



# p53 gene therapy for hepatocellular carcinoma

## Hepatosellüler karsinomda p53 gen tedavisi

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### Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy with a very high morbidity and mortality [1]. It has a poor prognosis due to its common infiltration. The underlying liver parenchyma displays various histological changes like steatosis, inflammation and fibrosis to cirrhosis. The limits of the possibility for curative treatments are histological changes of the underlying parenchyma and the risk of multi-centric carcinogenesis from chronically injured liver tissue [2]. Liver carcinogenesis is driven by genetic alterations in combination with viral and environmental factors. In the treatment of HCC, some conditions must take into consideration. The stage of HCC, the severity of chronic liver disease, and co-morbidities and performance status of the patient should be taken into consideration during the treatment of HCC (Table 1).

Table 1: ECOG performance status

Grade 0	Fully active, able to carry on all pre-disease performance without restriction
Grade 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Grade 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Grade 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Grade 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
Grade 5	Dead

Currently, no effective treatment modality is available for HCC [3]. Available treatments are liver transplantation or surgical resection for selected patients with early tumor development, and chemotherapy and/or radiation therapy for advanced stages of the tumor. Although liver transplantation and resection are the only curative treatments, these two therapies can only be applied to a small percentage of the patients because of the shortage of human tissues and the fact that HCC is usually in unresectable stages when diagnosed. Additionally, the recurrence rate after resection is seen in more than 80% of patients [4]. The aim of this article is to review p53 gene therapy as a new modality of hepatocellular carcinoma.

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### Carcinogenesis

HCC is a pathologically and clinically heterogeneous disease condition. The prognosis depends on the aggressiveness of HCC and residual liver function [5]. The progression of HCC is thought to involve the deregulation of genes that are critical to cellular processes such as cell cycle control, cell growth, apoptosis, and cell migration and spreading [6, 7]. Liver carcinogenesis is driven by genetic alterations in combination with viral and environmental factors.  $\beta$ -catenin and p53 mutations representing the two main genetic alterations described in HCC [8].

p53 is a tumor suppressor gene, and is responsible for apoptotic signals in tumor progression, and thus for their uncontrolled proliferation and recurrence. p53 mutations represent main genetic alteration described in HCC. New approaches to HCC treatment are needed to improve patient survival. Therefore, p53 gene therapy has been proposed as a potential treatment. It was reported that the incidence of p53 mutation is 61% in HCC [9]. Gene therapy of the delivery techniques includes systemic intravenous injection, intra-arterial injection, intra-tumoral injection, intra-portal injection, intra-biliary delivery and intra-splenic injection. Gene therapy has the potential to provide therapeutic benefits to HCC patients and has been the subject of intense pre-clinical and clinical research in recent years [10].

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