Treatment of hepatocellular carcinoma at the dawn of the third millennium : liver transplantation and its alternatives

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For the Geneva Liver Cancer study group.

Abstract

Hepatocellular carcinoma is one of the most frequent tumors worldwide, and its frequency is increasing. The management of hepatocellular carcinoma has changed in recent years, this because screening allows to discover tumors at an earlier stage, and because of effective treatments are available, such as liver transplantation, liver resection, percutaneous ablation and transarterial chemoembolization. Each one of these treatments has its own advantages and drawbacks, and range of application according to the stage of the tumor and of the underlying liver disease. This review summarizes the recent progress in the management of HCC and the practice in our unit. (Acta gastroenterol. belg., **2004**, 67, **206-222**).

Abbreviations used in the article

AFP = alpha-fetoprotein
CT = computerized tomography
HCC = hepatocellular carcinoma
LDLT = Living-donor liver transplantation
MRI = magnetic resonance imaging
PEI = percutaneous ethanol injection
RFTA = radiofrequency thermal ablation
TACE = trans arterial chemoembolization
US = ultrasound

Introduction

HCC is the fifth cause of mortality by cancer worldwide, responsible for an estimated 500 000 deaths per year[i]. In the western world HCC is associated with cirrhosis in approximately 90% of the cases, and the incidence of this tumor is increasing, in part because of the epidemic of hepatitis C, in part because – with better management of portal hypertension – patients with cirrhosis live longer. The pattern of the disease at presentation is also changing : while most patients used to be diagnosed too late, at present the wide acceptance of screening of patients with liver disease is leading to the discovery of the tumor at a stage when cure or significant palliation can be offered by existing treatments. However, because the natural history of this cancer and the outcome of treatments are influenced by the severity of the underlying liver disease as well as by the tumor, the choice among treatments is difficult, requires the collaboration of several specialties, and is sometimes limited by lack of resources, such as organs for transplantation. For this reason the management of patients – if more rewarding – has become more complex.

A remarkable effort of summarizing the present knowledge on HCC has been done by the European Society for the Study of the Liver (EASL), and has been published in a dense consensus conference report (2). On each of the main topics, the conference identified the solid ground that already exists, and the items on which additional studies are needed before clear-cut recommendations can be given. In the following paragraphs we will maintain the main headings of the consensus conference highlighting recent advances, and presenting the point of view of our group on controversial issues.

Screening and diagnosis

HCC develops in livers affected by chronic disease in 90% of the cases – at the cirrhotic stage in approximately 80% of patients, and at the stage of chronic hepatitis in 10% – and more rarely in patients in whom no liver disease can be found. According to the regional prevalence of liver disease, therefore, the incidence of HCC varies from 5 to 15 cases per 100 000 population per year. For patients with cirrhosis, the risk of developing HCC ranges from 2% to 7% per year according to the underlying condition – it is low in autoimmune and primary biliary cirrhosis and high in viral hepatitis and hemochromatosis (3,4,5,6,7). Among patients with cirrhosis, patients of male sex, with raised alpha-fetoprotein (AFP), and with large-cell dysplastic changes on a liver biopsy have the highest risk (5,8,9,10).

Since the early ‘90s, HCC meets the main requirements of a disease for which screening is recommended : it develops in a defined and recognizable population, diagnostic tools are available, and useful treatments can be offered (11). Although there is no prospective randomized trial showing that screening is cost effective and that it improves survival, cohort studies show that the proportion of screened patients in whom a tumor is diagnosed beyond the curative stage can be reduced to

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approximately 10% (11,12), and the practice is widely accepted. The effectiveness of screening is reflected by a proportion of patients in referral centers who can be offered a curative treatment of 30% to 40% in Europe (12) and of 60% to 90% in Japan (13,14) in sharp contrast to a figure of less than 10% 20 years ago (15).

The screening strategy recommended by the conference was ultrasound (US) and AFP measurement every 6 months, but high-risk patients may benefit from more intensive surveillance. In our center, we recommend US every 4 months as this interval probably decreases the risks of a lesion being missed, fits well to the need of optimizing the management of patients with cirrhosis, and corresponds to the high demands of our population. The question of which investigation should replace US in poorly echogenic patients – whether computerized tomography (CT) or magnetic resonance imaging (MRI) – is still open, and will be answered by screening protocols comparing contrast MRI and CT. It is likely that, as access to facilities and to contrast media will improve, contrast MRI will prove superior to CT as screening method in these patients. The place of contrast-enhanced ultrasound will also need defining, and at present the technique remains investigational (16).

The conference recommended that only patients who are susceptible to benefit from *curative* treatments HCC are screened, limiting the practice to patients in the A category of the Child-Pugh classification who can qualify for liver resection, liver transplantation or percutaneous ethanol injection (PEI), and patients in the B category who can benefit from liver transplantation. This recommendation stemmed from the following assumptions : 1) the outcome of Child C patients is dictated by the stage of the underlying liver disease rather than by the HCC. These patients should be offered liver transplantation because of the decompensated cirrhosis, and HCC would only represent a co-indication (although affecting the priority of allocation of grafts in some countries). Conversely, the stage of the cirrhosis precludes any other treatment. 2) the lack of proof that Child B patients benefit from treatments of HCC other than liver transplantation, and 3) the lack of consensus on the benefit of any *palliative* treatment, a state that has changed when transarterial chemoembolization was proven effective in selected patients with relatively advanced disease (17,18).

