Gut and Liver
https://doi.org/10.5009/gnl220542
pISSN 1976-2283 eISSN 2005-1212

Editorial

Are the Immunohistochemistry-Based Biomarkers Helpful for Predicting Prognosis in Patients with Surgically Resected Cholangiocarcinoma?

Dong Uk Kim

Department of Internal Medicine, Pusan National University College of Medicine and Biomedical Research Center, Pusan National University Hospital, Busan, Korea

Corresponding Author
Dong Uk Kim
ORCID https://orcid.org/0000-0002-7208-7753
E-mail amlm3@hanmail.net

See "Postoperative Prognostic Predictors of Bile Duct Cancers: Clinical Analysis and Immunoassays of Tissue Microarrays" by Hwe Hoon Chung, et al. on page 159, Vol. 17, No. 1, 2023

Cholangiocarcinoma (CCA) is representative cancer with a poor prognosis. Surgery is the only way to expect a cure, but most of the patients presented with inoperable, advanced diseases. Even in patients who undergo resection, the 5-year survival rate is less than 30% and the average survival rate is about 30 months.[1] Therefore, biomarkers that predict the recurrence of surgically resected cholangiocarcinoma are very necessary. However, CCA is a tumor with diverse phenotypes which express different prognoses and responses to anticancer therapy. Even though many studies on prognostic biomarkers have been ongoing for a long time in patients with CCA, there are no definite prognostic biomarkers in clinical practice. Recently, the predictive value of multiplex immunohistochemistry (IHC)-based markers has been emerging especially in the clinical aspect as this IHC method could be widely used.

In this issue of *Gut and Liver*, Chung *et al.*[2] reviewed 91 CCA patients who underwent surgical resection with clinicopathologic features including American Joint Committee on Cancer (AJCC) 8th stage, pathological difference, carcinoembryonic antigen, carbohydrate antigen 19-9, and IHC-based biomarkers such as E-cadherin, Snail, interleukin 6, membranous EGFR (EGFR-M), and cytoplasmic EGFR (EGFR-C). AJCC 8th stage and tumor location were clinicopathologic factors associated with shorter overall survival, and pathologic differentiation and tumor location were associated with shorter disease-free survival. In addition to clinicopathological factors, an IHC-based biomarker, EGFR-M, was associated with shorter overall survival and disease-free survival.

In a meta-analysis for the prognostic value of all IHC-based biomarkers in patients with resected cholangiocarcinoma, they evaluated 77 biomarkers from 4,126 patients in a total of 73 studies.[3] In the integrated analysis, the prognostic biomarkers of overall survival were fascin (hazard ratio [HR], 2.58; 95% confidence interval [CI], 1.19 to 5.58), EGFR (HR, 1.79; 95% CI, 1.14 to 2.8), MUC1 (HR, 2.52; 95% CI, 1.49 to 4.26), MUC4 (HR, 2.45; 95% CI, 1.56 to 3.86) and p27 (HR, 0.29; 95% CI, 0.14 to 0.60). Among them, EGFR is more meaningful because it could be a target for anticancer therapy as well as a prognostic marker.

In a recent trial, immune-related biomarkers were evaluated for predicting recurrence-free survival in patients with resected cholangiocarcinoma.[4] They selected 16 prognostic immune biomarkers including CD66b and PD1 for tumor growth, CD3, CD4, CD8, CD57, CD68, Foxp3, and PD-L1 for tumor prognosis, CD14 for antitumor function and CD20, CD27, and CD45RO for local immune response, which could be tested with the IHC method. This novel histopathology-related immunoscore was an independent risk factor for predicting recurrence-free survival.

Multiple biomarkers should be considered to distinguish all phenotypes of cholangiocarcinoma. A recent typical example is the subtyping of tumors using RNA sequencing. Along with the development of technology, many studies have been conducted on the subclassification of cholangiocarcinoma according to RNA expression. In one study,[5] RNA expression-based clustering defined 4

Copyright © Gut and Liver.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

molecular classes of cholangiocarcinoma, including mesenchymal (47%), proliferative (23%), metabolic (19%), and immune (11%) classes. The most common mesenchymal class (47%) was characterized by epithelial-mesenchymal transition, abnormal TGFβ signaling, and poor overall survival. Tumors classified into metabolic classes displayed a characteristic hepatocyte-like phenotype with enrichment of gene signatures associated with activation of the transcription factor HNF4A and bile acid metabolism. The proliferative class (23%) was characterized by the enrichment of MYC targets, ERBB2 mutation/amplification, and activation of mTOR signaling. Finally, tumors of the immune class (11%) had higher lymphocyte infiltration, PD-1/PD-L1, and molecular features associated with better response to immune checkpoint inhibitors.

Chung's study had several disadvantages. First, it did not consider the selection of biomarkers according to tumor location. Second, multiplex IHC panels were not used for the 5 biomarkers. Therefore, it was not possible to test various markers in small biopsy tissues. In the future, it is necessary to determine multiplex IHC panels for different biomarkers depending on the location of the tumor.

I assume that a panel of IHC-based biomarkers could replace the profiling of RNA expression in patients with cholangiocarcinoma. In order to profile RNA expression, a sufficient amount of RNA sample must be collected from tissue. Since RNA extraction is difficult for accurate RNA sequencing from formalin-fixed paraffin-embedded (FFPE) tissues which are widely used as a tissue preservation method, fresh-frozen tissues are sometimes required for enough extraction of RNA samples. Therefore, it is needed to find an IHC-based biomarker that could be easily tested in FFPE and represent RNA expression for predicting prognosis and response to therapy in patients with cholangiocarcinoma.

In conclusion, many methods of predicting prognosis are being made, but IHC using FFPE, which can be most widely used in clinical practice, is the best test method for predicting prognosis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This work was supported by clinical research grant from Pusan National University Hospital in 2022.

ORCID

Dong Uk Kim https://orcid.org/0000-0002-7208-7753

REFERENCES

1. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg 2007;245:755-762.
2. Chung HH, Seo SH, Kim H, et al. Postoperative prognostic predictors of bile duct cancers: clinical analysis and immunoassays of tissue microarrays. Gut Liver 2023;17:159-169.
3. Ruys AT, Groot Koerkamp B, Wiggers JK, Klümpen HJ, ten Kate FJ, van Gulik TM. Prognostic biomarkers in patients with resected cholangiocarcinoma: a systematic review and meta-analysis. Ann Surg Oncol 2014;21:487-500.
4. Tian MX, Zhou YF, Qu WF, et al. Histopathology-based immunoscore predicts recurrence for intrahepatic cholangiocarcinoma after hepatectomy. Cancer Immunol Immunother 2019;68:1369-1378.
5. Montal R, Sia D, Montironi C, et al. Molecular classification and therapeutic targets in extrahepatic cholangiocarcinoma. J Hepatol 2020;73:315-327.