HEPATOCELLULAR CARCINOMA (HCC)

Hepatocellular Carcinoma (HCC) is the world's most common form of primary liver cancer – cancer that starts in the liver

Primary liver cancer is the sixth most common cancer in the world and the second leading cause of cancer-related death.[1] It affects mainly patients with cirrhosis from any cause, including viral hepatitis and alcohol misuse. HCC represents more than 90% of primary liver cancers and is a major global health problem.[2]

As HCC originates in the liver, it is not the same as metastatic liver cancer, in which tumours spread to the liver from another primary site, such as the colon or breast. The prognosis for patients with advanced, unresectable HCC is bleaker than for patients with liver metastases.

HCC results in more than 670,000 deaths globally per annum.[3] Estimates for the coming decade suggest that the global burden of the disease will increase considerably as large segments of the world's population continue to age.[1] The incidence of HCC increases progressively with advancing age, reaching a peak at around 70 years.[2]

Radical therapies such as liver transplantation, surgical resection or ablation of the tumours may cure HCC. Unfortunately, only about 30–40% of HCC patients are eligible for these potentially curative therapies.[4] For the majority of HCC patients who present with advanced, unresectable HCC, life expectancy generally does not exceed 11 months with treatment.[5] No new first-line treatment alternative has become available for patients with advanced, unresectable HCC for more than a decade.

Causes of HCC

Most patients with HCC have underlying cirrhosis of the liver, which develops following long periods of chronic liver disease. Although major risk factors of HCC vary across regions, the most common ones include Hepatitis B and C viruses, as well as alcohol misuse.

Overall, one-third of cirrhotic patients will develop HCC during their lifetime.[6]

- Worldwide, approximately 54% of HCC cases can be attributed to Hepatitis B virus infection (affecting 400 million people) while 31% can be attributed to Hepatitis C virus infection (affecting 170 million people).[2]
- In Africa and East Asia, the largest attributable fraction is due to Hepatitis B virus infection (60%) whereas in the developed Western world, chronic Hepatitis C virus infection appears to be the major risk factor.[7,8]

In addition to these causes, it is now thought that in up to one in eight (12.8%) of non-alcoholic steatohepatitis (NASH) patients with cirrhosis the liver disease will progress to HCC.[9] NASH, which is widely considered to be triggered by type II diabetes, insulin resistance, obesity, hyperlipidemia and hypertension, has become the number one cause of liver disease in Western countries. Progression of NASH dramatically increases the risks of cirrhosis, liver failure, and HCC. This is thought to be related to the worldwide epidemic of diabetes and obesity.[10]

HCC occurs more often in men than women, except in Africa, where more women are affected.[2]

Staging for HCC

The contemporary care of HCC is heavily dependent on how advanced the cancer is at the time of diagnosis. The most commonly widely accepted staging system is the Barcelona Clinic Liver Cancer (BCLC) system. [4,11,12]

STAGE	PRESENTATION SUMMARY
Very early	Defined as the presence of a single tumour up to 2 cm in diameter in patients with good health status and well-preserved liver function
Early	Defined as the presence of a single tumour nodule, or as many as 3 nodules up to a total diameter of 3 cm, with good health status and well-preserved liver function
Intermediate	Unresectable patients with multinodular asymptomatic tumours without an invasive pattern and a good performance status
Advanced	Unresectable patients with cancer-related symptoms that limit performance status, symptomatic tumours, portal vein invasion and extrahepatic spread (lymph node involvement or metastases)
End-stage	Unresectable patients with extensive disease and very poor performance status

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Treatment for HCC

Like most cancers worldwide, HCC requires the management by multiple medical disciplines, such as but not limited to surgery, transplant, interventional radiology and medical oncology. Additionally, with most cases arising in a cirrhotic liver, research is often limited and patients commonly require the supportive care of a skilled Hepatologist. As a result, the strength of evidence for most interventions in HCC lags behind other cancers.[2]

Examples of therapies where significant research has been done and/or those that are commonly used in the clinical care of HCC are:

1. Surgery

Wherever possible, the standard of care for HCC is surgical resection. Resection and transplantation (from either healthy or deceased donors) achieve the best outcomes in well-selected candidates and are the first option in patients with early tumours.[2]

Surgical resection is the first-line option for patients with early-stage HCC (BCLC 0 or A) with solitary tumours, and confers 5-year survival rates of 70% but recurrence rates following resection ranges from 60−70% at 5 years.[13,14] Survival following transplant can be as high as 74% after 5 years.[15]

2. Local ablation

Local ablation with radiofrequency, microwaves or ethanol injection is considered the standard of care for patients with small tumours (very early and early stages) not suitable for surgery.