We have adopted the pragmatic attitude that optimal management of cirrhotic patients requires US examinations anyway, and we do not necessarily limit screening to Child A patients or to patients potentially candidate to liver transplantation (Fig. 1). Furthermore, it is not uncommon to see the Child stage improving after treatment of precipitating factors such as alcohol intake, hepatitis B virus replication, bleeding or infection, and preliminary data in our cohort indicate that worthwhile palliation can be obtained by chemoembolization or percutaneous treatments even in child B patients with favorable tumor location or vascularity.

The panel of experts agreed on recall strategies and diagnostic criteria for patients *with cirrhosis* in whom a nodule is detected by ultrasound. Nodular lesions in a cirrhotic liver can either be HCC or regenerative, low-grade dysplastic and high-grade dysplastic nodules (19). The probability of a nodule being HCC varies according to the size and its radiological features. Accordingly, lesions < 1 cm should be followed-up with a repeat ultrasound every 3 months (less than 50% are carcinomas, growth is diagnostic of HCC while stability *is not* proof of benignity), lesions between 1 and 2 cm should be biopsied to establish the diagnosis between HCC, dysplastic or regenerative nodules, and lesions > 2 cm that are hypervascular and consistent on two radiological investigations (US-Doppler, CT, MRI, angiography) can be assumed to be HCC and treated as such. Hypervascular lesions >2 cm seen on *one* investigation and associated with an alpha-fetoprotein levels > 400 ng/ml do not need to be confirmed by a second radiological study (Fig. 2).

The recommendation of a biopsy for 1-2 cm nodules was soft, because knowledge is evolving rapidly, and should be adapted to the clinical context and local expertise. In our unit, for instance, we tend to be more restrictive with liver biopsy for this group, for the following reasons : a) overall, nodules detected by US, even if confirmed as benign by a biopsy, define a group at increased risk of HCC (31% after a median follow-up of 33 months) (20) ; b) liver biopsies in nodules below 3 cm in size have a high false negative rate (30%)**,** and a small but quantifiable risks of seeding (1-2%) (21). Therefore we tend either to wait with close follow-up until the lesion is over 2 cm in size, or we proceed to confirmatory CT or MRI and if the nodule is consistent we treat as if the nodule were HCC. We reserve biopsy of 1-2 cm nodules either for patients within research protocols, or to patients for whom the diagnosis of an *additional* HCC would change the treatment strategy. In the conference there were no recommendations on *hypo*-vascular nodules. In our clinic, below 2 m in size they are followed-up, but no treatment is offered unless they grow, between 2 cm and 3 cm they are investigated by IRM with ferro-magnetic particles and are considered HCC if no uptake is demonstrated (Küpffer cells are generally absent in HCC) and followed-up otherwise, and above 3 cm they are biopsied even if there are Küpffer cells as some well differentiated HCC do harbor Küpffer cells and missing the diagnosis of HCC could have severe consequences. The algorithm for screening in patients with cirrhosis and for the investigation of liver nodules detected in these patients is illustrated in figure 3.

Staging of the disease

Once HCC is diagnosed, it is convenient to stage the disease into prognostic and therapeutic categories. The conference suggested a classification featuring an *early*,

