Cancer Association of South Africa (CANSA)

Research • Educate • Support

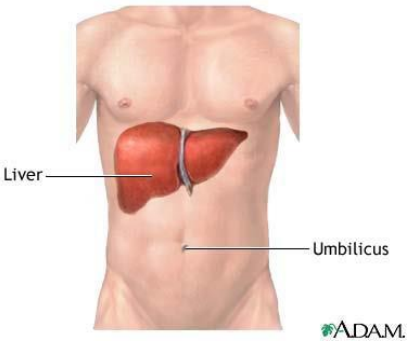
Fact Sheet on Liver Cancer

Introduction

The liver has a wide range of functions, including detoxification, protein synthesis, as well as the production of various biochemicals necessary for digestion. The liver is necessary for survival.

Medical terms related to the liver often start in *hepato-* or *hepatic* from the Greek word for liver, *hēpar* (ἡπαρ).

[Picture Credit: Liver]



Liver Cancer

Liver cancer (hepatocellular carcinoma) is a cancer arising from the liver. It is also known as primary liver cancer or hepatoma.

Chang, C.W., Lo, J.F. & Wang, Z.W. 2019.

"Primary liver cancer (PLC) is heterogeneous and it is an aggressive malignancy with a poor prognostic outcome. Current evidence suggests that PLC tumorigenesis is driven by rare subpopulations of cancer stem cells (CSCs), which contribute to tumor initiation, progression, and therapy resistance through particular molecular mechanisms. Energy metabolism and mitochondrial function play an important role in the regulation of cancer stemness and stem cell specifications. Since the role of mitochondrial function as central hubs in cell growth and survival, studies on the critical physiological mechanisms of the liver underlying their therapy-resistant phenotype is important. In this review, we focus on liver CSC-related mitochondrial metabolism that contributes to the liver CSC features, in terms of enhanced drug-resistance and increased tumorigenicity, and to discuss their roles on potential therapies windows for PLC therapies."

Incidence of Cancer of the Liver and Bile Duct in South Africa

According to the outdated National Cancer Registry (2014), known for under reporting, the following number of liver and bile duct cancer cases was histologically diagnosed in South Africa during 2014:

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Group - Males 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	248	1:693	0,67%
Asian males	9	1:383	0,99%
Black males	152	1:812	1,37%
Coloured males	23	1:892	0,54%
White males	65	1:522	0,31%

Group - Females 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	165	1:1 277	0,44%
Asian females	10	1:622	0,85%
Black females	93	1:1 537	0,58%
Coloured females	15	1:2 295	0,37%
White females	47	1:810	0,29%

The frequency of histologically diagnosed cases of liver and bile duct cancer in South Africa for 2014 was as follows (National Cancer Registry, 2014):

Group - Males 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	4	10	28	39	54	48	53	8
Asian males	0	0	1	0	1	4	3	0
Black males	4	5	24	30	34	21	24	2
Coloured males	0	2	1	5	6	5	3	0
White males	0	1	2	4	13	16	22	5

Group - Females 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	5	8	7	19	39	33	28	17
Asian females	0	0	0	1	3	1	1	1
Black females	4	7	6	15	24	15	12	2
Coloured females	0	1	0	2	1	4	2	5
White females	1	0	1	1	11	10	13	9

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

According to **Bruni, *et al*.,** (2019), the burden of liver cancer for South Africa for 2018 is estimated as (based on Globocan estimates):

- Annual number of liver cancer cases 2 495
- Annual number of liver cancer deaths 2 388

Causes of Liver Cancer

Hepatocellular carcinoma accounts for most liver cancers. This type of cancer occurs more often in men than women. It is usually seen in people age 50 or older. However, the age varies in different parts of the world.

In most cases, the cause of liver cancer is usually scarring of the liver (cirrhosis). Cirrhosis may be caused by:

- Alcohol consumption
- Autoimmune diseases of the liver
- Hepatitis B or C viral infections
- Chronic inflammation of the liver
- Iron overload in the body (haemochromatosis)

Risk Factors for Liver Cancer
Factors that may increase the risk of primary liver cancer include:

- Alcohol consumption – alcohol has been declared a Group 1 carcinogen, which means that there is sufficient evidence that it causes cancer in humans
- Exposure to aflatoxins - consuming foods contaminated with fungi that produce aflatoxins
- Age - In developing countries of Asia and Africa, liver cancer diagnosis tends to occur between 20 and 50
- Liver diseases that can increase the risk for liver cancer include haemochromatosis and Wilson's disease
- Individuals with this blood sugar disorder have a greater risk of liver cancer
- Gender – research shows that men are more likely to develop liver cancer than are women
- Non-alcoholic fatty liver disease
- Obesity - having an unhealthy body mass index increases the risk of liver cancer.

