Can gamma-glutamyl transferase levels contribute to a better prognosis for patients with hepatocellular carcinoma?

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Hepatocellular carcinoma (HCC) is the fifth most common type of liver cancer. Hepatic resection has long been considered a main treatment option for HCC, but the high rate of recurrence after hepatic resection remains a problem that impacts the prognosis and survival of patients with HCC. Thus, clarifying the factors for survival and risk factors for tumor recurrence after hepatic resection is crucial. Imaging studies are currently emphasized before selecting a treatment and predicting the prognosis for patients with HCC. Recently, laboratory testing of des-gamma-carboxyprothrombin (DCP), alpha-fetoprotein (AFP), indocyanine green 15 min after administration (ICG-R15), and \(\gamma\)-glutamyl transpeptidase (\(\gamma\)-GTP) has garnered attention as a way to select treatment and predict the prognosis of patients with HCC. \(\gamma\)-GTP in particular has critical clinical significance as an indicator of prognosis. This indicator helps to predict prognosis and it helps with the selection of further treatment, as was revealed by studies based on different subgroups of patients published in the past 5 years. The reason for the association between \(\gamma\)-GTP and early recurrence and poor survival is being investigated. Preoperative laboratory results (DCP, AFP, ICG-R15, and \(\gamma\)-GTP) may warrant attention and need to be fully evaluated before selecting a treatment and predicting prognosis in order to improve the prognosis for patients with HCC.

**Summary**

Hepatocellular carcinoma (HCC) is the most common type of liver cancer. Hepatic resection has long been considered a main treatment option for HCC, but the high rate of recurrence after hepatic resection remains a problem that impacts the prognosis and survival of patients with HCC, as indicated by a cumulative recurrence rate of 50-60% at 3 years and a cumulative recurrence rate of 60-80% at 5 years (3-7). Thus, clarifying the factors for survival and risk factors for tumor recurrence after hepatic resection is crucial. This could help with the selection of an optimal treatment, help with monitoring to reduce the rate of recurrence, and also improve the quality of care for patients with HCC.

**Keywords:** Hepatocellular carcinoma (HCC), laboratory results, \(\gamma\)-glutamyl transpeptidase (\(\gamma\)-GTP), prognosis, recurrence
a tumor may recur in about 60.0% of patients with a single tumor smaller than 2.0 cm (12). Thus, more approaches to predict prognostic factors are urgently needed in addition to imaging studies. Pathology cannot confirm pathologic changes prior to surgery. In contrast, laboratory testing of des-gamma-carboxyprothrombin (DCP), alpha-fetoprotein (AFP), indocyanine green 15 min after administration (ICG-R15), and γ-glutamyl transpeptidase (γ-GTP) can be performed preoperatively. Thus, these indices warrant further attention as a way to select a treatment and predict prognosis for patients with HCC.

Patients with positive laboratory results for DCP, AFP, ICG-R15, and γ-GTP have a higher risk of recurrence and worse survival (13-15). These patients should receive more active treatment including anatomical hepatic resection, liver transplantation, preoperative and postoperative transcatheter arterial chemoembolization (TACE), and closer follow up. Laboratory results for DCP and AFP are related to malignancy features such as vascular invasion and metastasis. ICG-R15 is thought to be related to liver function (13,16). Most recently, γ-GTP has been identified as an independent prognostic risk for patients with HCC (14,17).

γ-GTP is a nearly ubiquitous epithelial enzyme that initiates the degradation of extracellular glutathione and its conjugates, and γ-GTP is correlated with biotransformation, nucleic acid metabolism, and tumorigenesis (10). γ-GTP was investigated and utilized as a liver function test or liver enzyme in the 1960s and 1970s (18). An increase in γ-GTP can be detected in patients with hepatitis, liver cirrhosis, or primary or secondary liver cancer (19,20). γ-GTP was used as a diagnostic tumor marker for liver disease with a high sensitivity of 83-100% but a low specificity of 32% (21). Thus, for a long time γ-GTP was not considered to be a useful tumor marker for the detection of liver disease. However, γ-GTP has critical clinical significance as an indicator of prognosis. This indicator helps to predict prognosis and it helps to select further treatment, as was revealed by studies based on different subgroups of patients published in the past 5 years (10,22-29).

As shown in Table 2, patients with high levels of γ-GTP had a greater risk of early recurrence and shorter
in carcinogenesis was reviewed by Weinberg (31). This mechanism is thought to lead to the death of normal liver cells or the loss of normal liver function. The pro-oxidant role of γ-GTP has been reported and the subsequent production of reactive oxygen species (ROS) may promote certain intra- and extracellular molecular signals (32). Recently, ROS were reported to promote epithelial-to-mesenchymal transition via the Snail-E-cadherin pathway (33) and to induce inflammation and invasion via the NF-κB pathway (34,35). A study of U937 lymphoma cells found that γ-GTP may play a role in anti-apoptotic signaling (36). A study has confirmed that cysteinyl-glycine, which is catalyzed by γ-GTP, is able to form complexes with cisplatin and that such adducts are not readily transported through the cell membrane (37). These mechanisms are thought to account for the progression of HCC. Although the molecular-biological significance of γ-GTP to worse liver function and the progression of HCC is suggested (Figure 1), this significance should be clarified in further studies.

In conclusion, preoperative laboratory results (DCP, AFP, ICG-R15, and γ-GTP) should be fully evaluated before selecting a treatment and predicting prognosis in order to improve the prognosis for patients with HCC. Recent studies have identified γ-GTP as an independent prognostic factor for patients with HCC, and further studies of the reason for the association between γ-GTP and early recurrence and poor survival are urgently needed.

Acknowledgements

This work was supported by Grants-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan.

References


Figure 1. The molecular mechanism of γ-GTP in cancer cells. γ-GTP can promote chemotherapy resistance by increasing cysteinyl-glycine, which complexes with cisplatin. Ion channels are overactivated by γ-GTP to induce damage at the genetic level. Moreover, γ-GTP plays a role in countering apoptosis in lymphoma cells. In addition, ROS is elevated by γ-GTP and subsequently leads to damage at the genetic level, inflammation, invasion, and metastasis.
19. Sheehan M, Haythorn P. Predictive values of various
17. Kim SH, Choi SB, Lee JG, Kim SU, Park MS, Kim do Y ,
15. Fukuda S, Itamoto T, Amano H, Kohashi T, Ohdan H,
12. Shirabe K, Kajiyama K, Harimoto N, Masumoto

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(Received May 3, 2014; Accepted June 22, 2014)