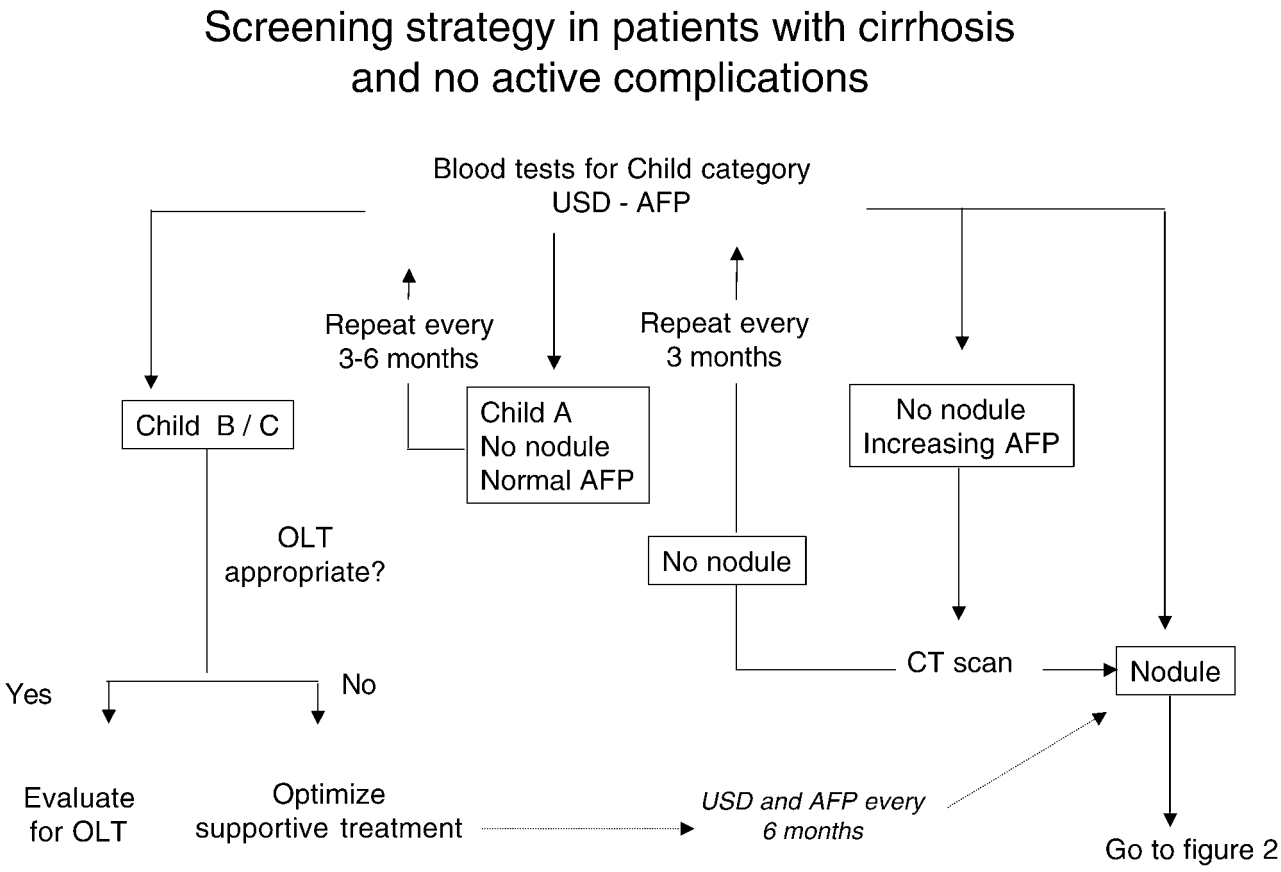

Fig. 1

Screening strategy in patients with liver disease.
Broken arrows and Italic characters signify practices currently used in our clinics but unsupported by available evidence.
USD : Ultrasound-Doppler examination.
AFP : Alfa-fetoprotein.

intermediate, *advanced* and a *terminal* stage corresponding to curative and palliative treatments for the first and second stage respectively, and to supportive treatments for the last two. This basically reproduced the BCLC categories that had been defined as follows (Fig. 4) (22) : patients with *early* HCC qualify for curative treatments such as percutaneous ablation, liver resection and liver transplantation. The underlying assumption is that the tumoral disease is confined to the liver, regardless of the severity of the cirrhosis. Accordingly, the features of the tumor(s) reproduce the criteria that are associated to low rate of recurrence after liver transplantation. These patients have either 1 tumor less than 5 cm or up to three tumors < than 3 cm, and no vascular invasion (23,24). Patients beyond these limits are in the *intermediate* category because of a high risk of occult tumor dissemination, but have no constitutional symptoms, no vascular invasion, no extrahepatic spread, and a normal performance status (25). Three-year survival in these patients may reach 50% in the absence of any treatment (26). These patients can benefit from palliative treatments (still undefined at the time of the consensus conference, and accepted as since TACE). Patients in the *advanced* stage have either constitutional symptoms (pain, or a performance status of 1 or 2) or an invasive tumor behavior defined as vascular invasion or extrahepatic spread, with a 3 year survival of approximately 10%, and patients in a *terminal* stage have either a performance status > 2, or extensive intrahepatic dissemination (the former Okuda stage III, with > 50% of the liver invaded by the tumor (27). There is no proven effective treatment yet, beyond supportive measures, that can benefit patients in the advanced and terminal stages. Although alternative classifications exist (28,29, 30,31), and the allocation of borderline patients to each category is likely to change as new treatments and prognostic determinants are identified, the BCLC classification is becoming accepted worldwide.

There are three limitations in this classification as it stands : the first is that the boundary between the early stage (curable) and the intermediate stage (palliative) based on the *size* of a *single* tumor is less meaningful for liver resection than for liver transplantation. Resection of the tumor is indeed the best option in patients with single tumors larger than 5 cm and preserved liver function, and it would be wrong to consider that all of these

