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Hepatocellular carcinoma

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The incidence of hepatocellular carcinoma (HCC) has been rising steadily and varies between 2 and 5 per 100 000 per year in Europe and the USA. These tumours are associated with cirrhosis in 80% of cases.

The major goals in this disease are to clarify the natural history of HCC, to evaluate the efficacy of a wide range of treatments and to carry out controlled trials in order to define which treatments are best in terms of risk and benefit.

These recommendations relate to the management of primary hepatocellular carcinoma and its variants (e.g. fibrolamellar, clear cell and giant cell carcinoma) in both cirrhotic and normal livers.

These guidelines were validated in June 1999 by the working group and an update is planned for 2001.

DIAGNOSIS

With the exception of the cirrhotic patient with an alpha-fetoprotein (AFP) level greater than 500 mg ml^{-1}, the diagnosis of hepatocellular carcinoma (HCC) is based on the histopathological examination of one or more liver sample. These are obtained at open surgery, by laparoscopy or by ultrasound or CT scan-guided biopsy (standard). Fine-needle aspiration for cytology is an option for the diagnosis of HCC and can be considered if a liver biopsy is not possible. The ease of diagnosis depends on the quality and nature of the biopsy specimens and the histologic type of the lesions. If the level of AFP is normal in a cirrhotic patient, the level of gamma-carboxyprothrombin (in patients without a Vitamin K deficiency) can be measured (option).

STAGING

Assessment of locoregional extension depends on clinical examination, liver ultrasonography and hepatic CT scanning (standard). MRI of the liver is an option. Standard investigations to assess distant spread include a chest X-ray (CXR), a spiral CT and a bone scan if this is clinically indicated. If a liver transplant is planned and the CXR is normal, a thoracic CT scan should be done. The evaluation of hepatic function depends on liver enzyme levels, serum albumin and a coagulation screen (standard). Endoscopy must be undertaken in the case of hepatic cirrhosis to exclude the presence of oesophagogastric varices (standard). In the case of diagnostic difficulty in differentiating an adenoma, a cholangiocarcinoma or a metastatic lesion, immunohistochemical staining to identify keratin subtypes and/or reticulin staining can be considered.

CLASSIFICATION

Primary HCC is classified according to the WHO classification (standard). There is no standard classification for the differentiation or grade of HCC. This can be done according to the grading of Edmonson or following the recommendations of the WHO (option). The standard classification for patients having a surgical resection is the TNM classification, where multiple tumours, large-diameter tumours and the invasion of vasculature and nodes are adverse prognostic factors. The associated pathological standard is the classification of Child–Pugh. For non-operable patients, the clinical classification system of Okuda can be used. This is useful but not without problems.

TREATMENT MODALITIES

Resection is indicated for HCC in a cirrhotic liver when the tumour is single and non-metastatic and if there is no portal invasion (level of evidence C). The liver function must allow for the type of excision necessary according to the localization and size of the tumour. The majority of teams will undertake liver transplantation for unifocal HCC of less than 3 cm in diameters that is secondary to cirrhosis and has been discovered by chance.

In the case of HCC in a healthy liver, excision by partial hepatectomy is the only surgical modality to be considered. It should be undertaken where there is no vascular involvement, no extra-hepatic spread and when the tumour is uni-focal. Elective incomplete excision should be avoided. Percutaneous techniques (intratumoral injections of absolute alcohol or acetic acid) or ultrasonic thermo-ablation are alternatives when surgery is not possible (level of evidence C). Randomized studies are necessary to determine the exact place of these techniques in the treatment of HCC as compared to surgery and other techniques of local treatment.

Chemo-embolization is not recommended for the treatment of HCC (option, level of evidence B). This therapy has no proven benefit with respect to survival over no therapy or systemic chemotherapy. This technique must be evaluated within randomized trials of adjuvant or neoadjuvant treatment.

'In situ' radiotherapy is an option for the treatment of inoperable patients with portal thrombosis (level of evidence C).

Chemotherapy represents an area of research for the treatment of inoperable HCC, but the results to date are inferior to those of other treatment modalities.

Immunotherapy is an option for the treatment of inoperable hepatocellular carcinoma (level of evidence C). It has questionable efficacy when compared to systemic chemotherapy. It place as adjuvant treatment within complex therapeutic strategies must be evaluated in randomized trials.

