

Seminar

Hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer, and its incidence is increasing worldwide because of the dissemination of hepatitis B and C virus infection. Patients with cirrhosis are at the highest risk and should be monitored every 6 months. Surveillance can lead to diagnosis at early stages, when the tumour might be curable by resection, liver transplantation, or percutaneous treatment. In the West and Japan, these treatments can be applied to 30% of patients, and result in 5-year survival rates higher than 50%. Resection is indicated among patients who have one tumour and well-preserved liver function. Liver transplantation benefits patients who have decompensated cirrhosis and one tumour smaller than 5 cm or three nodules smaller than 3 cm, but donor shortage greatly limits its applicability. This difficulty might be overcome by living donation. Most HCC patients are diagnosed at advanced stages and receive palliative treatments, which have been assessed in the setting of 63 randomised controlled trials during the past 25 years. Meta-analysis shows that only chemoembolisation improves survival in well-selected patients with unresectable HCC.

Primary liver cancer is a major health problem worldwide. It is the fifth most common neoplasm in the world, and the third most common cause of cancer-related death (table 1).¹ More than 500 000 new cases are currently diagnosed yearly, with an age-adjusted worldwide incidence of 5.5–14.9 per 100 000 population. In some areas of Asia, hepatocellular carcinoma (HCC) is the most common cause of death due to cancer. In Europe² and the USA,³ HCC has gained a major interest because of the rising incidence in the past decade. Estimates of the burden of HCC in the USA—mainly related to hepatitis C virus infection—suggest that its incidence will increase within two decades, probably to equal that currently reported in Japan.⁴ HCC is now the leading cause of death among patients with cirrhosis in Europe.⁵ Therefore, prevention and treatment of HCC is of great concern.

Risk factors and prevention

HCC is one of the few cancers with well-defined major risk factors.^{6,7} In 80% of cases HCC develops in cirrhotic livers, and cirrhosis is the strongest predisposing factor.⁷ Geographical differences in incidence reflect variations of the main causal factors (tables 2 and 3).⁶ In Asia and Africa, hepatitis B virus infection is common,⁸ together with aflatoxin B, intake from contaminated food.⁹ In the West and Japan, hepatitis C virus infection is the main risk factor,^{10–13} as well as other causes of cirrhosis, such as alcohol and haemochromatosis.¹⁴ The role of other carcinogenic agents, such as tobacco, is not clearly established. The multifactorial causes of HCC might explain its complex molecular pathogenesis, and have been reviewed elsewhere.^{15,16}

HCC is frequently the long-term result of chronic viral infection. In developing countries it affects young patients with chronic hepatitis B virus infection (non-cirrhotic in up to 40% of cases),¹⁷ whereas in developed countries it appears in older patients with cirrhosis related to hepatitis C virus infection.^{11,12} Worldwide, 380 million individuals have hepatitis B virus infection, and in endemic areas the carrier rate is up to 10–20% of the population.¹⁸ The presence of occult persistent hepatitis B virus infection further increases the oncogenic relevance of this virus.¹⁹ Chronic hepatitis B virus carriers have a 100-fold relative risk of developing HCC compared with non-carriers, which decreases if infection is acquired in adulthood.²⁰ Cirrhotic patients have a higher risk; their annual HCC incidence is 2.0–6.6%,²¹ whereas it is 0.4% in non-cirrhotic patients.²⁰ Environmental carcinogens such as aflatoxin B, increase the neoplastic risk three-fold, which correlates with a specific mutation on codon 249 of the p53 tumour suppressor gene.⁹ Characteristically, in developing countries HCC related to hepatitis B virus infection results from acquired infection at birth or early in life, and involves individuals aged 40 years or younger at a symptomatic phase when treatments are not effective. This situation can be prevented by vaccination, such as in Taiwan where nationwide vaccination of infants between 1984 and 1986 reduced the prevalence of hepatitis B virus carriers in childhood from 15% to 1%, and simultaneously of HCC by 60% compared with non-immunised children.^{22,23}

Search strategy

We searched PubMed, Cancerlit (National Cancer Institute), and the Cochrane Library database, using hepatocellular carcinoma, liver cancer, and primary liver carcinoma as free text words, and in combination with randomized, controlled clinical trials, clinical trials, phase III studies, double-blind, placebo, review, meta-analysis, therapy, and treatment. We also did a manual search and review of reference lists. We selected for inclusion randomised controlled trials published as full papers in English between 1978 and May, 2002, in peer-review journals and assessing survival benefits derived from medical therapies as primary treatment of unresectable HCC, reporting 1-year or 2-year death rates.

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Site	Incidence (%)	Mortality (%)
Lung	1238.9 (12.3)	1103.1 (17.7)
Breast	1050.3 (10.0)	373.0 (6.0)
Colon/rectum	944.7 (9.4)	492.4 (7.9)
Stomach	876.3 (8.7)	646.6 (10.4)
Liver†	564.3 (5.6)	548.6 (8.8)
All sites	10 055.6 (100)	6208.7 (100)

*Numbers of cases and deaths (1000s). †Including HCC and cholangiocarcinoma (<10%). Modified from reference 1.

Table 1: Incidence and mortality of five most common cancers worldwide, 2000*

In developed countries, HCC arises in cirrhotic livers because of hepatitis C virus infection^{11,12} or excessive alcohol intake,¹³ the annual incidence being 3–5%.^{10,12,13} Around 170 million people are infected with hepatitis C virus.²⁴ Unfortunately, vaccination is not available.²⁵ Prevention of infection with hepatitis C virus relies on preventing transmission by transfusion of blood products, but further efforts are needed to prevent nosocomial infections and infections among populations at risk. Prevention of progression from chronic hepatitis C virus infection to advanced fibrosis or cirrhosis is feasible in 40% of patients who are sustained responders to new antiviral strategies, such as pegylated interferon and ribavirin.²⁶ Interruption of the sequence of chronic hepatitis developing into cirrhosis will ultimately prevent HCC development. Conversely, with established cirrhosis, the preventive effect of these agents is not proven.