Radiofrequency ablation (RFA) is recommended in most instances as the main ablative therapy in tumours smaller than 3 cm.[16] The best results obtained for HCC patients treated by RFA provide 5-year survival rates of 48–61%.[17]

Microwave ablation is a relatively new technique that may have some advantages over RFA.[18]

Ethanol injection is recommended in cases where radiofrequency ablation is not technically feasible (around 10-15% of cases).[2]

3. Chemoembolisation

Transarterial Chemoembolisation (TACE) is the most widely used initial treatment for HCC tumours that cannot be resected or ablated and the recommended first-line therapy for patients with intermediate stage disease.[2] There are two types of TACE – Conventional TACE (cTACE) and Drug-Eluting Bead TACE (DEB-TACE).

cTACE involves injecting a chemotherapy agent directly into an artery supplying a tumour. Scientific literature surrounding cTACE is equivocal. Only two of eight randomised controlled trials (RCT) showed a significant survival benefit for cTACE; the remaining six RCTs failed to demonstrate a benefit.[19-26] Although one systematic review in 2003 demonstrated that cTACE improved survival in unresectable HCC, a Cochrane analysis in 2011, reported no firm evidence to support or refute TACE or TAE (Transarterial Embolisation) for unresectable HCC.[27,28]

DEB-TACE involves injecting small particles loaded with chemotherapeutic agents into an artery directly supplying a tumour.

These two techniques interrupt the tumour's blood supply and stall tumour re-growth.[2] Studies have shown no difference in survival between cTACE and DEB-TACE.[29,30]

Both forms of TACE normally involve multiple treatments and in many cases several days of hospitalisation.[31,32]

4. Sorafenib

Sorafenib is the standard systemic therapy for advanced HCC. It is indicated for patients with advanced disease and well-preserved liver function.

Sorafenib, which was first approved in 2007, remains the only drug that has demonstrated survival benefits in patients with advanced HCC. Subsequently, numerous agents have been tested against sorafenib or in combination with it and have failed to improve survival or reduce treatment-related adverse events.[33-36]

The pivotal trial demonstrated an increase in median overall survival (mOS) from 7.9 months to 10.7 months in patients with advanced disease.[5] In Asia Pacific, mOS was 6.5 months in patients treated with sorafenib, compared with 4.2 months in those who received placebo.[37]

5. Selective Internal Radiation Therapy (SIRT)

SIRT (also known as radioembolisation) is an innovative type of radiation therapy that targets high doses of radiation directly to liver tumours *in situ*. The therapeutic agent consists of microscopic resin beads (microspheres) bound with radioactive Yttrium-90 (Y-90). These are injected directly into the hepatic artery via a catheter inserted through a groin incision.

The microspheres become lodged in the capillaries in and around the liver tumours. The short-range radiation is delivered in high doses to the immediate location of the tumour.

The main candidates for SIRT have either intermediate-stage or advanced HCC and are generally considered poor candidates for TACE, progressed after TACE or failed TACE.

There have been several clinical explorations of SIRT that have yielded non-confirmatory signals to validate further research:

- For patients with unresectable HCC, SIRT using SIR-Spheres Y-90 resin microspheres has shown to be at least as safe and effective as multiple TACE procedures and is well tolerated.[38,39]
- SIR-Spheres Y-90 resin microspheres have also shown to be at least as effective as systemic therapy of HCC with daily doses of sorafenib, but with fewer side effects and less impact on patient quality of life.[40-42]
- Smaller SIRT studies and retrospective analyses have reported a median survival time of 16.9–23.8 months for patients at intermediate stages, and 9.2–11.8 months for patients at advanced stages of HCC treated with SIR-Spheres Y-90 resin microspheres.[43-45]

Based on these signals, two large multi-centre randomised controlled studies were launched in 2010 and 2011 to compare the efficacy and safety of SIR-Spheres Y-90 resin microspheres with sorafenib in patients with intermediate or advanced HCC - The SIR*ve*NIB trial in Asia and the SARAH trial in Europe.[46,47]

The results from SARAH and SIR*ve*NIB were presented at the European Association for the Study of the Liver (EASL) congress in April 2017 and at the American Society of Clinical Oncology (ASCO) 2017 Annual Meeting in June 2017, respectively.

Neither study achieved its primary endpoint of increased OS for patients treated with SIR-Spheres Y-90 resin microspheres delivered directly to liver tumours *versus* systemic oral therapy with the standard of care, sorafenib. OS did not significantly differ between the 2 groups:

- in the SARAH study, patients in the SIRT "intention-to-treat" (ITT) group had a median survival of 8.0 months *vs*. 9.9 months in the sorafenib arm (HR= 1.15: p=0.18); [46]
- in the SIR*ve*NIB study, median OS in the SIRT ITT group was 8.84 *vs*. 10.02 months in the sorafenib group (HR=1.12: p=0.360).[47]

Interestingly, no difference in OS time occurred when calculated based on the actual rather than intended numbers of patients treated with SIRT (9.9 months for patients in either group in the SARAH study (HR=0.99: p=0.92) and 11.27 in the SIRT group *versus* 10.41 months in the sorafenib arm in the SIR*ve*NIB study (HR=0.86: p=0.273)).

In terms of planned secondary endpoints, SIRT using SIR-Spheres Y-90 resin microspheres was associated with significantly fewer and less severe treatment-related adverse events than systemic treatment with sorafenib. Moreover, it was demonstrated in the SARAH study that patient-reported Quality of Life measured with the global health status sub-score of the QLQ-C30 questionnaire was significantly better in the SIRT arm than in the sorafenib group.

In addition to these two “head-to-head” studies, a third large European study called SORAMIC is comparing treatment of HCC with SIR-Spheres Y-90 resin microspheres followed by sorafenib to treatment with sorafenib alone. Results from SORAMIC are expected to be presented at a major medical congress in 2018.

For more information please visit:
www.sirtex.com/HCC
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