Puigvehí, M., Moctezuma-Velázquez, C., Villanueva, A. & Llovet, J.M. 2019.
"Hepatitis delta virus (HDV) is a small defective virus that needs hepatitis B virus (HBV) to replicate and propagate. HDV infection affects 20-40 million people worldwide and pegylated interferon (PegIFN) is the only recommended therapy. There is limited data on the contribution of HDV infection to HBV-related liver disease or liver cancer. Evidence from retrospective and cohort studies suggests that HBV/HDV coinfection accelerates progression to cirrhosis and is associated with an increased risk of hepatocellular carcinoma (HCC) development compared to HBV monoinfection. Although the life cycle of HDV is relatively well known, there is only ancillary information on the molecular mechanisms that can drive specific HDV-related oncogenesis. No thorough reports on the specific landscape of mutations or molecular classes of HDV-related HCC have been published. This information could be critical to better understand the uniqueness, if any, of HDV-related HCC and help identify novel targetable mutations. Herein, we review the evidence supporting an oncogenic role of HDV, the main reported mechanisms of HDV involvement and their impact on HCC development."

Signs and Symptoms of Liver Cancer
Most people don't have signs and symptoms in the early stages of primary liver cancer. When signs and symptoms do appear, it may include:

- loss of appetite
- upper abdominal pain

- nausea and vomiting
- losing weight without trying to do so
- general weakness and fatigue
- enlargement of the liver
- enlarged spleen
- distended abdomen
- yellow discoloration of the skin and the white of the eyes (jaundice)
- dark urine
- pale (sometimes nearly white), chalky stools
- easy bruising or bleeding
- fever

Diagnosis of Liver Cancer

The following procedures contribute towards the diagnosis of liver cancer and may be ordered by your treating physician:

- Ultrasound - this test uses sound waves to look for masses in the liver
- Computed tomography (CT) - The CT scan is an x-ray test that produces detailed cross-sectional images of your body.
- Magnetic Resonance Imaging (MRI) - Like CT scans, MRI scans provide detailed images of soft tissues in the body, but use radio waves and strong magnets instead of X-rays.
- Angiography - An angiogram is an x-ray test for looking at blood vessels. Contrast medium, or dye, is injected into an artery to outline blood vessels while x-ray images are taken.

Other Procedures

Other types of tests may be done if the doctor thinks the patient might have liver cancer but the imaging test results are not conclusive.

- Laparoscopy - in this procedure, a doctor inserts a thin, lighted tube with a small video camera on the end through a small incision (cut) in the front of the abdomen to look at the liver and other internal organs.
- Biopsy - a biopsy is the removal of a sample of tissue to see if there is cancer present.

Laboratory Tests

The treating doctor may order laboratory tests:

- Alpha-fetoprotein blood (AFP) test – this is a blood test to look for alpha-fetoprotein (AFP) in the blood.
- Liver function tests (LFTs) - A series of blood tests that measure levels of certain substances in the blood that show how well the liver is working
- Blood clotting tests - a damaged liver may not make enough of these clotting factors, which could increase the risk of bleeding. The treating doctor may order blood tests such as a prothrombin time (PT) to help assess this risk
- Tests for viral hepatitis - blood tests to check for hepatitis B and C
- Kidney function tests - tests of blood urea nitrogen (BUN) and creatinine levels

- Complete blood count (CBC) - this test measures levels of red blood cells, white blood cells (which fight infections) and platelets (which help with blood clot)
- Other blood chemistry tests - blood chemistry tests check the levels of a number of minerals and other substances in the blood.

Jeffrey, G.P., Gordon, L.G., Hill, M.M. & Ramm, G.A. 2020.
"Clinicians need to be aware of the powerful new technologies that are being directed toward early diagnosis of hepatocellular carcinoma (HCC). A recent article by Qu C, Wang Y, Wang P, et al. Detection of early-stage hepatocellular carcinoma in asymptomatic HBsAg-seropositive individuals by liquid biopsy. Proc Natl Acad Sci U S A. 2019;116:6308-6312 reported that the presence of somatic mutations and HBV integrations in circulating cell free DNA (cfDNA), the concentration of cfDNA and concentration of protein tumor markers in blood were combined with age and gender to develop a "liquid biopsy" to identify early stage HCC."