Surveillance and diagnosis

In established cirrhosis, surveillance to detect early HCC is recommended to decrease tumour-related deaths.²⁷ Despite the lack of randomised controlled trials, in cohort studies of surveillance, the early detection rate and applicability of curative treatments increases. Randomised controlled trials with non-screened groups are unlikely to be developed, at least in the West, and, thus, the survival benefit cannot be proven.^{28,29} A panel of specialists set up by the European Association for the Study of the Liver endorsed surveillance based on the use of ultrasonography and serum α fetoprotein every 6 months.²⁷ Only patients with cirrhosis that could be treated with potentially curative treatment for HCC should undergo surveillance. These patients include Child-Pugh class A patients, in whom surveillance is cost effective by Markov decision analysis modelling,³⁰ and Child-Pugh class B patients if transplantation is available. By contrast, Child-Pugh class C individuals should be considered as candidates for

Geographical area	Age-adjusted incidence (men/women)
Europe	
Western	5.8/1.6
Southern	9.8/3.4
Northern	2.6/1.3
North America	
Northern	4.1/1.6
Southern	4.8/3.6
Asia and Africa	
East Asia	35.4/12.6
Southeast Asia	18.3/5.7
Middle Africa	24.2/12.9
Developed countries	8.7/2.8
Developing countries	17.4/6.7
World	14.9/5.5

Modified from reference 6.

Table 2: Age-adjusted incidence of HCC per 100 000 inhabitants worldwide, by geographical area, 2000

transplantation because of liver failure. If such a procedure cannot be done in these patients, surveillance is not cost effective in any case.²⁷

Surveillance and the advances in imaging techniques have made early diagnosis possible. However, diagnostic procedures are expensive, associated with potential risk, or both. Thus, cost-effective recall policies are crucial to accurately diagnose the different nodule types that might emerge in a cirrhotic liver.^{31,32} Macroregenerative and low-grade dysplastic nodules are common. Being frequently smaller than 5 mm, they have a marginal risk of malignant transformation. High-grade dysplastic nodules are less common, but become malignant in a third of cases.³³ Other tumours, such as atypical haemangiomas, might resemble malignant disease. Finally, malignant tumours may arise as unifocal or multicentric disease (20–60% of cases),^{12,29} this being the result of intrahepatic metastases or of synchronous occurrence.

The European Association for the Study of the Liver expert panel proposed the following surveillance recall and diagnostic strategy (figure 1).²⁷ In nodules smaller than 1 cm, which are malignant in less than 50% of cases, reliable HCC diagnosis is difficult. Thus, close follow-up is recommended. In nodules of 1–2 cm, HCC diagnosis requires positive cytohistology. However, there is a 30–40% false-negative rate with fine-needle biopsy.³⁴ A negative result, therefore, does not rule out malignant disease. Non-invasive diagnostic criteria to be applied solely in patients with cirrhosis and tumours larger than 2 cm were proposed. HCC diagnosis is established by the concomitant finding of two imaging techniques, showing a nodule larger than 2 cm with arterial hypervascularisation, or by one positive imaging technique, showing hypervascularisation associated with α fetoprotein concentration higher than 400 μ g/L.²⁷

The accuracy of imaging techniques is rapidly evolving. Ultrasonography plays a key part in the detection of HCC, but its sensitivity to detect additional small nodules is low.³⁵ New contrast agents might increase the accuracy of this technique and might be relevant to assess treatment response.³⁶ The best techniques are helical CT and MRI with contrast enhancement, which have an accuracy exceeding 80%.³⁷ They have replaced angiography and CT hepatic angiography, whereas lipiodol CT is not reliable.²⁷ CT and MRI sensitivity decreases when assessing the extent of the disease. In a comparison of CT and MRI with pathological examination of explanted livers, MRI angiography was more precise in detecting nodules of 1–2 cm than CT scan.³⁸ However, 20–30% of intrahepatic tumours, especially those smaller than 10 mm, are not diagnosed preoperatively with any technique. Preliminary data with positron emission tomography are not encouraging for detection of small nodules. Extrahepatic spread has to be ruled out in selected patients (ie, candidates for transplantation, inclusion in trials) by spiral CT of the chest and by bone scintigraphy.

	Risk factor			
	Hepatitis C virus	Hepatitis B virus*	Alcohol	Other
Europe	60–70%	10–15%	20%	10%
North America	50–60%	20%	20%	10%
Asia and Africa†	20%	70%	10%	<10%‡

*Estimates from HbsAg carriers. Occult hepatitis B virus infection might involve additional patients. †Except Japan, for which hepatitis C virus 70%, hepatitis B virus 10–20%, alcohol 10%, other <10%. ‡Aflatoxin is main co-factor enhancing oncogenic risk of patients with hepatitis B virus infection. Modified from reference 6.

Table 3: Risk factors for HCC worldwide, by geographical area, 2000

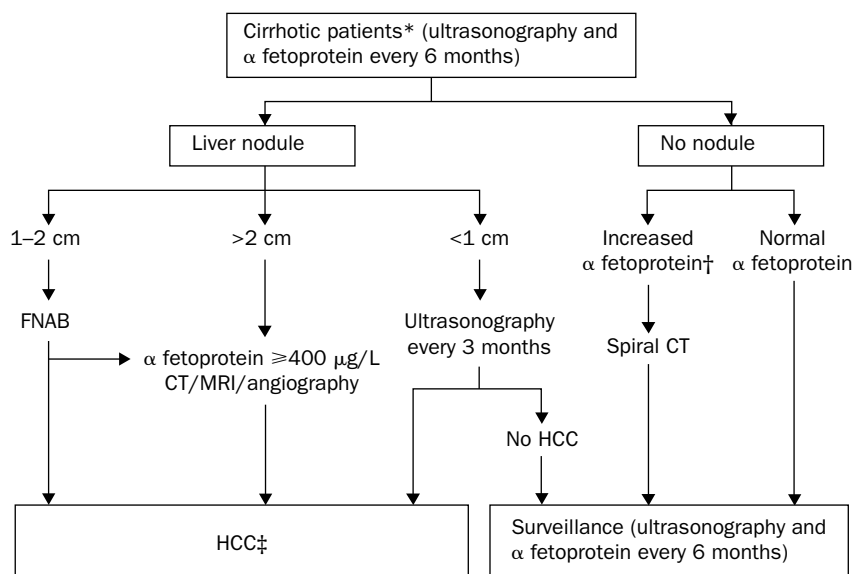


Figure 1: Surveillance and recall strategy for HCC

FNAB=fine-needle aspiration biopsy. *Available for curative treatments if diagnosed as having HCC. †α fetoprotein concentrations to be defined. ‡Cytohistological or non-invasive criteria. Reproduced from reference 27 with permission from The European Association for the Study of the Liver (EASL).

Natural history and prognosis

Two decades ago, the reported prognosis of HCC was dismal. Most patients died within 1 year, irrespective of treatment.³⁹ In developed countries this outcome has completely changed, since 30–40% of patients are now being diagnosed at initial stages when curative treatments can be optimally applied.⁴⁰ Therefore, estimates of outcome need to take into account the stage at diagnosis.