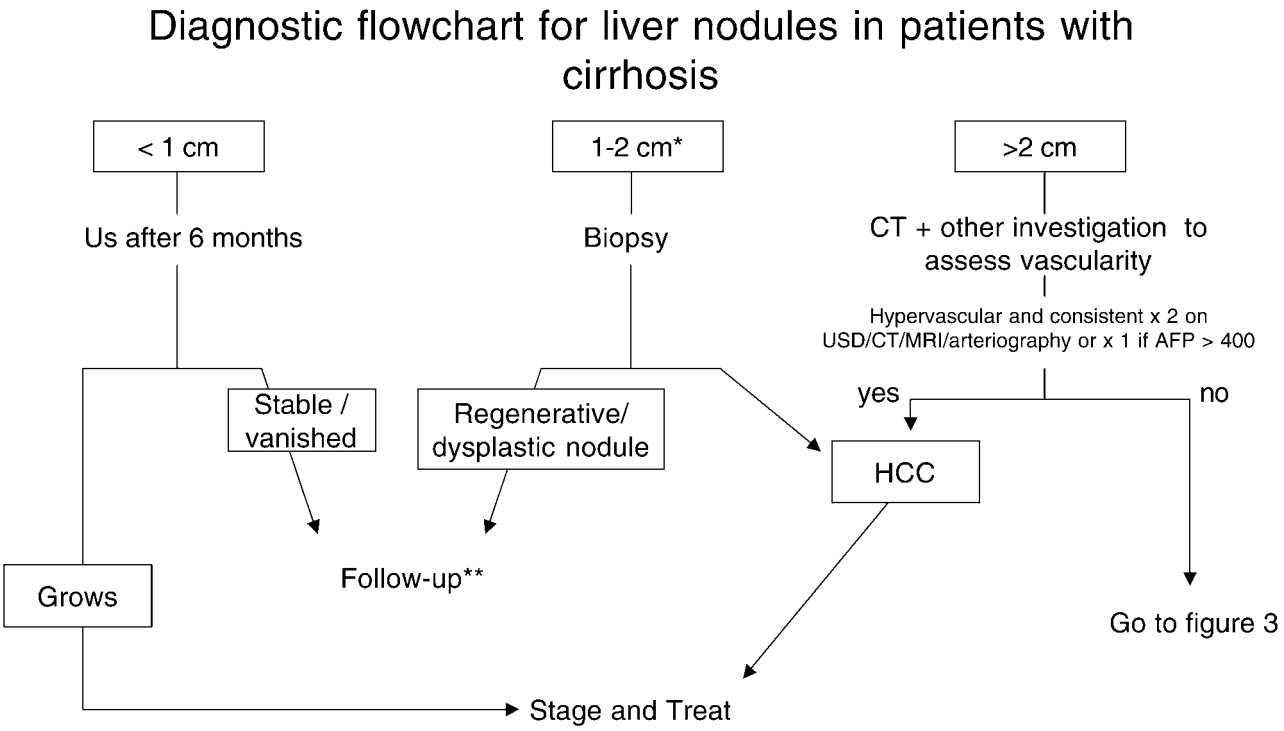

Fig. 2
Diagnostic strategy in patients with cirrhosis in whom a liver nodule is detected on ultrasound, according to the Barcelona consensus conference (Ref 2).

patients are beyond cure. The second is that the criteria of size and number used to separate early and intermediate disease correlate to *probabilities* and are not *proof* of extrahepatic spread, a point that will be developed below, and an effort should be made to refine this boundary. The third is that treatments have evolved and TACE can offer meaningful palliation to selected patients with advanced disease, such as patients with limited vascular invasion, or with constitutional symptoms such as fatigue or a performance status of 1 (17).

Curative treatments

Local destruction by percutaneous ethanol injection (PEI) or by radiofrequency thermal ablation (RFTA), liver resection and liver transplantation can cure a proportion of tumors in patients with HCC. In addition, liver transplantation can remove the underlying disease, diminish the risk of recurrence associated with cirrhosis, and offer the best chances of long-term survival. In the following paragraph the main features of each therapeutic modality and the advantages of each in selected clinical situations will be presented.

Percutaneous treatments

In recent years percutaneous treatments have been accepted as potentially curative therapies, to be discussed on the same grounds as liver resection or transplantation. Because of the lack of solid information on long-term results with other techniques, only PEI and RFTA will be discussed in this review.

Series from centers with a special interest in PEI have been published, summarized in a previous publication in this journal (32). Overall it can be said that in very experienced hands, and for lesions < 3 cm, PEI has similar local recurrence rates and disease-free survival than liver resection in many series, while being cheaper, less invasive, and more widely applicable because less restricted by the decreased functional hepatic reserve associated with the cirrhosis (33,34). Together with the expertise of the operator, the size of the lesion is the critical determinant for local recurrence (35). This because of the physical limits of the agent that has to diffuse in the nodule, and because even small HCC may have extra-capsular invasion or satellite lesions which are not treated with the injection. In theory, limited extra-capsular invasion

