Editorial

Value of alpha-fetoprotein in hepatocellular carcinoma

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Comment on: Chan MY, She WH, Dai WC, *et al.* Prognostic value of preoperative alpha-fetoprotein (AFP) level in patients receiving curative hepatectomy- an analysis of 1,182 patients in Hong Kong. Transl Gastroenterol Hepatol 2019;4:52.

Received: 03 December 2019; Accepted: 23 December 2019; Published: 25 October 2021.

doi: 10.21037/tgh.2019.12.19

View this article at: http://dx.doi.org/10.21037/tgh.2019.12.19

In July issue of this Journal, Chan *et al.* published a paper focusing on prognostic value of pre-operative alpha-fetoprotein (AFP) level in the patients receiving hepatectomy for hepatocellular carcinoma (HCC) (1). They collected 1,182 patients who had curative hepatectomy for HCC. The patients were divided into 3 groups: AFP <20, 20–400 and >400 ng/mL. The patients with AFP >400 ng/mL were younger than the patients with AFP <20 or 20–400 ng/mL. Because they were young, the patients with AFP >400 ng/mL have less incidence of comorbid diseases. The patients with AFP >400 ng/mL had larger tumors and up to 65.9% of the patients had vascular invasion. The 5-year overall and disease-free survival were significantly lower than the patients with AFP <20 ng/mL and the patients with AFP between 20 to 400 ng/mL. Dr. Chan also used receiver operating characteristic curve to search the optimal cut off value of AFP for disease-free and overall survival. They found that the survival rate was compatible to one stage up for disease-free survival if AFP was >9,000 ng/mL and one stage up for overall survival if AFP was >14,000 ng/mL. Finally, they claimed that pre-operative AFP level was a significantly prognostic factor to predict survival. High level of AFP >9,000 and >14,000 ng/mL warrant an up stage of the diseases for disease-free and overall survival, respectively.

AFP is produced from embryonic endoderm tissue cells during fetus. After birth, production of AFP is reduced to a very low level. In 1968, Dr. Alpert *et al.* found that AFP was produced in 50% of HCC patients (2). Since then, AFP becomes a tumor marker of hepatocellular carcinoma (HCC). Currently, AFP is applied as one of the parameters to screen HCC in chronic hepatitis patients and is also applied as one of the diagnostic criteria of HCC (3). When AFP is more than 400 ng/mL, HCC is diagnosed excluding pregnancy (4). Clinically, AFP will appear in two-third of HCC patients.

Early stage HCC can be treated by liver resection, liver transplantation and local ablation (5). Liver resection is still the most popular curative treatment for early stage HCC in Asia because liver transplantation needs a liver graft and liver grafts are always lack. However, HCC is easy to recur even the tumor is resected completely. The reported 5-year recurrent rate is around 50% which compromises the 5-year tumor-free and overall survival (6,7). The risk factors are analyzed by many studies and the results show that liver cirrhosis, tumor size, tumor number, AFP level, blood loss, blood transfusion, resection margin, encapsulation of tumor, micro-/macro-vascular invasion, stellate tumors, and tumor histological differentiation all are the prognostic factors for liver resection (6,8,9). All these factors can be classified into three categories: liver inflammation, surgical technique and tumor pathology. That is the prognosis of HCC is already determined preoperatively by liver biology and tumor behavior. Until now, several biomarkers such as Des-c-carboxy prothrombin (DCP) or Lens culinaris agglutinin reactive AFP (AFP-L3) are suggested to be biomarkers for HCC (10,11), however, AFP is still the most popular biomarker for HCC although AFP is elevated in only two-third of HCC patients. AFP has been studied to correlate to tumor biology. Dr. Ma *et al.* divided their patients into 3 groups according to AFP ≤20, 20–400 and ≥400 ng/mL which was similar to Dr. Chan's study and they found that tumors in the patients with AFP ≤20 ng/mL

had higher cell differentiation, lower vascular invasion and lower 2-year recurrent rate than other groups (12). Dr. Peng *et al.* reported that the patients with AFP ≥200 ng/mL were associated with p53 mutation and early tumor recurrence (13). Dr. Wu *et al.* also mentioned that hazard ratio of early tumor recurrence after liver resection was 3.891 when AFP was more than 20 ng/mL (14). Therefore, high level of AFP is recognized as aggressive behavior of HCC and is associated with microvascular invasion, poor cellular differentiation, and poor prognosis.