Early HCC

The natural course of early HCC is unknown, since almost all individuals in this stage are treated.⁴⁰ Thus, available series of untreated early HCC may present a selection bias and underestimate outcome. The best reported survival a decade ago was 65% at 3 years for Child-Pugh class A patients who had one tumour,⁴¹ whereas tumours have since become more amenable for radical treatments, leading to 5-year survival rates of 50–70%.^{42–44} Thus, these treatments are assumed to improve survival. The prognosis at early stages relies on tumour status, liver function, and the treatment applied. Tumour status is defined by size of the main nodule and multicentricity (one <2 cm, one 2–5 cm, 3 nodules <3 cm), with all classifications showing very different outcomes.⁴⁴ Liver function is highly relevant for resection or percutaneous treatments. Among Child-Pugh class A patients undergoing resection, the best predictors of survival are: bilirubin concentrations (<17.1 µmol/L),⁴³ absence of notable portal hypertension (hepatic venous pressure gradient <10 mm Hg),⁴⁵ and indocyanine-green clearance at 15 min below 20%.⁴⁶

The definition of early HCC has been variable. Two decades ago it was defined as one tumour smaller than 5 cm in diameter. Since then, an empirical rule of multiple (2–3) nodules smaller than 3 cm has been incorporated, reflecting the excellent outcomes achieved after liver transplantation.^{42,47} However, pathological and clinical data challenge this definition. Treatment response and outcomes of early tumours are variable. For instance, complete response rates after percutaneous treatments vary according to size, ranging from 90% to 100% for tumours of 2 cm, to 50% for tumours of 5 cm.⁴⁸ The same

applies to survival. The term early HCC, therefore, covers different stages with a heterogeneous biological behaviour.

Very early HCC or carcinoma in situ

Knowledge about small tumours has led to the concept of very early HCC, which correlates with the pathological carcinoma in situ stage. Carcinoma in situ is the earliest clinical entity currently recognised, and it refines the concept of minute HCC⁴⁹ or subclinical HCC⁵⁰ proposed by Asian researchers, and is consistent with the stage 0 disease defined by Takayama and colleagues.⁵¹

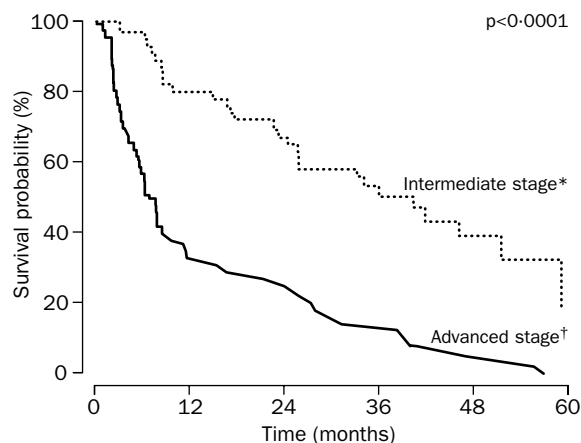
From the pathological perspective, carcinoma in situ is a well-differentiated HCC that contains bile ducts and portal veins, has ill-defined nodular appearance, and, by definition, has not invaded any structure.^{51–53} Cancer invasion can occur before the 2 cm cut-off size,⁵² so that some tumours smaller than 2 cm have already disseminated, but

others behave as carcinoma in situ. Kojiro⁵² analysed 106 resected HCC smaller than 2 cm and distinguished the so-called indistinct type (mean size 1.2 cm), without local invasiveness, from the distinct nodular type (mean size 1.6 cm), which showed local invasiveness. In the distinct nodular type, local metastases surrounding the nodule were seen in 10% of cases, and microscopic portal invasion in up to 25%. Although both types were detected by ultrasonography, the indistinct type appeared hypovascular on CT, and the latter hypervascular. This pathological-radiological correlation agrees with the finding that early tumours have portal blood supply without tumour staining at angiography, while advanced HCC show tumour staining.⁵³

The very early HCC stage is defined by well-preserved liver function and a diagnosis of carcinoma in situ. In Japan, these patients have the best outcomes published with resection (5-year survival from 89%⁵³ to 93%⁵¹) or with percutaneous treatment (5-year survival 71%).⁵³ These outstanding findings are better than those reported for conventional HCC smaller than 2 cm: 71% 5-year survival with resection and 54% with percutaneous ablation.⁴⁴ Furthermore, according to Takayama and colleagues,⁵¹ these tumours are not prone to relapse after curative treatments, compared with more advanced HCC smaller than 2 cm (8% vs 74% at 3 years). Clearly, these tumours have to be differentiated from high-grade dysplastic nodules, for which there is no consensus agreement on the histological criteria to be applied.³² Neoplastic invasion into portal tracts within the tumour might help to identify the malignant nature of early cases,^{51–53} but in the future, molecular analysis should become the optimum tool.

Intermediate and advanced HCC

Most HCC patients are still diagnosed at advanced stages that preclude the optimum use of radical treatments. The natural course and prognostic factors that define these stages are now reasonably well known,⁵⁴ compared with two decades ago when patients survived no longer than 1 year after diagnosis.³⁹ The 1-year and 2-year survival rates of patients assigned no treatment in 25 randomised

**Patients at risk**

BCLC stage B	48	37	30	16	7
BCLC stage C	54	17	9	2	–

Figure 2: **Survival, according to tumour stage, in untreated HCC**
 BCLC=Barcelona-Clinic liver cancer. *Multinodular asymptomatic tumours, median survival 40 months. †Cancer-related symptoms, vascular invasion or extrahepatic spread, median survival 5.4 months. Reproduced from reference 56 with permission from The American Association for the Study of Liver Disease.

controlled trials were 10–72% and 8–50%, respectively.⁵⁵ This wide range underscores the heterogeneity of the non-surgical HCC population and the need to stratify them into separate categories. For this purpose we assessed a joint cohort of 102 patients from two untreated control groups recruited within randomised controlled trials.⁵⁶ Survival at 1, 2, and 3 years was 54%, 40%, and 28%. The independent prognostic factors were the presence of cancer-related symptoms (performance status test 1–2) and an invasive pattern, defined as vascular invasion or extrahepatic spread. Survival among patients at intermediate stages (asymptomatic patients, no invasive pattern) at 1, 2, and 3 years was 80%, 65%, and 50%, whereas among those with advanced disease (symptomatic, invasive pattern, or both), survival was 29%, 16%, and 8% (figure 2). Similar outcomes have been reported in Europe.^{48,57} Concentrations of α fetoprotein and alkaline phosphatase, Child-Pugh score, and ascites might further refine prediction of prognosis.^{46,58–60}