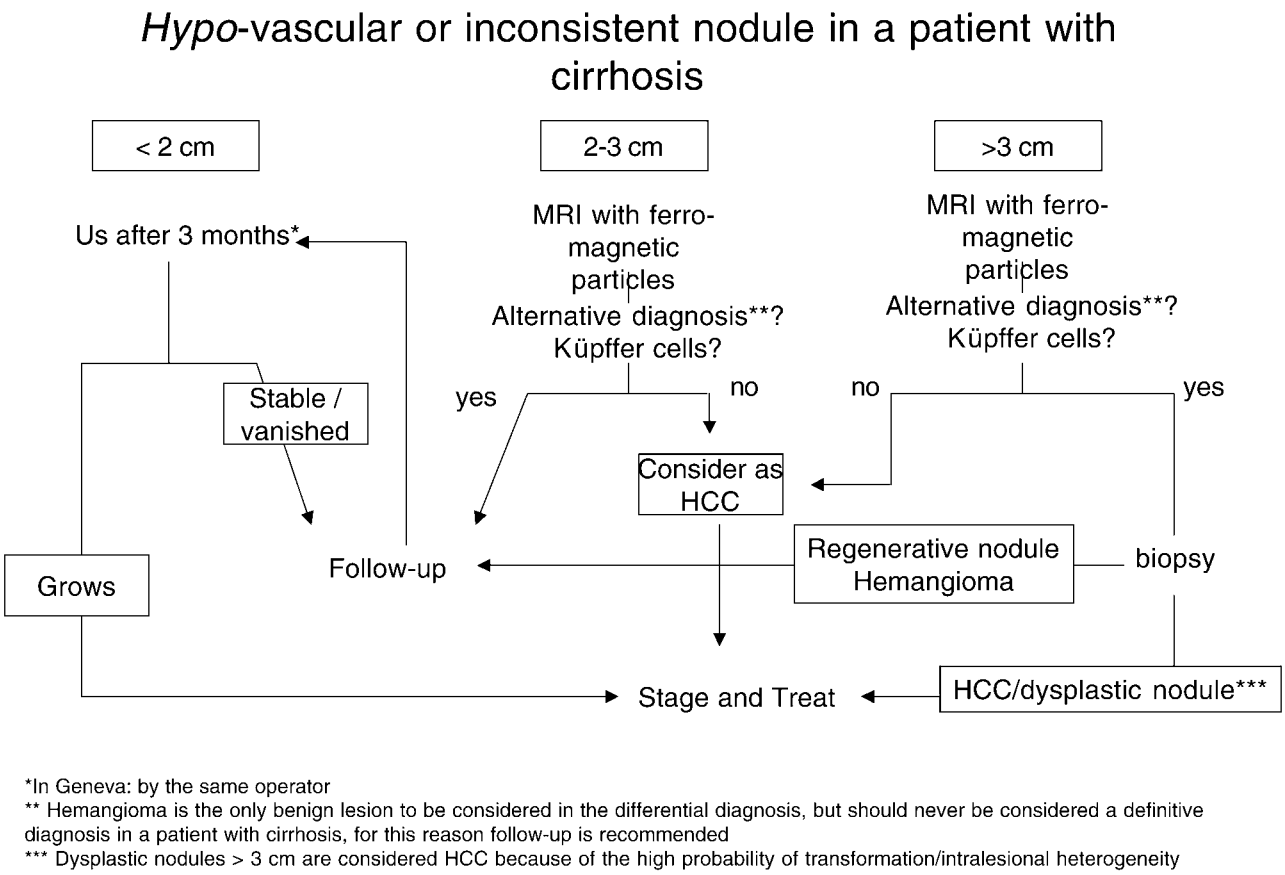

Fig. 3
Diagnostic strategy in patients with cirrhosis to characterize a hypovascular liver nodule, or a nodule that can be seen on US but not on CT, according to the practice in Geneva.

and satellites should be treated more efficiently by RFTA, and the most significant update since the consensus conference, which accepted only PEI as a proven therapeutic modality, is the finding that RFTA was more effective than PEI in a well designed prospective randomized trial showing a two-year local-recurrence free survival of 96% for RFTA vs. 62% for PEI (36). These figures can be assumed as the most realistic estimates for local control of the disease with either technique. One of the concerns with RFTA was needle tract seeding, with a worrying proportion of 12.5%, mainly concerning patients with peripheral tumors, reported by the Barcelona group (37). Centers with a large practice criticized such a high incidence as due to a learning curve (38,39,40). The realistic figure for seeding is still a matter of debate, as the true extent of the problem may appear only in studies with a follow-up stringent and long enough to allow the seeding of minute amounts of viable cells to become clinically evident (such as when RFTA is made in patients who are subsequently transplanted). The figure we quote is 2%, based on the experience our center (no seeding in a consecutive series of 55 nodules) and of series of experienced interventional radiologists (De Baere T, 3 local recurrences in a series of 167 liver nodules, Lencioni R, X recurrences in a series of XX nodules, personal communications 2004).

At present in our center, RFTA is the preferred percutaneous treatment, because a one-session approach is possible, as opposed to the multiple sessions needed with PEI. The procedure is routinely performed under a short general anesthesia, generally with ultrasound guidance, but CT is used if the nodule or the patients are poorly echogenic, and MRI-compatible equipment has been used in our center for nodules that are not well defined with CT (41). We found that procedures under local anesthesia are uncomfortable. The question on which type of equipment is still unsettled, but recently we found bipolar electrodes particularly effective. Lesions up to 3 cm can be treated by RFTA alone, and larger lesions are treated with a combined approach associating TACE and RFTA (42). This is done either during the same session or sequentially with several courses of TACE treatment to decrease the size of the nodule within the borders of the highest success rate for RFTA (3 cm). We consider that with a combined approach using RFTA and TACE, the maximum size of a lesion that can be treated effectively is 5 cm. PEI is reserved for peripheral tumors that present a large risk of