Hormone therapy represents an option for palliative treatment in patients with inoperable or metastatic hepatocellular carcinoma in whom neither percutaneous techniques, chemo-embolization, nor in situ radiotherapy are possible (level of evidence C). The place of somatostatin must be confirmed by prospective randomized trials.

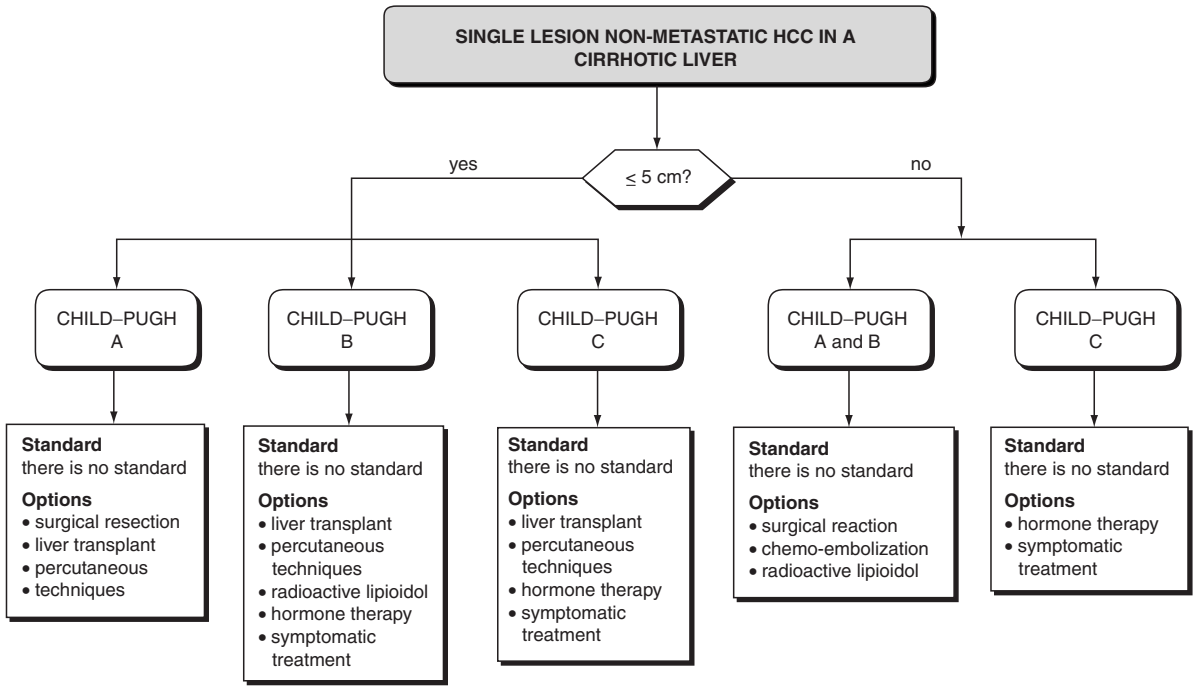

Figure 1 Unifocal HCC in a cirrhotic liver

THERAPEUTIC STRATEGY

HCC in a cirrhotic liver

The objective of treatment in these patients is to improve survival and/or to provide palliation. There are no standard therapeutic approaches.

Unifocal HCC (Single lesion HCC <5 cm maximum diameter)

Child–Pugh A disease Surgical excision, hepatic transplantation and percutaneous techniques can be considered (options) (Figure 1). It is recommended that surgical excision be undertaken if at all possible and within a specialist setting (level of evidence C). The role of adjuvant treatment remains to be established.

Child–Pugh B disease Hepatic transplantation, percutaneous techniques, the use of radioactive lipioidal or chemo-embolization can be considered (option) (Figure 1). It is recommended that the place of hepatic transplantation be evaluated within a formal protocol. Any surgery must be undertaken within a specialist setting (level of evidence C). In the case of a Child–Pugh B lesion of small size, percutaneous techniques are recommended (level of evidence C).

Child–Pugh C disease Hepatic transplantation, hormone therapy or best supportive care can be considered (option).