End-stage HCC

A high proportion of patients is still identified by terminal cancer-related symptoms, particularly in Asia and Africa. Their outlook remains poor, with less than 6 months' life expectancy and no survival benefit from treatment.^{54,55} Old series characterised patients with end-stage disease as Okuda stage III, or with performance status test score 3–4.³⁹ Similarly, advanced tumours in Child-Pugh class C patients unsuitable for transplantation should be classified as end stage.⁶¹

Staging systems

Staging systems should separate patients into groups with homogeneous prognosis, and serve to select appropriate treatment. In oncology, tumour stage is the main outcome predictor, but prognostic modelling in HCC is more complex. Survival is also determined by liver function, which in turn affects the applicability of treatments. This pattern is relevant, since survival at early stages is modified by treatment and thus prognostic prediction has to include treatment-related variables.²⁷

Classically, HCC was classified by tumour node metastasis staging⁶² or the Okuda classification.³⁹ Tumour node metastasis staging has been modified repeatedly because it has poor accuracy. The latest proposal improves the prognostic prediction in resected patients, but is still limited because it mostly relies on pathological findings and liver function is not taken into account.⁶² The Okuda staging includes variables related to tumour burden and liver function (bilirubin, albumin, ascites) and has been extensively used. However, it cannot distinguish between early and advanced stages and mostly serves to identify end-stage individuals. Five new classifications have attempted to overcome these difficulties: Japanese,⁴⁶ French,⁵⁸ Cancer of the Liver Italian Program,⁵⁹ Barcelona-Clinic Liver Cancer staging,⁵⁴ and the Chinese University Prognostic Index score.⁶⁰ These classifications have been reviewed elsewhere,^{63,64} but none has received universal acceptance. The Barcelona-Clinic Liver Cancer staging classification guides treatment, particularly in early tumours,⁶⁴ and the other systems seem to be useful in the prediction of outcomes of advanced cases.^{58–60} A consensus staging classification for HCC is needed.

Treatment of HCC

Treatments for HCC have been conventionally divided into curative and palliative. Curative treatments, such as resection, liver transplantation, and percutaneous ablation, induce complete responses in a high proportion of patients and are expected to improve survival. Palliative treatments are not aimed to cure, but in some cases can obtain good response rates and even improve survival. Table 4 summarises the sources of evidence of the benefits of all these treatments in HCC patients. Tables 5, 6, and 7 show the results from selected cohort studies and randomised controlled trials, assessing most of the treatments.

	Number of trials
Randomised controlled trials*	
Large (>1000 patients)	0
Small	
Percutaneous ethanol injection	5
Arterial embolisation/chemoembolisation	17
Arterial chemotherapy (lipiodolisation)	10
Internal radiation I ¹³¹	3
Tamoxifen	9
Systemic chemotherapy	9
Interferon	4
Octeotide	2
Antiandrogens, megestrol	2
Other treatments	2
Total	63
Meta-analysis	
Individual data (randomised controlled trial)	0
Pooled data (randomised controlled trial)	
Arterial embolisation/chemoembolisation	7
Tamoxifen	7
Cohort studies†	
Surgical resection	
Liver transplantation	
Cadaveric liver transplantation	
Living donor liver transplantation	
Percutaneous treatments	
Percutaneous ethanol injection	
Radiofrequency ablation	
Cryoablation	
Microwave coagulation	

*Published in English as full papers in peer-review journals. †No randomised studies have been published, assessing resection or liver transplant. There are too many cohort or observational studies to count.

Table 4: **Sources of evidence for treatment options of HCC, 1978–2002**

Treatment	Number of patients	Actuarial survival	
		1 year	5 years
Surgical resection			
Takayama et al, 1998 ⁵¹			
Very early HCC	15	100%	93%
Overt HCC	52	92%	54%
Fong et al, 1999 ⁶⁷	100	83%	42%
Llovet et al, 1999 ⁴³	77	85%	51%
No portal hypertension, normal bilirubin	35	91%	74%
Portal hypertension, normal bilirubin	15	93%	50%
Portal hypertension, abnormal bilirubin	27	74%	25%
Takayama et al, 2000 ⁶⁸	74	100%	62%
Arii et al, 2000 ⁴⁴			
Stage I HCC <2 cm	1318	96%	72%
Stage I HCC 2–5 cm	2722	95%	58%
Stage II HCC <2 cm	502	92%	55%
Stage II HCC 2–5 cm	1548	95%	58%
Wayne et al, 2002 ⁶⁹	249	83%	41%
Liver transplantation			
Iwatzuki et al, 1991 ⁷⁰	71	70%	49%
Mazzaferro et al, 1996 ⁴²	48	84%	74%*
Bismuth et al 1999 ⁷¹	45	82%	74%
Llovet et al, 1999 ⁴³	79	86%	75%
Intention-to-treat analysis	87	84%	69%
Jonas et al, 2001 ⁷²	120	90%	71%
Yao et al, 2001 ⁷³	64	87%	73%
Percutaneous ethanol injection			
Livraghi et al, 1995 ⁷⁴			
Child A, HCC <5 cm	293	98%	47%
Child B, HCC <5 cm	149	93%	29%
Lencioni et al, 1997 ⁷⁵			
Child A, 1 HCC or 3 nodules <3 cm	127	98%	53%
Child B, 1 HCC or 3 nodules <3 cm	57	88%	28%
Arii et al, 2000 ⁴⁴			
Stage I HCC <2 cm	767	96%	54%
Stage I HCC 2–5 cm	587	95%	38%
Stage II HCC <2 cm	426	92%	33%
Stage II HCC 2–5 cm	483	87%	28%
Sakamoto et al, 1998 ⁶³	88	98%	71%
Radiofrequency ablation			
Rossi et al, 1996 ⁷⁶	39	94%	40%
Buscarini et al, 2001 ⁷⁷	88	89%	33%

*4 year survival.