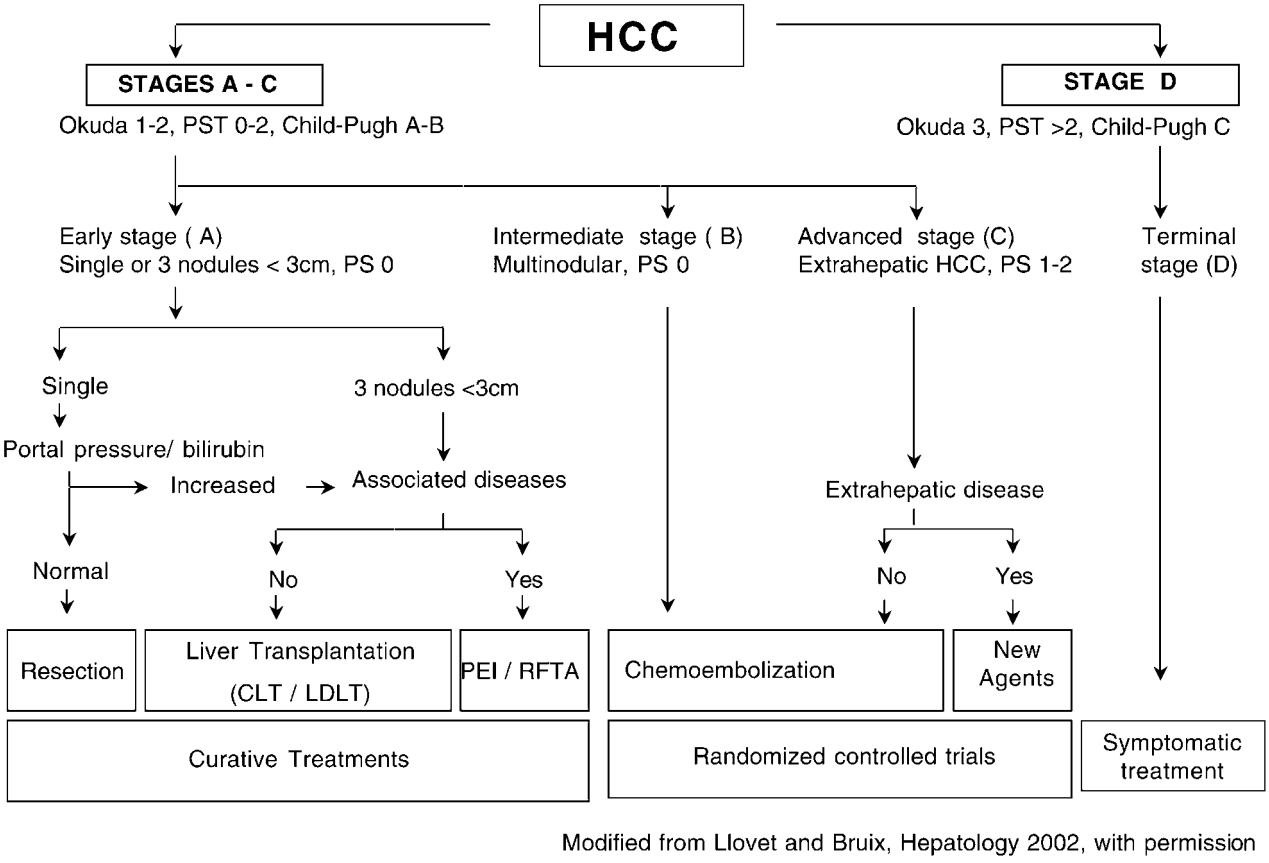

Fig. 4

Staging classification of the Barcelona Clinic Liver Cancer (BCLC) study group. Abbreviations : Okuda : Okuda stage. PST : performance status. CLT : cadaveric liver transplantation. LDLT : living-donor liver transplantation. PEI : percutaneous ethanol injection. RFTA : radiofrequency thermal ablation.

capsular rupture, of for tumors in close proximity to the biliary tree, for which the diffusion of the electrical current can not be controlled as precisely as the diffusion of ethanol with real-time US PEI. The use of RFTA in patients during the waiting time to liver transplantation will be discussed below.

Liver resection

Liver resection by partial hepatectomy remains the standard curative option for HCC in patients with single tumors and preserved liver function, and the results of the main series can be found in previous review articles (43). The significant acquisitions of the studies appeared since 2000, show that a) careful surgery (starting with patient selection) is accompanied not only by a very low operative mortality (44,45,46), but also by excellent long-term survival, approaching 60% at 5 years in patients with normal bilirubin and with no portal hypertension (47). b) if the above-mentioned restrictive criteria are followed, liver resection can be applied only to a small fraction of patients with HCC. This proportion is 5% in Barcelona, a figure confirmed in our clinic. The restricted applicability is the main limit of liver resection as a curative treatment for HCC, although the proportion of patients who can be treated by liver resection can be increased by more effective screening (in Japan resection is applied to 30% of HCC patients, a considerable difference even taking into account the higher proportion of patients with chronic hepatitis rather than fully developed cirrhosis) (48), and by pro-generative techniques that favor the preoperative increase of the remnant liver such as portal vein – and arterial – embolization in the territory that will be sacrificed by the hepatectomy (49,50). The second limit of liver resection in the treatment of HCC is that, because of the carcinogenic potential of the underlying liver disease, recurrences are almost inevitable, at a rate of 15%-25% per year, as summarized in a previous publication (43). Four strategies can be opposed to this problem.

1) *to offer resection preferentially to patients at low risk of recurrence*. To some extent the propensity of the cirrhotic liver to develop new nodules can be determined. Recurrences are particularly likely to develop in patients with increased transaminases and active hepatitis (51,52,53), and probably in the presence of macro-regenerative nodules and large cell

dysplasia (10). Although the propensity of the underlying liver to develop *de novo* tumors can probably no be altered, in our unit a high hepatitis activity or increased transaminases weight towards alternatives to liver resection, and in these patients we prefer either liver transplantation, that eradicates the cirrhosis, or RFTA, that will allow treatment of new lesions more easily.

2) *to argue that survival, and not disease-free survival is what matters* : this point of view corresponds to a more pragmatic view of the advantages of liver resection as opposed to liver transplantation, that is more complex, poorly available, and subject to the danger of hepatitis C recurrence in the graft. Furthermore, recurrences can be treated in their own right, and with good liver function are compatible with relatively long-term survival (54).
3) *to consider that resection can be followed by liver transplantation for recurrence in a more global strategy.* This point and the preceding one, both crucial in the choice between resection and transplantation, will be treated more extensively below.
4) *to rely on adjuvant treatments.* Unfortunately this field has not held the promise of initial reports. Pharmaco-prevention by a retinoid was associated with a markedly diminished recurrence rate in a prospective randomized study (55) ; this drug however, and for unknown reasons, has not gained the expected popularity. Adoptive immunotherapy with tumor cells was also associated with diminished recurrences (56), but this result has not been confirmed in a larger scale. Similarly new studies are needed to recommend postoperative TACE, internal irradiation with I^{1} (31) lipiodol (57,58), or interferon (59). Any of the quoted studies needs to be confirmed and is not enough as a basis to adopt new practices (60).

The two latter points, that are crucial in the issue of the choice between liver resection and liver transplantation will be developed below.

On the ground that local control of the disease and overall survival, rather than disease-free survival, should be the endpoint, and that the best local control of the disease can be offered by partial hepatectomy, some groups are offering liver resection to patients with multiple tumors who are not candidate for liver transplantation (48), (Mazzaferro, personal communication). This approach may increase the number of patients who undergo resection from 5% to 15%-20%, with proper targeting of the screened population (child A patients). Whether this approach is better than percutaneous treatments or combination of TACE and percutaneous treatments is unproven. Figures from Japan show a similar survival for both approaches (61). In our unit, we reserve resection to patients with *single* lesions, child A, with normal bilirubin and no portal hypertension (< 10 mmHg wedge hepatic gradient) on a portal hemodynamic study and transjugular biopsy that is part of the evaluation protocol of cirrhotic patients candidate for surgery.