Unifocal HCC (Single lesion HCC > 5 cm maximum diameter)

Child–Pugh A and B disease Liver resection, chemo-embolization (± alcohol injection) and radioactive lipioidal can be considered. If at all possible, resection should be undertaken within a specialist centre (level of evidence C).

Child–Pugh C disease The objective of treatment is palliation. There is no standard therapy. Hormone therapy or best supportive care can be considered (option).

Multifocal HCC without portal thrombosis

Child–Pugh A and B If there are less or equal to three lesions of less than 5 cm in diameter, surgical resection, transplantation and percutaneous procedures can be considered (Figure 2). In other cases, chemo-embolization or radioactive lipioidal injections can be considered (option). Surgical excision is recommended for peripheral tumours (level of evidence C), hepatic transplantation for central tumours and percutaneous techniques for microtumours (tumours of less than 5 cm diameter) (level of evidence C).

Child–Pugh C disease The objective of treatment in the management of these patients is palliation. Hormone therapy or symptomatic management alone can be considered (option) (Figure 2).

Multifocal HCC with portal thrombosis

Child–Pugh A and B disease These patients have inoperable disease. Radioactive lipioidal, chemo-lipioidal (without embolization) and external-beam irradiation (for lateral tumours) can be considered (option).

Child–Pugh C disease The objective of treatment is palliation. Hormone therapy or symptomatic care can be considered (option).

Metastatic HCC

Child–Pugh A and B disease The objective of treatment is palliation. Chemotherapy, hormone therapy or symptomatic care can be considered (option) (Figure 3). Inclusion in ongoing therapeutic trials is recommended.

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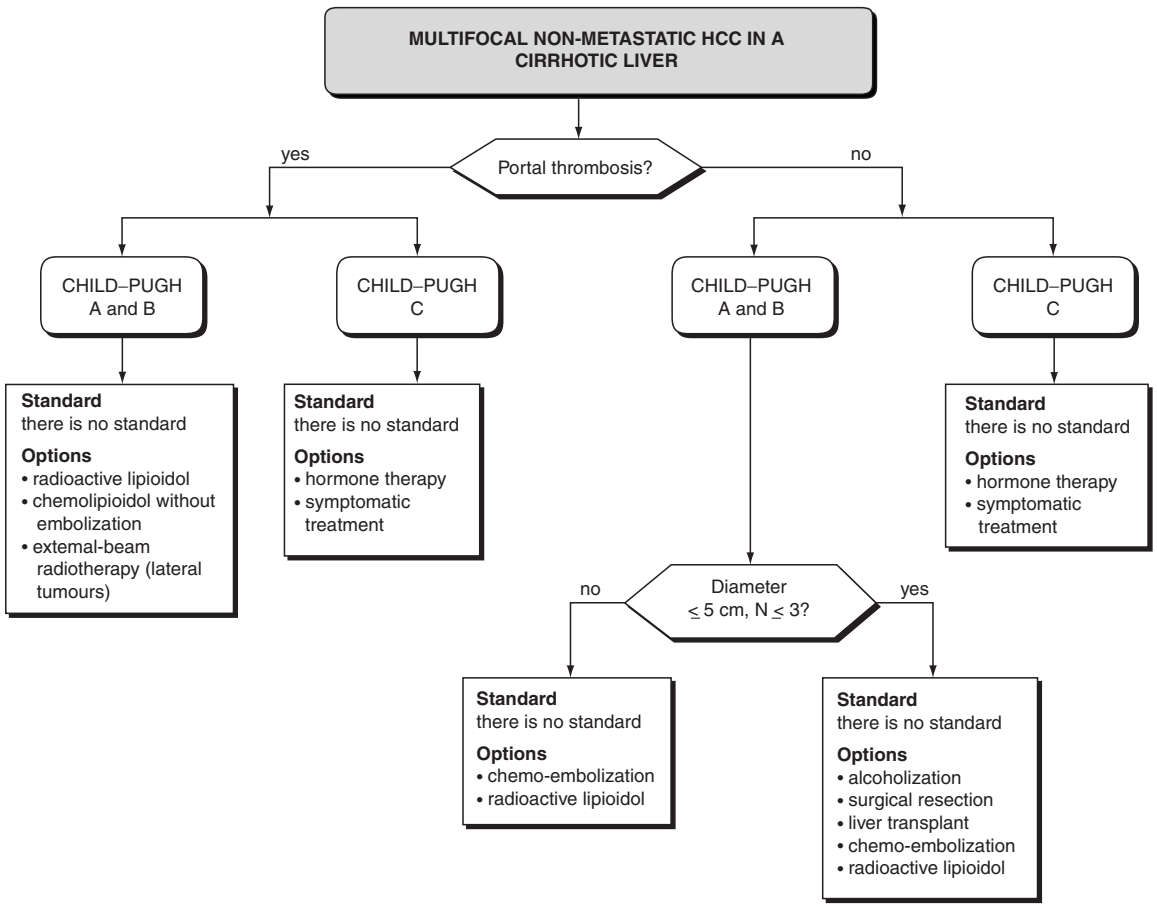

