Editorial

Can combination of osteopontin and peritumor-infiltrating macrophages be a prognostic marker of early-stage hepatocellular carcinoma?

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Abstract: Hepatocellular carcinoma (HCC) is one of the most frequent malignancy worldwide. The increasing incidence of HCC in the worldwide has sparked an emerging interest in prognostic markers of HCC. Osteopontin (OPN) is a secreted phosphoprotein which has been associated with progression and metastasis of HCC. Also, peritumoral macrophage (PTM) have been reported to facilitate tumor progression and metastasis. Recently, one study reported that combination of OPN with PTM may predict the prognosis of HCC after curative resection. The authors successfully identified that combination of these two markers is an independent predictor of tumor recurrence and survival in patients with HCC, especially for those with early-stage disease. These findings might support the possibility that combination of OPN and PTM levels can be a prognostic tool. However, further investigations should be conducted before tumor OPN combined with PTMs can be accepted as a valid prognostic marker in clinical practice.

Keywords: Osteopontin (OPN); peritumoral infiltrating macrophages; prognosis; marker; hepatocellular carcinoma (HCC)

Submitted Feb 13, 2014. Accepted for publication Feb 18, 2014.
doi: 10.3978/j.issn.2304-3881.2014.02.11
View this article at: http://www.thehbsn.org/article/view/3557/4538

Hepatocellular carcinoma (HCC) is an aggressive tumor that typically occurs in patients with chronic liver disease or cirrhosis (1). HCC is different from other cancers in terms of its frequent recurrence or metastasis after curative therapy (2). Thus, a number of markers have been proposed to predict the prognosis of HCC, especially in its early stage (3). However, none of the proposed prognostic markers has been universally adopted owing to their lack of sensitivity and specificity.

Osteopontin (OPN) is a secreted multifunctional phosphoglycoprotein that has been demonstrated to be overexpressed in multiple malignant tumors (4-6). Several studies report about the role of OPN expression as a prognostic tool for a variety of cancers, including HCC (7,8), although the sensitivity and specificity of OPN expression for early-stage HCC are not reliable.

Meanwhile, host microenvironment associated-macrophages have been suggested to facilitate tumor progression and metastasis (9,10). However, the interaction between tumor-secreted OPN and macrophages that facilitates tumor progression and metastasis still remains unclear in clinical practice.

In a recent issue of *Annals of Surgical Oncology*, Zhu *et al*. reported that tumor OPN expression levels, when combined with peritumoral macrophage (PTM) levels, have a prognostic value for HCC in patients with early-stage disease (11). The authors previously reported that OPN expression level is a potential prognostic marker and therapeutic target for metastatic HCC (12-14). In their current study, the authors enrolled 374 patients with HCC, including learning and validation cohorts of 96 and 278 early-stage HCC patients, respectively, from the same institution. In the learning cohort, OPN level when combined with PTM levels was an independent prognostic factor for both overall survival (OS; P<0.0001) and time to recurrence (TTR; P=0.003). Moreover, the combination of OPN and PTM levels were significantly associated with OS

(P=0.003) and TTR (P=0.013) in the patients with early-stage HCC. They validated the prognostic value of this co-index by using an independent cohort (OS, P<0.001; TTR, P=0.001). In addition, they found that the combination was predictive of early recurrence/death risk from HCC in both cohorts. Only HCCs that were positive for OPN expression showed a significant correlation between the PTM levels and OS (P=0.01) or TTR (P=0.011). These results indicate that both the OPN and PTM levels might have influenced the prognosis and progression of the disease.

The authors successfully revealed that the high densities of tumor-derived OPN and macrophages were associated with a high incidence of early recurrence and poor survival after curative resection of HCC. This study adds new evidence to patient prognosis in HCC and provides valuable resources to further research. Nevertheless, several issues should be resolved before the combination of OPN and PTM levels can be accepted as a valid prognostic tool. It is important to confirm whether the findings of the present study can be applied consistently to other ethnic populations and whether the combination of the two prognostic markers has any therapeutic potential for early-stage HCC patients. Future studies warranted to validate these results should aim at various ethnic populations with long-term clinical results.

Furthermore, the underlying mechanisms of OPN-induced HCC metastasis and OPN/PTM interactions remain poorly understood. Recently, the authors reported that peritumoral CD68+ macrophage levels were associated with poor prognosis after curative resection in patients with HCC (15). In their current study, they presumed that OPN expression may regulate PTM function to facilitate HCC aggressiveness (11). Although the CD68+ macrophage is a pan-macrophage, it can be helpful to evaluate the mechanism of action between OPN expression and HCC progression via CD68+ macrophage levels.

Validation studies are also needed in patients with other potential confounding factors such as a different etiology of HCC (hepatitis B or C infection, or alcohol intake) or other relevant cancers, including cholangiocarcinoma. In this way, we may confirm that the combination of OPN and PTM levels is a promising prognostic marker that are not influenced by other clinical parameters.

In this study, the positive OPN and PTM expressions as a co-index were an independent prognostic factor for both OS and TTR, whereas no statistical differences were found in both the negative OPN and PTM expressions groups and either of the positive OPN or PTM expression group. However, the authors previously suggested that both OPN and PTM expressions were solely identified as a prognostic biomarker for HCC (13,15,16). These slightly conflicting results might limit the clinical application of this marker. Thus, more investigations need to be reported before such prognostic marker can be used in clinical practice.

In conclusion, although the well-designed study of Zhu *et al*. suggests that the combination of OPN and PTM expressions are well capable of predicting patient outcomes in HCC, we think that further studies should be conducted to confirm the role of the marker.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Lee YJ, Jang BK. Can combination of osteopontin and peritumor-infiltrating macrophages be a prognostic marker of early-stage hepatocellular carcinoma? Hepatobiliary Surg Nutr 2014;3(2):57-59. doi: 10.3978/j.issn.2304-3881.2014.02.11