Percutaneous techniques vs. liver resection

Given the excellent results of PEI or RFTA in patients with small nodules, can these be considered as equivalent or better solutions than liver resection in all patients ? Prospective randomized trails comparing PEI to liver resection do not and may never exist, probably because of marked center preferences (48). Recent multicentric cohort studies in Japan using either techniques, however, show a small advantage for liver resection, reflecting in part the bias that patients with liver resection have a better liver function, but also that the wider safety margin offered by partial hepatectomy is a real advantage in a proportion of cases. Also, the criteria to define that a nodule is sterilized after percutaneous treatments (lack of contrast uptake on CT or MRI) may overestimate the true effectiveness of percutaneous ablation, as demonstrated by the increasing proportion of viable cells that are found in explanted nodules as the interval from a seemingly successful RFTA and transplantation increases (62). In our center, percutaneous treatments are preferred to liver resection in a) patients with central liver lesions and diminished hepatic reserve or with extrahepatic surgical risk factors who do not qualify for liver resection b) patients with multiple tumors who do not qualify for liver transplantation c) in patients at high risk of recurrence after resection, as discussed above. In borderline patients, we consider arguments in favor of resection a tumor size approaching 3 cm (larger lesions are treated less effectively by percutaneous ablation), and the peripheral location of a tumor (resection can be accomplished with minimal sacrifice of hepatic function).

In the practice of our HCC clinic, therefore, the dilemma between RFTA and liver resection is more theoretical than practical as the evaluation of the patient, of the cirrhosis and of the tumor usually makes the decision obvious.

Preoperative and postoperative management for resection and percutaneous treatments

The use of neo-adjuvant treatments before liver resection can not be recommended on the basis of available studies (Schwartz), and the approach in our unit is to use preoperative TACE only to stabilize the tumor when preparatory strategies, such as portal vein embolization, are implemented, or to increase the resectability of large tumors, a concept that is difficult to justify within the framework of evidence-based medicine, but that is obvious in surgical practice (63).

After surgery or percutaneous ablation, on the arguments stated above, we do not follow any postoperative regimen beyond surveillance with US and alpha-fetoprotein measurement every three months and a baseline CT on the first postoperative day, at three months and six

monthly thereafter for RFTA, and at one month and six monthly for 2 years for resection, treating recurrence as appropriate when they appear.

Liver transplantation

The excellent result of liver transplantation in terms of mortality and recurrence for patients fulfilling the criteria of Paul Brousse (23) (1 or 2 tumors up to 3 cm) or of Milan (up to 3 tumors, up to 3 cm or 1 tumor up to 5 cm) (24) have been confirmed in several series (64), and a selection of recent publications with original features is summarized in table 1 (65,66,67,68,69,70,71,72, 73,74). Indeed liver transplantation has been demonstrated to be an excellent treatment also for patients outside these criteria, despite higher recurrence figures. In part because of its success, liver transplantation for HCC is confronted to two opposing pressures. On one side, organs are scarce, and patients wait longer on the transplant waiting list, facing the risks of contraindications to transplantation developing, with a negative impact on intention-to-treat results that are inferior to the reported post transplantation figures. On the other side, it appears that the criteria are too strict, and exclude patients who could potentially benefit from transplantation. Both issues are passionately debated in HCC groups and we will summarize the present knowledge and our points of view below.

Intention to treat results

The BCLC group highlighted that intention-to-treat results of OLT for HCC were markedly affected by the longer waiting time experienced in recent years, with 24% of the patients either dying or developing contraindications while waiting (47). This despite the fact that disease progression in size or number was not considered as a dropout criterion (in the study, only vascular invasion or distant metastases were considered as contraindications to transplantation). It is noteworthy, however, that this group – unconvinced of the benefits of TACE – did not offer any treatment to slow the progression of the tumor while waiting. A decision analytic approach from the same team concluded that PEI was a good option for waiting times less than 6 months, and liver resection for waiting times in excess of one year (75). However, this study was published before two prospective randomized trials and a meta-analysis showed that TACE is an effective treatment for HCC, indeed in patients whose disease was more advanced than in patients qualifying for transplantation (17,18). Stimulated by the Barcelona group, other centers – mostly using TACE in the waiting period – reported their intention to treat and dropout figures as lower than the BCLC's, although all experiences reaching different results can be criticized (summarized in Table 2) (76, 77). The San Francisco group quoted better intention to treat results and lower dropout figures in a population treated with TACE (71). This study, however, is biased by inaccurate preoperative staging (25% of the tumors were discovered incidentally, up to a size of 5 cm) and by the retrospective histological – rather than prospective radiological – basis of for their conclusions. The best published evaluation so far comes form the Innsbruck group that reports a 0% dropout rate in a series of 45 patients within the Milan criteria and excellent disease-free short-term survival. The waiting time, however, was relatively short to be able to conclude firmly on the true progression rate of the tumor on the waiting list in patients undergoing pre-transplant TACE. In our unit we use TACE systematically unless the tumor is hypovascular, based on a very favorable experience in terms of complications, and of the extrapolation of the available literature on TACE to the situation of the waiting list (78). Patients are followed-up with three monthly AFP and ultrasound, and six-monthly CT and bone scan. In a cohort of 68 patients with a known HCC on the waiting-list for a median of 5.5 months, there was 1 tumor-related dropout among 42 patients Child A and B within Milan's criteria, and 2 tumor-related dropouts among 10 patients outside Milan's criteria. As waiting time lengthened, however, our program experienced 6 tumor-unrelated deaths in patients who were either Child B or Child C at the time of listing.