Table 5: Outcomes in patients with HCC receiving potentially curative treatments

Overview of curative treatments

In the West, curative treatments are applied to 30–40% of patients in referral centres,⁴⁰ whereas in Japan 60–90% benefit because of widespread implementation of surveillance and a broad application of treatments.^{44,65}

The three major treatments have not been compared in any randomised controlled trial, which is not feasible because of the need for large sample size and the resources required. Attempts to compare resection with percutaneous treatments have failed in Italy and Japan.⁶⁶ Therefore, no firm evidence establishes the optimum first-line treatment for patients who have one small HCC and well-preserved liver function.²⁷ Evidence of relative benefit is derived from many non-randomised cohort studies. Resection and transplantation achieve the best outcomes in well-selected candidates (5-year survival 60–70%),^{42,43,51,67–73} and compete as the first option from an intention-to-treat perspective (table 5).⁴³ Percutaneous treatments provide good results (5-year survival 40–50%),^{44,74–77} but cannot achieve response rates and outcomes comparable to surgical treatments, even when applied as the first option.^{44,65} Patients with carcinoma in situ might constitute an exception, but this effect is unknown. Transplantation is deemed the best treatment for patients with one tumour and decompensated cirrhosis or multicentric small tumours.⁴⁰

Treatment	Number of patients	Actuarial survival	
		1 year	2 years
Arterial embolisation and chemoembolisation			
Kawai et al, 1992 ¹⁰²			
Embolicisation	148	74%	51%
Chemoembolisation with doxorubicin	141	65%	42%
Kawai et al, 1994 ¹⁰³			
Chemoembolisation with farmorubicin	208	69%	44%
Chemoembolisation with doxorubicin	207	74%	57%
GETCH, 1995 ¹⁰⁶			
Chemoembolisation with cisplatin	50	62%	38%
Bruix et al, 1998 ¹⁰⁷			
Embolicisation plus coils	40	70%	50%
Pelletier et al, 1998 ¹⁰⁸			
Chemoembolisation with cisplatin	37	51%	24%
Llovet et al, 2002 ¹¹⁰			
Embolicisation	37	75%	50%
Chemoembolisation with adriamycin	40	82%	63%
Arterial chemotherapy (lipiodolisation)			
Kawai et al, 1997 ¹¹¹			
Arterial lipiodolisation with epidoxorubicin	208	75%	45%
Arterial lipiodolisation with doxorubicin	207	82%	55%

GETCH=Group d'Etude et de Traitement du Carcinome Hépatocellulaire.

Table 6: Outcomes in patients with HCC receiving palliative treatments

Resection

Hepatic resection is the treatment of choice for HCC in non-cirrhotic patients (5% of cases in the West, 40% in Asia). Major resections can be done with low rates of life-threatening complications.⁷⁸ Conversely, among patients who have cirrhosis, strict selection criteria are required to avoid treatment-related complications—eg, liver failure. Modern day standards in surgery are blood transfusion in fewer than 10% of cases, treatment-related mortality lower than 1–3%, and 5-year survival higher than 50%.⁴⁰ Resection was conventionally indicated for Child-Pugh class A patients with one HCC, but with this classification surgical standards are not met. Careful selection of candidates allows 70% survival at 5 years in all patients, with use of hepatic resection in patients who have one asymptomatic HCC and extremely well-preserved liver function (so-called Child-Pugh hyper A, table 5)^{43,44,68} Japanese researchers use the indocyanine-green retention rate to identify the best candidates,⁷⁹ whereas portal pressure and bilirubin are the variables used in Europe.^{43,45} Clinically relevant portal hypertension is defined as presence of an hepatic vein pressure gradient higher than 10 mm Hg, oesophageal varices, or splenomegaly with platelet count lower than $100 \times 10^9/L$. Thereby, patients without relevant portal hypertension and normal bilirubin achieve 70% survival at 5 years,

Treatment	Number of patients	Actuarial survival		
		1 year	3 years	5 years
Okuda et al, 1985⁶⁹				
Stage I	33	35%	0	..
Stage II	134	10%	0	..
Stage III	62	0
Barbara et al, 1992⁴¹				
Child A, 1 HCC <5 cm	19	94%	65%	..
Livraghi et al, 1995⁴⁸				
Child A, 1 HCC <5 cm	73	86%	26%	11%
Child B, 1 HCC <5 cm	43	65%	13%	0
Llovet et al, 1999⁶⁶				
Intermediate stage	102	54%	28%	7%
Advanced stage	48	80%	50%	16%
Villa et al, 2000⁶⁷				
Advanced stage	54	29%	8%	0
Intermediate stage	96	72%	38%	20%

Table 7: Outcomes in patients with untreated HCC

whereas survival is 50% among patients with portal hypertension, and even lower with both adverse factors.⁴³ With application of these criteria the resectability rate is 5–10%.

Tumour recurrence complicates 70% of cases at 5 years, combining true recurrence and de-novo tumours.⁷⁸ Microvascular invasion, poor histological differentiation, and satellites predict true recurrence.^{43,80} Preventive strategies assessed in randomised controlled trials have been reviewed.⁸¹ Adjuvant chemoembolisation or chemotherapy do not add benefit, whereas internal radiation with iodine-131-labelled (¹³¹I) lipiodol and interferon showed promising results.^{81,82} Adoptive immunotherapy by activated lymphocytes reduced recurrence in a trial of 150 patients,⁶⁸ and a similar effect was described with retinoids in a randomised controlled trial of 89 patients.⁸³ All interventions need validation.

Liver transplantation

HCC is the only solid neoplasm in which transplantation plays a relevant part. Liver transplantation has completely changed the treatment strategy for HCC. Cadaveric liver transplantation has been a major breakthrough in the West, but the applicability of this procedure in Asia remains marginal. Theoretically, transplantation might simultaneously cure the tumour and the underlying cirrhosis. The broad selection criteria applied two decades ago led to poor results for recurrence (32–54%) and survival (5-year survival <40%),⁸⁴ but allowed the identification of the best candidates for transplantation. Such candidates have one HCC smaller than 5 cm or up to three nodules smaller than 3 cm who, in tertiary referral centres, achieve 70% survival at 5 years, with a recurrence rate lower than 15% (table 5).^{42,43,71–73} Some studies based on explant examination have suggested that these criteria could be expanded, but this decision should be based on robust analysis of imaging data at the time of treatment indication or transplantation, rather than on pathological data made available when the operation has already taken place.⁷³ Vascular invasion is postulated to be a major predictor of recurrence and survival, but attempts to confirm its usefulness have not discriminated between microvascular or macrovascular types.⁷²

A crucial point is that benefit is obtained only if the waiting time is shorter than 6 months. The shortage of donors curtails the potential benefits of cadaveric liver transplantation. Therefore, since waiting time can exceed 12 months in some Western countries, there is a drop-out rate of 20–50% of cases. This rate constitutes a major clinical problem for most programmes.^{43,85} More than 18 000 patients await cadaveric liver transplantation in the USA, whereas the number of available cadaveric donors remains stable at 5000 per year.⁸⁶ Such high numbers forced the United Network of Organ Sharing to adapt the model for end-stage liver disease to prioritise the waiting list.⁸⁷ The model provides a composite score ranging from six to 40 points (40 being the sickest patients) that includes bilirubin, international normalisation ratio, and serum creatinine, for non-cancer patients, and a variable score between 24 (one HCC <2 cm) to 29 points (one HCC 2–5 cm or three nodules <3 cm) for patients with HCC.⁸⁸ The external validation of the score was published,⁸⁹ although it was also questioned.⁹⁰ These controversies lead the United Network of Organ Sharing to adopt a new proposal ascribing HCC patients 20–24 points.

