PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

GASTROINTESTINAL

HEPATOCELLULAR CARCINOMA

GI Site Group – Hepatocellular Carcinoma

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These guidelines are evidence-based and thus subject to change. Some recommendations are currently funded in this jurisdiction, while others are in negotiation.

1. Introduction

Primary hepatocellular carcinoma (HCC) is a highly lethal cancer. Hepatocellular carcinoma represents more than 90% of primary liver cancers.

2. Prevention

Primary prevention of HCC can be achieved with universal vaccination against hepatitis B infection, with vaccination being recommended for all newborns and high risk groups.

In patients with chronic hepatitis, antiviral therapies leading to maintained HBV suppression in chronic hepatitis B and sustained viral response in hepatitis C are recommended since they have been shown to prevent progression to cirrhosis, and hence HCC development. Interferon, lamivudine, adenovir, entecavir, telbivudine and tenofovir are available for hepatitis B treatment, but long term follow up data assessing their effect in secondary prevention are only available with interferon and lamivudine.

Once cirrhosis is established, the benefits of anti-viral therapy in preventing HCC development are not as well defined.

3. Screening and Early Detection

Patients at high risk for developing HCC include those with cirrhosis secondary to hepatitis B and C, alcohol, genetic hemochromatosis, autoimmune hepatitis, non-alcoholic steatohepatitis, primary biliary cirrhosis and alpha 1-antitrypsin deficiency.

Patients at risk without cirrhosis include hepatitis B carriers and those with non-alcoholic steatohepatitis. Groups at high risk should be entered into surveillance programmes by experienced personnel using abdominal ultrasound every 6 months and alphafetoprotein levels (AFP).

Groups in whom HCC screening and surveillance is recommended:

Hepatitis B carriers (HSBsAG positive)

Asian males >40y*
Asian females >50y*
All cirrhotic hepatitis B carriers
Family history of HCC
Africans over age 20y

Non Hepatitis B cirrhosis

Hepatitis C
Cirrhosis
Alcoholic cirrhosis

Genetic hemochromatosis
Primary biliary cirrhosis
Possibly α-1 antitrypsin deficiency, non-alcoholic steatohepatitis, autoimmune hepatitis

* While there is insufficient data in non-Asian hepatitis B carriers, most providers apply these recommendations to all hepatitis B carriers regardless of race/ethnicity.

4. Diagnosis

Diagnosis of HCC can be based on non-invasive criteria or definitive pathology. Non-invasive criteria can only be applied to cirrhotic patients and are based on imaging techniques obtained by dynamic contrast-enhanced CT scan, MRI and/or contrast-enhanced ultrasound. Diagnosis should be based on the identification of the typical hallmark of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases). While one imaging technique is required for nodules beyond 1cm in diameter, two techniques are recommended in suboptimal settings. When any finding is not typical, a biopsy is required. Biopsies should always be considered for advanced HCC in patients suitable for systemic therapies, not only to make a diagnosis and provide better characterization of the tumor but also for provision of information to check for appropriate eligibility to research/ clinical trials.

5. Pathology

Three gross morphologic types of HCC have been identified:

> **Nodular** – often associated with cirrhosis, characterized by well-circumscribed nodules.
>
> **Massive** – usually associated with non-cirrhotic liver, occupies large area with or without satellite nodules in surrounding liver.
>
> **Diffuse** – less common. Diffuse involvement of many small indistinct tumour nodules throughout liver.

The American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) TNM staging system (Hepatobiliary cancers) is available online at www.nccn.org

6. Management

6.1 Surgery

6.1.1 For **hepatocellular carcinoma**, hepatic resection is indicated as a potentially curative option for those patients with:

(a) adequate liver function (Child-Pugh A with mild or moderate hypertension; platelet count generally > 100 x 10^9/L)

(b) Absence of major vascular invasion

(c) adequate future liver remnant (at least 20% without cirrhosis and at least 30%-40% with Child-Pugh A cirrhosis, adequate vascular and biliary inflow/outflow)

6.1.2 Liver transplant

Orthotopic and living donor liver transplants have resulted in long term survival in selected cases. Hepatocellular carcinoma patients with liver confined disease should be seen in consultation with a liver transplant team for potential work up and listing. This should be done at a centre for excellence and according to hepatocellular carcinoma transplant consensus guidelines.

Recurrence of HCC (metastatic) despite transplant generally has a poor prognosis. Consideration for local therapies to control disease are sometimes recommended, especially for oligo (e.g. limited number (1-3) of metastases. Currently there is no evidence that systemic therapy prolongs life or palliates this population; however, some patients may benefit from systemic therapy, and decision making should be on a case-by case basis. Clinical trials should be prioritized if they are available.

6.2 Locoregional therapy

All hepatocellular carcinoma patients should be evaluated for potential curative therapies (resection, transplantation). Those patients not candidates for curative treatments may be treated with locoregional approaches such as most commonly, **ablation** or **transarterial embolization (TAE) techniques** (CCO guidelines, ref. 1,2). These cases are accessed by treating interventional radiologist or surgeon and generally followed by their liver cancer specialist

(a) Appropriately positioned tumours </= 3cm may be adequately treated with radiofrequency ablation (RFA) particularly in patients with mild/moderate cirrhosis as supported by randomized trial data. Microwave ablation and other ablative interventions are also options, particularly for selected unresectable larger tumors (3-5 cm), which have a higher risk of recurrence.

(b) Unresectable HCC and multi-focal HCC unsuitable for ablation, transplant or resection are generally considered for treatment with transarterial chemoembolization **(**TACE).