Howell, J., Atkinson, S.R., Pinato, D.J., Knapp, S., Ward, C., Minisini, R., Burlone, M.E., Leutner, M., Pirisi, M., Büttner, R., Khan, S.A., Thursz, M., Odenthal, M. & Sharma, R. 2019.
BACKGROUND: Hepatocellular carcinoma (HCC) is increasing globally. Prognostic biomarkers are urgently needed to guide treatment and reduce mortality. Tumour-derived circulating cell-free DNA (ctDNA) is a novel, minimally invasive means of determining genetic alterations in cancer. We evaluate the accuracy of ctDNA as a biomarker in HCC.
METHODS: Plasma cell-free DNA, matched germline DNA and HCC tissue DNA were isolated from patients with HCC (n = 51) and livercirrhosis (n = 10). Targeted, multiplex polymerase chain reaction ultra-deep sequencing was performed using a liver cancer-specific primer panel for genes ARID1A, ARID2, AXIN1, ATM, CTNNB1, HNF1A and TP53. Concordance of mutations in plasma ctDNA and HCC tissue DNA was determined, and associations with clinical outcomes were analysed.
RESULTS: Plasma cell-free DNA was detected in all samples. Lower plasma cell-free DNA levels were seen in Barcelona Clinic Liver Cancer (BCLC A compared with BCLC stage B/C/D (median concentration 122.89 ng/mL versus 168.21 ng/mL, p = 0.041). 29 mutations in the eight genes (21 unique mutations) were detected in 18/51 patients (35%), median 1.5 mutations per patient (interquartile range 1-2). Mutations were most frequently detected in ARID1A (11.7%), followed by CTNNB1 (7.8%) and TP53 (7.8%). In patients with matched tissue DNA, all mutations detected in plasma ctDNA detected were confirmed in HCC DNA; however, 71% of patients had mutations identified in HCC tissue DNA that were not detected in matched ctDNA.
CONCLUSION: ctDNA is quantifiable across all HCC stages and allows detection of mutations in key driver genes of hepatic carcinogenesis. This study demonstrates high specificity but low sensitivity of plasma ctDNA for detecting mutations in matched HCC tissue.

Treatment of Liver Cancer
The treatment will depend on the size, location and stage of the tumour and whether it has spread or not and may include.

- Surgery - surgery often offers the best chance for a cure. Surgery may involve removing (resecting) the diseased part of the liver to eliminate the cancer or transplant surgery to remove the liver and replace it with a donor's healthy liver.

- Chemotherapy – chemotherapy which is delivered straight into the liver with a catheter can help, but it will not cure the disease.
- Radiation therapy – radiation treatments in the area of the cancer may also be helpful.

Syed, Y.Y. 2020.
"Ramucirumab (Cyramza®), a fully human anti-VEGFR-2 monoclonal antibody, has been approved as monotherapy for the treatment of patients with hepatocellular carcinoma (HCC) and α-fetoprotein levels ≥ 400 ng/mL who have been treated with sorafenib. Ramucirumab significantly prolonged overall survival (OS) and progression-free survival (PFS) relative to placebo in this population in the randomized, double-blind phase 3 REACH 2 trial. These benefits were seen in key prespecified subgroups based on demographic and disease characteristics. Ramucirumab had an acceptable tolerability profile and manageable safety profile in these patients, with the majority of treatment-related adverse events being mild or moderate in severity. The safety profile of ramucirumab was consistent with that expected for agents targeting the VEGF/VEGFR axis. Currently, ramucirumab is the only therapy specifically tested in patients with α-fetoprotein levels ≥ 400 ng/mL, which is associated with an aggressive disease and poor prognosis. Therefore, ramucirumab is an important treatment option for patients with HCC and α-fetoprotein levels ≥ 400 ng/mL who have been treated with sorafenib."

Juengpanich, S., Shi, L., Iranmanesh, Y., Chen, J., Cheng, Z., Khoo, A.K., Pan, L., Wang, Y. & Cai, X. 2019.
"A major obstacle for treatment of HCC is the inadequate efficacy and limitation of the available therapeutic options. Despite the recent advances in developing novel treatment options, HCC still remains one of the major causes of cancer morbidity and mortality around the world. Achieving effective treatment and eradication of HCC is a challenging task, however recent studies have shown that targeting Natural Killer cells, as major regulators of immune system, can help with the complete treatment of HCC, restoration of normal liver function and subsequently higher survival rate of HCC patients. Studies have shown that decrease in the frequency of NK cells, their dysfunction due to several factors such as dysregulation of receptors and their ligands, and imbalance of different types of inhibitory and stimulating microRNA expression is associated with higher rate of HCC progression and development, and poor survival outcome. Here in our review, we mainly focused on the importance of NK cells in HCC development and treatment."