Adjuvant treatments given while patients are on the waiting list are used in most centres to prevent tumour progression. Robust data from randomised controlled

trials are lacking and, thus, the potential benefits advocated for percutaneous ablation, chemoembolisation, or chemotherapy are derived from observational studies⁹¹ and cost-effectiveness analyses.⁹² Use of marginal livers, domino donors, and split transplantation have had a minor impact.

Living donor liver transplantation is emerging as the most feasible alternative to cadaveric liver transplantation.⁹³ This treatment started in Asia because of legal and societal constraints on cadaveric liver transplantation, and around 3000 interventions have been done worldwide with use of the right hepatic lobe. At present, only studies in small series of HCC patients have been published, and the long-term outcomes are still uncertain.⁹⁴ Decision analyses have shown that living donor liver transplantation is cost effective for early HCC compared with cadaveric liver transplantation, for which waiting times exceed 7 months.⁹⁵ However, the enthusiasm for living donor liver transplantation is tempered by the need of a highly skilled group of senior liver surgeons, since the procedure is extremely complex.⁹⁶ Despite this factor, 20–40% of recipients have surgical-related morbidity. Second, donor mortality is 0.3–0.5%.⁹³ A donor death has adversely impacted US programmes, and raised ethical concerns.⁹⁶ Third, the applicability of the procedure is low, and only 35% or less of the potential recipients undergo it.

Given the theoretical unlimited availability of donors, we have proposed expanded criteria for HCC patients. These criteria include: one tumour smaller than 7 cm, three nodules smaller than 5 cm, five nodules smaller than 3 cm, or a downstaging to conventional criteria after locoregional treatment lasting more than 6 months.⁴⁰ The aim is to achieve 5-year survival of 50%, significantly higher than the expected 20% survival obtained with palliative treatments. The applicability and results of this strategy are awaited.

Percutaneous treatments

Percutaneous treatments are the best option for early unresectable HCC.^{74–77,97} In some areas of Japan they are still applied as first-line treatment.^{44,65} New technologies to obtain tumour ablation continue to improve. Destruction of neoplastic cells is achieved by chemical substances (alcohol, acetic acid) or by modifying the temperature of neoplastic cells (radiofrequency, microwave, laser, and cryoablation).⁹⁷ Percutaneous ethanol injection is the seminal technique, and its advantages and limitations are widely reported. It is cheap, easy to do, and has few adverse effects. Percutaneous ethanol injection achieves responses of 90–100% in HCC smaller than 2 cm, to 70% in those of 3 cm, and 50% in HCC of 5 cm in diameter.^{74,75} Selected Child-Pugh class A candidates with complete responses achieve 5-year survival rates of 50% (table 5).^{44,74} This procedure is judged the gold standard for patients with one tumour smaller than 3 cm,⁴⁰ but alternatives are postulated for larger tumours.

Radiofrequency ablation constitutes the most assessed alternative.^{76,77,97,98} Several devices are available: single or multiple cooled-tip electrodes or single electrodes associated to J-hook needles. The technique can be applied percutaneously, laparoscopically, or during laparotomy, and is claimed to achieve at least the same objective responses as percutaneous ethanol injection but in substantially fewer sessions.^{98,99} Furthermore, it may provide better antitumoral benefits than percutaneous ethanol injections in tumours larger than 3 cm. The 5-year survival estimates for radiofrequency ablation are currently 33–40%, but new data are expected to improve

these figures.^{76,77} In one randomised controlled trial in which these two treatments were compared in 102 patients, no survival difference was identified, although radiofrequency ablation offered better local tumoral control.⁹⁹ In a review of 3670 patients treated by radiofrequency ablation, mortality was 0.5% and the complication rate 8.9%.¹⁰⁰ Subcapsular location and poor histological differentiation have been associated with needle-track seeding, a complication almost absent in intrahepatic well-differentiated tumours.¹⁰¹ Other techniques are associated with many complications (cryoablation), have no proven advantage (microwave coagulation), or are still experimental.⁹⁷

Predictors of treatment response are tumour size and morphology (well encapsulated *vs* invasive). Even small tumours of 2 cm can present satellites close to the nodule,⁵² which provides the rationale to produce a 1 cm ablation ring around the HCC, with whatever treatment. Conventionally, treatment response is assessed by CT scan 1 month after the procedure.²⁷ Contrast-enhanced ultrasonography might become a real-time alternative to assess response.³⁶ Treatment response is defined by WHO criteria, with the extent of tumour necrosis being seen as mass reduction.²⁷ Comparison with the new Response Evaluation Criteria in Solid Tumours proposal by the US National Cancer Institute is reviewed elsewhere.⁶³

Palliative treatment

Palliative treatments are applied among patients in advanced tumour stages.⁴⁰ We have reviewed the evidence obtained from randomised controlled trials published in English in peer reviewed journals in the past 25 years.⁵⁵ We identified 63 trials assessing primary treatments for HCC (table 4). In 26 studies control groups of conservative management were included, which is essential to identify survival benefit. Analyses were done of the effectiveness of embolisation or chemoembolisation,¹⁰²⁻¹¹⁰ arterial or systemic chemotherapy,¹¹¹ internal radiation with ¹³¹I lipiodol,¹¹² hormonal compounds,¹¹³⁻¹²² immunotherapy,^{123,124} and others (table 6).^{125,126} We did the meta-analysis of two treatments, arterial embolisation¹⁰⁴⁻¹¹⁰ and tamoxifen,¹¹³⁻¹¹⁹ for which there were enough trials and patients to obtain robust conclusions. Survival advantages were identified with embolisation or chemoembolisation in

well-selected candidates and, thus, constitute their standard treatment. By contrast, no survival benefit was detected for tamoxifen. Further randomised controlled trials are needed to show benefits of the remaining agents, particularly those leading to objective response rates of higher than 20%, as is the case with internal radiation with ¹³¹I lipiodol¹¹² or arterial lipiodolisation (chemotherapeutic agents and lipiodol).¹¹¹ The encouraging results of initial trials with interferon¹²³ and octreotide¹²⁵ have not been reproduced.^{124,126}

Because of the absence of survival benefit with the available treatments among patients not suitable for chemoembolisation, new agents should be compared with the best conservative support or placebo. Comparisons with a control group of a proven inactive or harmful treatment, such as systemic chemotherapy, should be discouraged for scientific and ethical reasons.

