallbladder cancer. CTC found in locally advanced tumors is a promising field of research,[1–5] focused on improving patient selection and prognostication before surgery. This appears to be signficant among aggressive epithelial tumors, such as gallbladder adenocarcinoma (GBAC),[6] defining the value of this study and proving the higher risk of micrometastatic disease among those patients with locally advanced tumors.

GBAC is a silent, although aggressive, epithelial malignancy that develops mostly in a chronically inflamed gallbladder mucosa generally due to gallstones disease.[7,8] Almost 50% of patients with gallbladder cancer are diagnosed unexpectedly after a cholecystectomy for benign acute/chronic cholecystitis. This is known as "incidental GBAC" and represents the early disease stages where the long-term survivors are mostly found.[9] On the contrary, survival is limited among patients with locally advanced disease, either suspected before surgery or those with residual disease after surgery in an unexpected cancer.[10]

This study has the strength of investigating a research question over a significant number of patients (N = 133) treated for gallbladder cancer, correlating survival after curative intent resection (N = 120) and the presence of CTC. Those patients who underwent curative intent surgery and positive CTC also were compared with a palliative group (N = 13) who did not complete surgery due to vascular involvement or metastatic disease.

The number of patients included is important as GBAC is a rare disease, except in those recognized countries with a higher incidence in East Asia and South America.[11] This low incidence has defined a lack of prospective data on this disease, most of which come from retrospective studies with limited number of patients, whereas those few prospective trials include mixed histologies, including cholangiocarcinoma.[12]

This study's cohort was divided into low-risk (N = 32) and high-risk tumor groups (N = 88) who underwent surgery. Patients defined as low-risk tumors were those within AJCC stages 0-I. These patients are generally, if not always, identified as an incidental finding in the postoperative pathology of a cholecystectomy for gallstones disease. Within this group, only pT1b have an indication for oncologic surgery after cholecystectomy, which is rather a stage completion operation with debated survival benefit.[13,14] As we would expect, in this study, none of those low-risk patients had positive lymphatic infiltration nor positive CTC (0/32). However, to our surprise, disease-free survival (DFS) and cancer-specific survival (CSS) within this group was lower than expected (90% approximately) at 12 months follow-up. This, maybe because seven of 32 patients (21.9%) did not have an R0 resection.

High-risk tumor patients included AJCC stages II and III (8th edn.), with 13.6% of them presenting positive CTC. Patients with positive CTC had a significant shorter median DFS and CSS compared with high-risk patients with negative CTC. Moreover, compared with those 13 patients with cT4 or metastatic disease, who did not undergo curative intent treatment, high-risk patients with positive CTC showed similar survival after surgery comparable to these palliative group of patients.

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These results highlight the increasing significance of liquid biopsy as part of the preoperative disease prognostication, as it proves a more advanced clinical stage. A variety of tumor analytes can be identified in a patient's blood sample, including circulating tumor DNA (ctDNA), circulating cell-free DNA and RNA (ccfDNA, ccfRNA), extracellular exomes and CTC.[15] Among these analytes, CTC are considered to be a preclinical source of metastases. Moreover, the number of CTCs in the blood has shown association with reduced progression-free and overall survival and may be of higher prognostic value than conventional imaging.[4] Results shown in this study correlate well with others proven in different high-risk tumors, with circulating tumor cells in peritoneal washings or peripheral blood samples, such as gastric adenocarcinoma and colorectal cancer.[16,17] The presence of circulating tumor cells represent the presence of micrometastasis not evident on standard pretreatment imaging, and therefore, treatment strategy should be defined accordingly.

In terms of future validation, the presence of CTC and survival should be compared by current AJCC staging groups, not merging stages II and III as a single high-risk cohort. It also would be interesting to learn if it is only the presence or the number of positive CTC that correlates with disease upstage. CTC also may be combined with ctDNA to identify specific tumor genotypes, to specify potential target therapies in what appears to be a stage of GBAC with systemic treatment advantages over upfront surgery.

Again, we congratulate the authors for this interesting research that helps to explain this rare disease with encouraging results for better patient selection and better treatment planning in the hopes of avoiding treatment futility.

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