Yau, T., Hsu, C., Kim, T.Y., Choo, S.P., Kang, Y.K., Hou, M.M., Numata, K., Yeo, W., Chopra, A., Ikeda, M., Kuromatsu, R., Moriguchi, M., Chao, Y., Zhao, H., Anderson, J., Dela Cruz, C. & Kudo, M. 2019.
BACKGROUND & AIMS: Nivolumab, an immune checkpoint inhibitor, is approved in several countries to treat sorafenib-experienced patients with hepatocellular carcinoma (HCC), based on results from CheckMate 040 (NCT01658878). Marked differences exist in HCC clinical presentation, etiology, treatment patterns, and outcomes across regions. This analysis assessed the safety and efficacy of nivolumab in the Asian cohort of CheckMate 040.
METHODS: CheckMate 040 is an international, multicenter, open-label, phase I/II study of nivolumab in adults with advanced HCC, regardless of etiology, not amenable to curative resection or local treatment, with/without prior sorafenib treatment. This analysis included all sorafenib-experienced patients in the intent-to-treat (ITT) overall population and Asian cohort. The analysis cutoff date was March 2018.

RESULTS: There were 182 and 85 patients in the ITT population and Asian cohort, respectively. In both populations, most patients were >60 years old, had Barcelona Clinic Liver Cancer stage C disease, and had received prior systemic therapy. A higher percentage of Asian patients had HBV infections, extrahepatic metastases, and prior therapies. Median follow-up was 31.6 and 31.3 months for the ITT and Asian patients, respectively. Objective response rates (ORRs) were 14% and 15% in the ITT population and Asian cohort, respectively. In the Asian cohort, uninfected, HBV-infected, and HCV-infected patients had ORRs of 21%, 13%, and 14%, respectively. Median duration of response was longer in the ITT (19.4months) vs. Asian patients (9.7months). Median overall survival was similar between the ITT (15.1months) and Asian patients (14.9months), and unaffected by etiology in Asian patients. Nivolumab safety profile was similar and manageable across both populations.
CONCLUSION: Nivolumab safety and efficacy is comparable between sorafenib-experienced ITT and Asian patients.
LAY SUMMARY: The CheckMate 040 study evaluated the safety and efficacy of nivolumab in patients with advanced hepatocellular carcinoma (HCC) who were refractory to prior sorafenib or chemotherapy. This sub-analysis of the data showed that treatment responses and safety in patients in Asia were similar to that of the overall treatment population, providing support for nivolumab as a treatment option for these patients.

Wang, L., Zhu, Z., Han, L., Zhao, L., Weng, J., Yang, H., Wu, S., Chen, K., Wu, L. & Chen, T. 2019.
"Hepatocellular carcinoma (HCC) is a common cancer type throughout the world. Due to the high occurrence rate and mortality, liver cancer is one of the leading causes of cancer associated death. With the development of monoclonal antibodies and immunotherapy, the mortality of HCC cancer patients has reduced. However, the recurrence and outcomes of patients remain poor. Therefore, there is an urgent need to develop more effective drugs for HCC therapy. WZ35, a novel curcumin derivative, exhibits potential anti-tumor activity in gastric cancer cells by regulating ROS dependent JNK activation and ER stress. Here, we evaluated the tumor suppressive activity of WZ35 in hepatocellular carcinoma in vitro and in vivo. CCK-8 was used to detect cell viability with or without curcumin or WZ35; cell apoptosis was determined by flow cytometry analysis; GFP-LC3 plasmids were used to investigate the level of autophagy-associated LC3; siRNA transfection was applied to silence endogenous YAP; and western blot was performed to detect the alteration of indicated molecules. Bioinformatics analysis and IHC assay were applied to evaluate the YAP level in normal and liver cancer tissues. In this study, we found that WZ35 effectively suppresses HCC cancer cell growth in vitro and in vivo by promoting cell apoptosis. Importantly, downregulation of YAP contributes to WZ35 caused autophagy inhibition which is different from that of curcumin. We also confirmed that WZ35 is more effective at suppressing HCC cell growth in vivo. Finally, we confirmed that YAP was significantly overexpressed in liver cancer tissues. Collectively, these data indicate that WZ35 could be considered as a promising compound for HCC therapy."

Complications of Liver Cancer
The complications of liver cancer may include:

- Budd-Chiari syndrome - hepatic vein obstruction prevents blood from flowing out of the liver and back to the heart. This blockage can cause liver damage. Obstruction of this vein can be caused by a tumour or growth pressing on the vessel, or by a clot in the vessel (hepatic vein thrombosis). Hepatic vein obstruction is the most common cause of Budd-Chiari syndrome
- cancer spread to other organs

- internal bleeding
- liver failure
- rupture of the tumour

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The **South African National Clinical Trials Register** provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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