Arterial embolisation

Arterial embolisation is the most widely used treatment for unresectable HCC.^{40,102-110} In early stages, this treatment may not be indicated as a first-line option, since an outcome review from Japan reports worse results than surgery or percutaneous treatments.⁴⁴ Obstruction of hepatic artery leads to extensive necrosis in large vascularised HCC.^{102,103} Embolisation agents—generally gelatin—may be administered together with selective intra-arterial chemotherapy mixed with lipiodol (chemoembolisation). Doxorubicin, mitomycin, and cisplatin are the commonly used antitumoral drugs. Arterial embolisation achieves partial responses in 15–55% of patients,¹⁰⁴⁻¹¹⁰ and substantially delays tumour progression and vascular invasion.^{106,110} In seven randomised controlled trials, including a total of 516 patients, embolisation has been compared with conservative management.¹⁰⁴⁻¹¹⁰ In five, chemoembolisation with doxorubicin^{105,110} or cisplatin was assessed.^{106,108,109} Survival benefits were identified in two studies,^{109,110} one of which identifies treatment response as an independent predictor of survival.¹¹⁰ Meta-analysis showed a beneficial survival effect of embolisation or chemoembolisation compared with conservative management (figure 3). Survival benefits were confirmed with chemoembolisation, but were not identified with

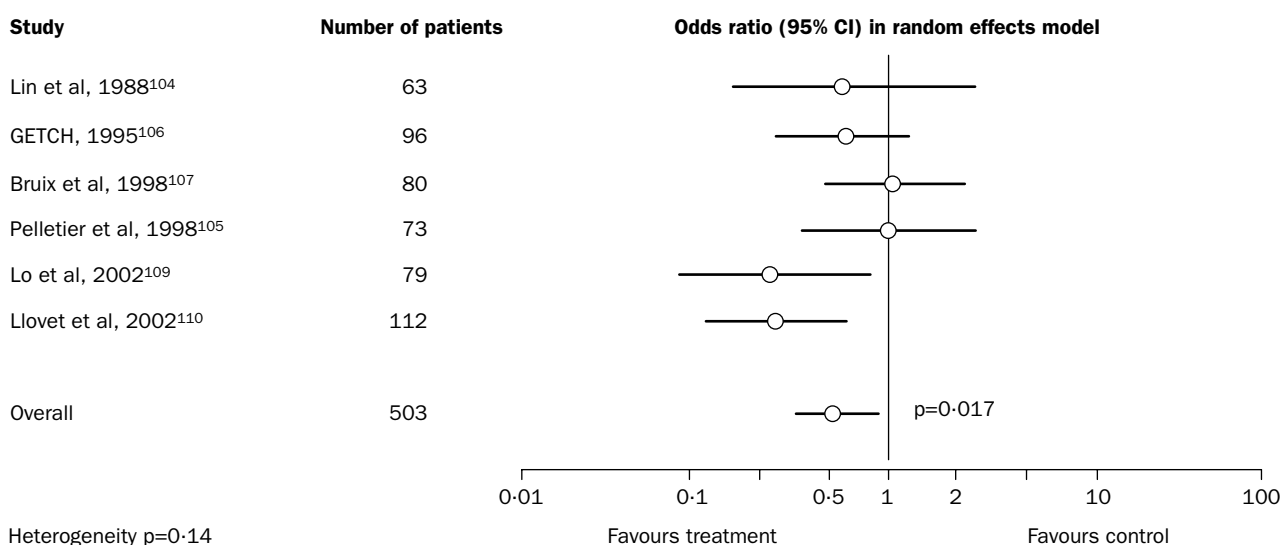


Figure 3: Meta-analysis of randomised controlled trials comparing 2-year survival of chemoembolisation or embolisation with conservative management for unresectable HCC

GETCH=Group d'Etude et de Traitement du Carcinome Hépatocellulaire. Reproduced from reference 55 with permission from WB Saunders.

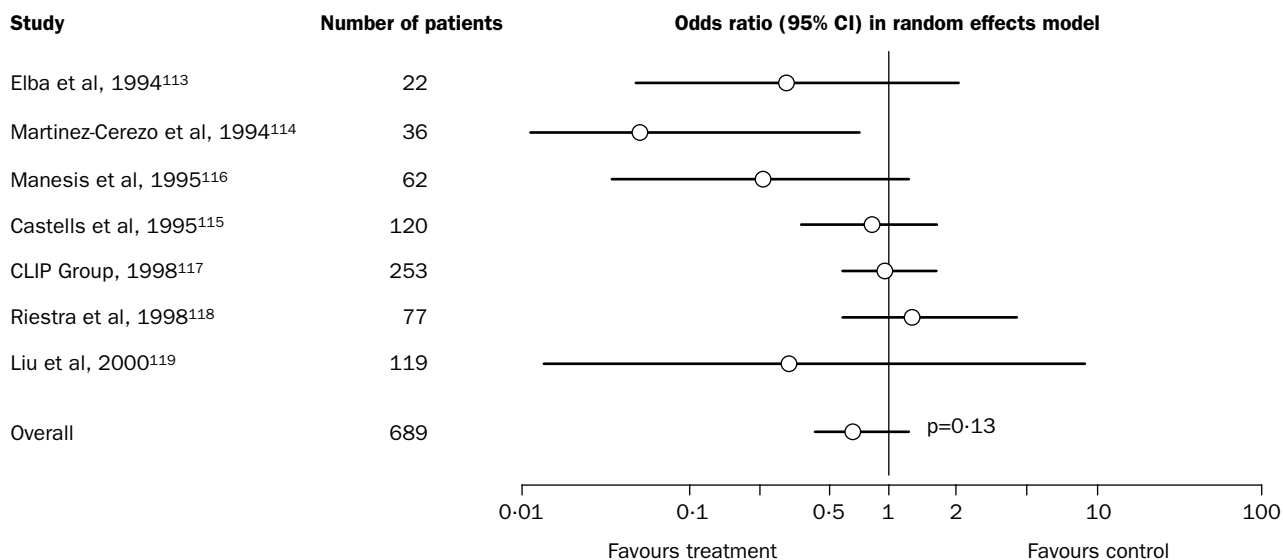


Figure 4: Meta-analysis of randomised controlled trials comparing 1-year survival of tamoxifen with conservative management for unresectable HCC