Figure 2 Treatment of multifocal HCC in a cirrhotic liver

Child–Pugh C disease The objective of treatment is palliation. Hormone therapy or symptomatic care can be considered (option).

HCC in a non-cirrhotic liver

Single peripheral lesions

Surgical excision by partial hepatectomy is standard treatment (Figure 4).

Single central lesions

Surgical excision by partial hepatectomy is standard treatment (Figure 4).

Multifocal disease

There is no standard treatment. Percutaneous techniques, chemo-embolization or radioactive lipoidal can be considered (option) (Figure 4).

Metastatic HCC

There is no standard treatment (Figure 3). Chemotherapy, high-dose interferon, hormone therapy, surgical excision (if feasible) or symptomatic treatment alone can be considered (option)

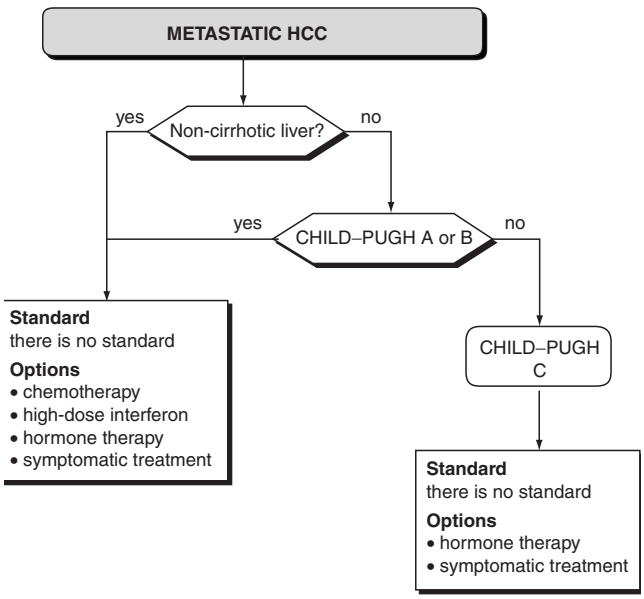

Figure 3 Treatment of metastatic HCC

FOLLOW-UP

There is no consensus regarding the pattern or modalities of follow-up in HCC apart from clinical examination. Hepatic ultrasonography, measurement of alpha-fetoprotein, abdominal CT scan, CXR and MRI imaging are all options. Surveillance should be planned according to the treatment given.

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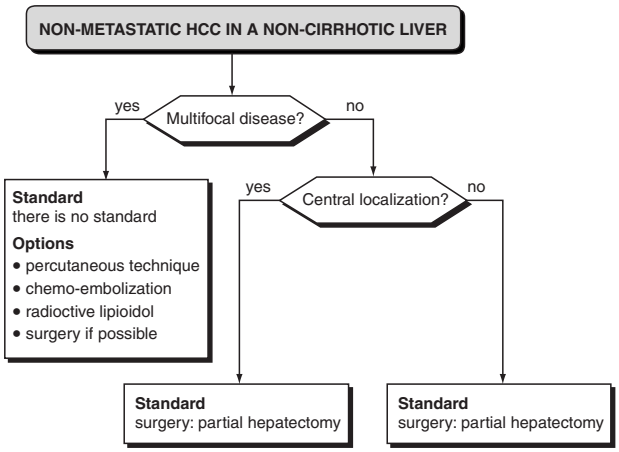

Figure 4 Multifocal HCC in a non-cirrhotic liver

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