The TAE component consists of gelatin sponge particles, polyvinyl alcohol particles, and polyacrylamide microspheres. TACE is distinguished from TAE by the catheter-based administration of a concentrated dose of chemotherapy (e.g. doxorubicin, epirubicin, cisplatin as single agents or in combinations) combined with an emulsifying agent. TACE is generally preferred over TAE based on randomized trial data supporting superior

survival. Suitable candidates should have preserved liver function (Child Pugh A or better), a patent main portal vein, preserved organ function and performance status. Doxorubicin eluting beads used as TACE show equivalence to standard TACE and can be used where funding is available (currently not funded at UHN).

c) Single institution series have shown tumour control rates > 90% after 12 months in early stage HCC following treatment with stereotactic radiation therapy (RT). Two recent randomized studies demonstrated improved outcomes following conformal RT for HCC with vascular invasion (Yoon 2018, Wei 2019). The Korean study by Yoon demonstrated benefit to conformal RT and TACE leading to improved PFS and OS compared to sorafenib alone (improved median survival from 43 to 55 weeks, p=0.04). The Chinese study by Wei et al reported improved survival in patients treated with neo-adjuvant low dose conformal RT and surgery versus surgery alone (12 months survival 75.2% with RT versus 43% for surgery alone). These studies have not changed standard practice in North America, and participating in clinical trials should be a priority in clinic. Outside of trials, radiotherapy (RT) may be considered as a treatment option in patients with focal HCC unsuitable for other established local therapies (e.g. early stage, at high risk for toxicity from other therapies or HCC with portal vein tumor thrombosis). RT can also be considered as bridge to liver transplant therapy, if other local modalities are contraindicated or high risk, with decision making made in a multi-disciplinary setting.

6.3 Summary of management of Hepatocellular carcinoma

Once HCC is confirmed, a multidisciplinary evaluation at a tumor board is the best approach. Considerations including liver reserve and comorbidity should determine if potentially resectable or transplantable. Patients with solitary HCC and well preserved liver function should be evaluated for resection or ablation (which is generally considered for very small HCC, e.g if <2cm). Patients with impaired liver function or multiple tumours that meet local eligibility criteria should be evaluated for transplantation.

6.3.1 If patient is unresectable, either due to inadequate hepatic reserve, tumour location or extensive liver disease consider:

- TACE (Child-Pugh A, patent portal vein, liver confined), with survival advantage.
- Sorafenib (Child-Pugh A) (Llovet et al., 2008). Survival advantage has been demonstrated in patients with progression post TACE, portal vein thrombosis and metastatic disease. Funding is available in Ontario for patients meeting these criteria.
- Lenvatinib has showed non-inferiority to Sorafenib in paients without main portal vein invasion and is an alternative systemic option (Kudo 2018)
- Systemic therapy + radiotherapy in the context of a clinical trial
- Clinical trial
- Conformal or stereotactic radiotherapy

- Supportive care

6.3.2 If patient is **inoperable** due to decreased performance status or comorbidity, consideration to the following approaches can be reasonable:

Sorafenib (Child Pugh A) (Llovet et al., 2008)
Lenvatinib (Kudo 2018)
Clinical trial
Locoregional therapy
Conformal or stereotactic radiotherapy
Supportive care

6.3.3 If patient has **metastatic** disease consider:

Sorafenib (Child-Pugh A) (Llovet et al., 2008)
Lenvatinib (Kudo 2018)
Supportive care
Palliative radiotherapy
Clinical trial

6.3.4 Second line systemic therapy for metastatic HCC

For patients with metastatic or inoperable HCC unsuitable for local regional therapy, and refractory of progressive despite first line systemic therapy, second line systemic therapy options now exist, for patients with intact liver function. Options are:

Regorafenib is the standard of care for patients with advanced HCC who have tolerated sorafenib but progressed, and it is recommended in patients with well-preserved liver function and ECOG PS 0–1 (Bruix 2017).

Cabozantinib can be considered for patients who had progressive disease on one or two systemic therapies with well-preserved liver function and ECOG PS 0–1 (Abou – Alfa 2018).

Trials: trials should be prioritized in this patient population, e.g. combined modality trials or trials of immunotherapy and radiation therapy (e.g. PEMRAD)

Clinical studies evaluating the use of chemotherapy (e.g. doxorubicin) in the treatment of patients with advanced HCC have typically reported low response rates to therapy, and evidence for a favourable impact on overall survival in patients with HCC is lacking (Thomas et al., 2008).

6.4 Oncology Nursing

Refer to general oncology nursing practices

7. Supportive Care

7.1 Patient Education

Refer to general patient education practices

7.2 Psychosocial Care

Refer to general psychosocial oncology care guidelines

7.3 Symptom Management

Refer to general symptom management care guidelines

7.4 Clinical Nutrition

Refer to general clinical nutrition care guidelines

7.5 Palliative Care

Best supportive care measures should be administered to patients with unresectable/inoperable disease who are not candidates for other therapies. For patients with a diagnosis of hepatocellular carcinoma who have decompensated liver disease (≥Child-Pugh B8), which has a poor prognosis despite stage, palliative care should be recommended as a priority. Patients with recurrent disease post liver transplant who are not candidates for local therapies are suitable for palliative assistance.

8. Follow-up Care

Surveillance recommended post resection of hepatocellular carcinoma is imaging every 3 months for 2 years, then every 6 months for years 3-5 followed by resumption of annual screening. AFP, if initially elevated, should be evaluated every 3 months for 2 years, then every 6 months. Re-evaluation according to the initial workup should be considered in the event of disease recurrence or progression. Response evaluation for patients treated for advanced disease with TACE or systemic agents, such as sorafenib, is recommended every 2-3 months by clinical evaluation, subjective symptom evaluation, blood tests and by repeating the initially abnormal radiological or ultrasound examinations.

9. References

1 https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/941

2 https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/901

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