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embolisation alone, although the number of individuals analysed is still low.⁵⁵ There is no good evidence for the best chemotherapeutic agent and the optimum re-treatment strategy. Advantages favouring doxorubicin were advocated in one randomised controlled trial,¹⁰³ and the two positive trials applied three to four treatments per year, with doxorubicin and cisplatin, respectively.^{109,110}

Selection of candidates for chemoembolisation is a key point. The benefits of the procedure should not be offset by treatment-induced liver failure. The best candidates are patients who have preserved liver function and asymptomatic multinodular tumours without vascular invasion or extrahepatic spread, whereas patients who have liver decompensation or hepatic failure (Child-Pugh

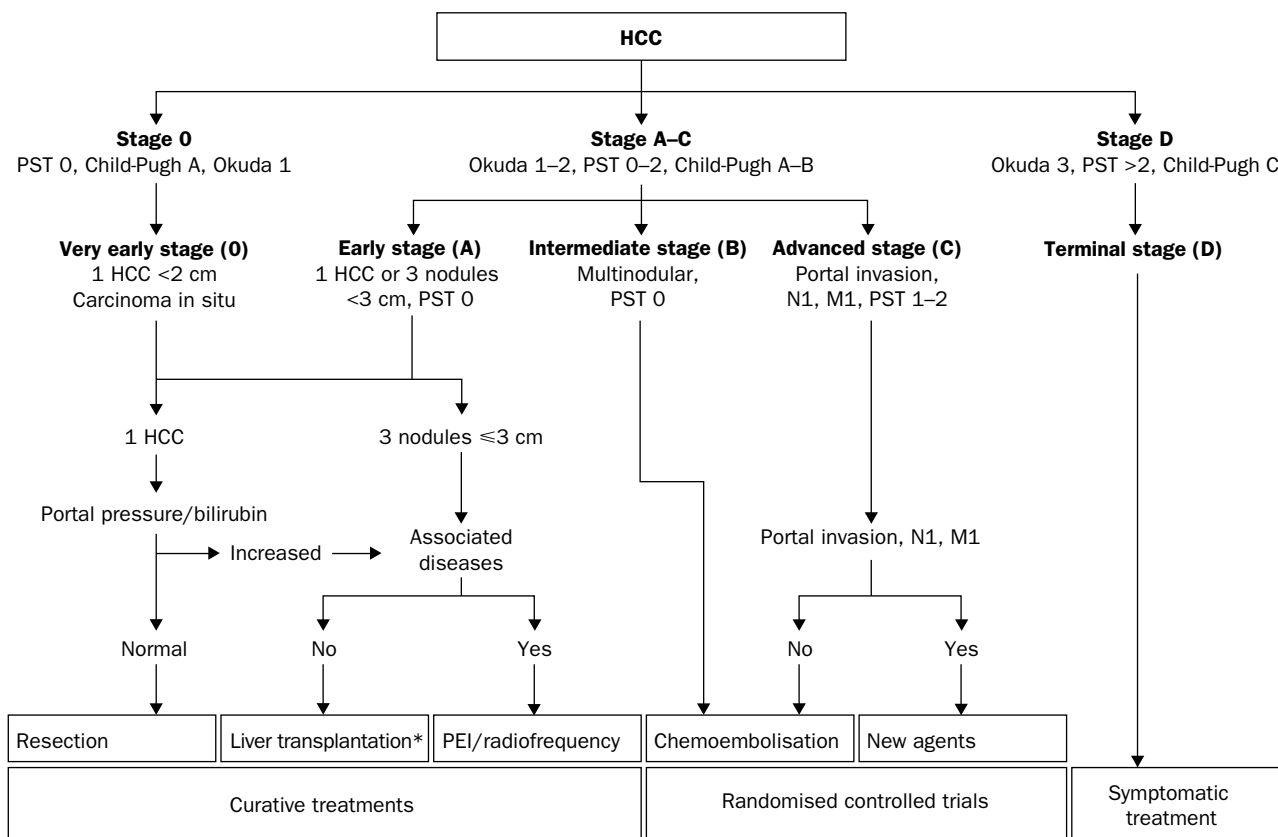


Figure 5: Barcelona-Clinic Liver Cancer staging classification and treatment schedule

PST=performance status test. N=nodules. M=metastases. PEI=percutaneous ethanol injection. *Cadaveric liver transplantation or living donor liver transplantation. Modified from references 54 and 40 with permission from The American Association for the Study of Liver Disease.

classes B and C), should be excluded, since the ischaemic insult can lead to severe adverse events.¹⁰⁶

Oestrogen blockade

The presence of oestrogen receptors in advanced HCC was the rationale for antioestrogen treatment.¹²⁷ Meta-analysis of seven randomised controlled trials in which tamoxifen was compared with conservative management, comprising 898 patients, showed no antitumoural effect or survival benefit with tamoxifen (figure 4).^{113–119} Findings of another randomised controlled trial confirm this evidence.¹²⁰ Other hormonal compounds, such as megestrol¹²¹ or antiandrogens¹²² have provided no robust survival advantage to date.

Treatment strategy

Evidence-based treatment for HCC relies on fewer than 100 randomised controlled trials and many observational studies. Furthermore, geographical differences in the incidence, presentation, and treatments available, have promoted the debate of a treatment strategy for this disease. Several treatment guidelines have been published.^{54,79,128,129} The Barcelona-Clinic Liver Cancer staging system links tumoural stage with a treatment strategy, and is aimed at incorporating prognosis estimation and potential treatment advancements in one unified proposal (figure 5).^{40,54} The system may be applied to most HCC patients, although individual cases might warrant special consideration, particularly candidates for cadaveric liver transplantation who have impaired liver function. Patients at very early stage (stage 0) or early stage (stage A) disease are optimum candidates for a radical approach. These patients are assessed for resection if they present with one tumour, absence of clinically relevant portal hypertension, and normal bilirubin. Transplantation is considered for patients with three nodules smaller than 3 cm or with one tumour smaller than 5 cm and liver-function impairment. When long waiting times exist, adjuvant resection or percutaneous treatments could be recommended. Living donor liver transplantation can also be considered. Percutaneous treatments—percutaneous ethanol injection or radio-frequency ablation—can be used in small unresectable HCC. Asymptomatic patients with multinodular non-invasive tumours (stage B) are the best candidates for chemoembolisation, particularly in Child-Pugh class A compensated cirrhosis. Patients who have advanced tumours (stage C) with vascular involvement or extrahepatic spread or physical impairment (performance status test score 1–2) can be assessed for treatment with new antitumoural agents. Finally, patients at a terminal stage (stage D) who have very impaired physical status (performance status test score >2) or tumour burden (Okuda stage III) should receive symptomatic treatment.

Conflict of interest statement
None declared.

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