When liver resection is performed to remove the tumor/tumors, a safe margin should be created to guarantee complete removal of the tumors. How wide of resection margin is adequate is still controversial. Dr. Zhou *et al.* have reported that 21.9% of the surgical specimens had micro-metastasis and the distance of micro-metastasis to resection margin was up to 6 mm for the HCC without macro-vascular invasion (15). If the tumors were associated with macro-vascular invasion, the distance of micro-metastasis to resection margin would be up to 19 mm. In our previous study, we found that the width of resection margin could be determined by pre-operative levels of AFP (16). Tumor-free margin is enough for the tumors with normal level of AFP, the width of resection margin should extend to ≥ 5 mm if AFP is between 15 and 200 ng/mL, and the width of resection margin should extend to ≥10 mm for the patients with AFP over 200 ng/mL. Taking together, production of AFP is an aggressive behavior of HCC and the width of resection margin should be extended for the HCC with high AFP levels.

Liver transplantation is another curative treatment for early stage HCC if the tumors are within Milan criteria (17). Liver transplantation is the best treatment for cirrhotic liver with HCC because it removes diseased liver and HCC simultaneously. However, even the diseased liver is completely removed and a new liver is implanted, HCC still recurs in around 10% of the patients. If the indication of liver transplantation is extended, the survival rate will be compromised by a higher tumor recurrent rate (18). To our knowledge, microvascular invasion is the major factor of tumor recurrence in liver transplantation. Dr. Amado *et al.* have mentioned that the actual value of AFP was associated with poor differentiation of tumor cells and microvascular invasion which increased post-transplant HCC recurrence and reduced overall survival (19). Dr. Hakeem *et al.* reviewed 12,159 patients with liver transplantation for HCC and they found that pre-operative AFP >1,000 ng/mL was associated with poor outcomes (20). AFP >1,000 ng/mL is recognized as a risk factor for liver transplantation and liver transplantation is not recommended if HCC is with AFP >1,000 ng/mL. Since liver transplantation needs liver graft, no matter deceased or living donor liver grafts, the expectation of liver transplantation for HCC is to cure the malignancy. Currently, criteria such as Milan and UCSF (21), only tumor size and tumor number are included. To prevent tumor recurrence after transplantation, the criteria must beyond tumor size and tumor number and tumor biology is suggested to be included in the criteria of liver transplantation. The serum level of AFP reflects the aggressive biology of the tumors and may put into the criteria for liver transplantation.

What is the biological effect of AFP in immunity is not very clear. In a review article, Dr. Wang *et al.* collected the information that when exogenous AFP was added into culture medium of HCC cells in laboratory study, proliferation of HCC cells would be promoted and resisted to apoptosis (22). When AFP was added into DC culture, caspase and P38-MARK would be upgraded to induce apoptosis and keep DC in immature status which impairs immune function of natural-killer cells and T-cells. Therefore, AFP is not only the surrogate of tumor aggressiveness, but also help HCC to escape from anti-tumor immunity.

AFP is applied as a tumor biomarker for HCC for several decades although AFP is elevated in only two-third of HCC patients. Currently, AFP is not just a biomarker, but also a risk factor of tumor recurrence for liver resection and liver transplantation. In Dr. Chan's study, the HCC stage will be upgraded if AFP is ≥9,000 ng/mL for disease-free and ≥14,000 ng/mL for overall survival. All these clinical findings support the clinical value of AFP. But, how are HCC cells transformed to produce AFP is still not clear. The detail role of AFP in HCC still needs further studies to explore. The future studies will include to determine the vascular invasion property of AFP-producing HCC, metabolic pathway of AFP-producing HCC, hepatitis B DNA insertion of AFP-producing HCC, molecular expression of AFP-producing HCC, etc.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This is an invited article

commissioned by the Editorial Office, *Translational Gastroenterology and Hepatology*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tgh.2019.12.19). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/tgh.2019.12.19
Cite this article as: Lee WC. Value of alpha-fetoprotein in hepatocellular carcinoma. Transl Gastroenterol Hepatol 2021;6:52.

