

MACC1 gene is an independent prognostic biomarker for survival in Klatskin tumor patients

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Bile duct cancer is rare and is usually detected too late. Often only extensive liver surgery can help or, in rare cases, liver transplantation. But which patients will benefit from surgery and which will not, because their risk of cancer recurrence is too high? With the oncogene MACC1 as a biomarker, physicians for the first time have a tool to decide which treatment option is best for patients with Klatskin carcinoma, one type of bile duct cancer. If MACC1 expression is low, the patients have a good chance that surgery will prolong survival. By contrast, if the gene is upregulated, the risk of recurrence is high. These were the findings of a study by Andri Lederer and Professor Ulrike Stein of the Experimental and Clinical Research Center (ECRC), an institutional cooperation between the Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC) and the Charité - Universitätsmedizin Berlin on Campus Berlin -Buch.

The bile ducts are the drainage system for the bile produced by the [liver](#) cells. There are bile ducts inside and outside the liver. The bile ducts of the right and left hepatic lobes join to form the common [bile duct](#), which opens into the small intestine (duodenum). There, the bile is required for the digestion of fat.

There are different types of [bile duct cancer](#). One type is Klatskin carcinoma, named after the American internist Gerald Klatskin, which develops just outside the liver. Another type is intrahepatic

cholangiocarcinoma (ICC), which starts inside the liver. Both types of bile duct [cancer](#) are rare - in Europe and the U.S. only one in 100 000 people is affected - but they comprise the second most common malignancy of the liver after primary liver cell cancer. Since both Klatskin tumors and ICC are usually detected too late, they are difficult to treat, and patients' life expectancy is severely reduced. Approximately 30 percent of patients survive the first five years after liver surgery.

In Klatskin tumors, bile flow is obstructed at the confluence (hepatic bifurcation) of the various bile ducts of the liver. Often the carcinoma is so extensive at the time of diagnosis that even a radical removal of the [cancer tissue](#) is impossible. In such cases, [liver transplantation](#) is the last resort, but it is currently only performed within the framework of clinical trials.

Until now, doctors had no evidence which patients might best be helped with a [liver transplant](#). This decision is made more difficult by the lack of donor organs. Andri Lederer, who worked for a year in the laboratory of Professor Stein at the MDC and who currently works in the Department of General, Visceral and Transplantation Surgery of the Charité under Professor Johann Pratschke, said, "Patients with Klatskin tumors may also benefit from liver transplantation and may live longer, under the condition that they have a low risk of recurrence."

MACC1 gene highly prognostic for metastasis risk

Using the MACC1 gene as biomarker, physicians can now for the first time determine the risk of metastasis in Klatskin carcinoma. This gene was discovered by Professor Stein, Professor emeritus Peter Schlag (MDC and Charité) and Professor Walter Birchmeier (MDC) in 2009 in tissue samples of colon cancer patients. MACC1 (Metastasis Associated In Colon Cancer 1) not only promotes cancer proliferation but also metastasis formation. The gene is also the main regulator of the

HGF/Met signaling pathway. It regulates cell proliferation, cell migration and metastasis formation. Furthermore, in this signaling pathway the Met gene plays an important role in the development of Klatskin carcinoma.

The surgeons Andri Lederer, Professor Daniel Seehofer, Professor Johann Pratschke and Professor Schlag, as well as the pathologist Professor Manfred Dietel and the cancer researcher Professor Stein examined tissue samples from 156 patients with Klatskin and ICC carcinomas, from whom between 1998 and 2003 a part of the liver was removed. Among them were 76 patients with Klatskin carcinomas. The [tissue samples](#) contained both malignant tissue as well as cancer-free tissue. Tissue samples from patients with benign liver diseases were also included.

MACC1 expression ten times higher in cancer tissue

The study showed that the MACC1 gene is expressed ten times higher in cancer tissue than in normal tissue. Moreover, in recurrent tumors that developed in the patient after surgery, MACC1 expression was much higher than in normal tissue. The survival time of patients with high MACC1 levels amounted on average to a little less than two years (613 days) in contrast to six years (2257 days) for patients with low MACC1. The relapse-free time, i.e. the time without cancer recurrence, in patients with high MACC1 levels was just under two years (753 days) in contrast to almost nine years (3119 days) for patients with low MACC1 levels.

However, MACC1 proved unsuitable as a biomarker for intrahepatic cholangiocellular carcinoma (ICC). The researchers hypothesize that ICC and Klatskin carcinomas behave differently, since they originate from different bile ducts inside and outside the liver.

MACC1 - not only a biomarker, but also a target

MACC1 is also responsible for the formation of secondary tumors (distant metastases). The clinicians and researchers therefore view MACC1 not only as an indicator of the severity of a disease, but also as a target for therapy. In preclinical studies, Professor Stein and her colleagues are already testing new substances which inhibit both the expression and the activity of the MACC1 gene.

Blood test for early detection

The earlier a cancer is detected, the greater the chances of successful treatment and a long survival time. Therefore Professor Stein has developed a blood test for early detection of cancer, based on the MACC1 gene. With the blood test, it is possible, at a very early stage of cancer (colon cancer, gastric cancer, lung cancer) to identify patients who are at high risk of developing life-threatening metastases. Meanwhile, the test for the detection of MACC1 in tumors and in blood has been patented in the U.S., Australia, Japan, Canada and Europe.

The aim is to develop such early detection tests with MACC1 for other cancers as well, including the Klatskin carcinoma. Since 2009 Professor Stein and researchers from various countries have shown that there is a correlation in many carcinomas between elevated MACC1 expression and a shorter survival time of the [patients](#). These include liver cancer, stomach cancer, pancreatic cancer, lung cancer, ovarian cancer, breast cancer, nasopharyngeal cancer, esophageal cancer, kidney cancer, bladder cancer, gallbladder cancer, glioblastoma and bone cancer.

More information: MACC1 is an independent prognostic biomarker for survival in Klatskin tumor patients, *Hepatology*; 2015;62:841-850

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