Based on the studies mentioned above, and of our experience, it seems that TACE is a reasonable option, and will probably be accepted as standard treatment for patients on the waiting list, despite the lack of direct comparative studies against no treatment. Whether PEI of RFTA - alone or in association to TACE - are better than TACE alone will probably be answered shortly. In Switzerland, a protocol comparing TACE vs. TACE + RFTA for waiting-list patients is running and it was judged that the evidence in favor of TACE was sufficient to consider a no-treatment arm unethical (79).

The above-mentioned studies have highlighted the need of common definitions for exclusion criteria, and whether these criteria should be the same in treated and untreated patients. Very low recurrence rate in centers applying restrictive criteria for listing and looser criteria for drop-out (Barcelona, Milan, Paris and Geneva, to quote a few) supports the concept that tumor progression in size or number while on the waiting list is not a contraindication to liver transplantation (Table 1).

Are traditional criteria too restrictive and how should they be enlarged ?

The experience in all centers that have transplanted patients with HCC shows that by the standards of surgical oncology, liver transplantation is a good option even for patients beyond the traditional criteria, with 5-year survival rates in the order of 50% or 25% (table 3) (80, 81,82). While from a *societal* perspective these figures are unacceptable in the face of the severe shortage of organs, they still show that from an *individual*

Table 1. — Selection of recent series of liver transplantation for hepatocellular carcinoma

Author	Ref	Patients	Features	Criteria (number size)	Recurrences	Survival	Comments
Bismuth	23	60	R	no extrahepatic spread	30%	49% (3 years)	Landmark series
Mazzaferro	24	48	P	Milan	8%	75% (4 years)	
Llovet	47	87	P	BCLC	3%	82/69/69	
Figueras	65	307	Multicentric	<3<5	21%	na/67/63	43% with AFP > 300 p 0.04
Herrero	66	47		1<6, 3 < 5	13%	87/79/79	
Tamura	67	53		na	26%	79/65/61	incidental included
Jonas	68	120		Milan	16%	90/-/71	incidental included. Vascular invasion and differentiation correlate with and refine size and number
Gondolesi	69	27	LDLT	MS	7%	81/na/na	Waiting time 83 days. Short FU (276+-213 days) precludes analysis recurrences
Moya	70	23	HCV-	Milan	11.5%	87/77/77	Short waiting time. Data on patients outside criteria not available
		81	HCV+			70/63/59	
Yao	71	60		UCSF	11%	90/82/75	33% incidental
Kaihara	72	56	LDLT	No PVT	11%	73/54/na	25% postoperative mortality, short follow-up (11 months, range 1-39) precludes reliable interpretation on recurrences and survival
Adam	73	195	PLT	PB(after 1992)	18%	80 68 61	High peroperative mortality and recurrence rate in SLT group. Probably biased by early experience
		17	SLT		54%	71 53 41	
Belghiti	74	70	PLT	Milan	4%	na/82/69	
		18	SLT		5%	na/82/61	
GLCG	–	49	P	Milan	4%	92/88/84	8 patients transplanted prospectively outside Milan's criteria

Statistics : descriptive : median and range unless specified. Survival : % patients surviving at 1/3/5 years.

Abbreviations :
BCLC : Barcelona Clinic liver cancer study group criteria :single tumor < 5 cm or 3 tumors up to 3 cm, no vascular invasion, no lymph nodes, no distant spread.
GLCG : Geneva Liver Cancer Group.
Milan : Milan criteria : single tumor < 5 cm or 3 tumors up to 3 cm, no vascular invasion, no lymph nodes, no distant spread.
MS : Mount Sinai criteria : tumor involves < 75% of liver; main portal vein free, if bilateral tumors, smallest tumor < 5 cm, no lymph nodes, no distant spread.
PVT : portal vein thrombosis.
P : prospective.
Paul Brousse : pauld Brousse criteria : up to 3 tumors, up to 3 cm, no vascular invasion, no lymph nodes, no distant spread.
PLT : Primary liver transplantation.
R : retrospective.
VI : Vascular invasion.
SLT : salvage liver transplantation.
UCSF : University of California San Francisco criteria :single tumor < 6.5 cm, up to 3 tumors < 4.5 cm, sum of all tumors < 8 cm.

perspective the traditional criteria fail to offer the best chances for a patients with more advanced disease. To compound the problem, with the advent of LDLT the responsibility to optimize the results of the grafts is arguably removed.

While the problem is topical, there is very little basis for recommendations (83). For the sake of clarity the issue can be split in different paragraphs.

a) The central issue in liver transplantation for HCC is the presence of occult extrahepatic disease that will ultimately reveal as recurrence. Traditional radiological criteria have served as surrogate markers for the probability of extrahepatic spread, the strongest correlation being with macroscopic vascular invasion, then with tumor size, then with tumor number, probably in a ragbag comprising i) intrahepatic metastases of the index tumor – with a high predictive value for distant spread- and ii) true independent tumors – for which the additional risk should only be added to the risk of the index nodule. As surrogate markers, the number and the size of tumors are imperfect, and better markers are needed, especially outside Milan's criteria.

b) Traditional criteria on number of lesions may be too restrictive now when better radiology decreases the gap between the number of nodules known preoperatively and the number of nodules discovered postoperatively. In other words, older radiology provided a discount in the number of lesions that is now being eroded by better imaging. This problem is frequently debated in HCC groups when listing or refusing patients. The only answer so far is empirical : the Barcelona group follows strictly the consensus conference definition of HCC, that the nodule has to be larger than 2 cm and concordant on at least two investigations (83). We use a similar approach with the difference that for borderline cases we biopsy one or two of the controversial nodules and list the

patient if no tumor is confirmed (minimizing the risk of seeding by performing the biopsy with the coaxial technique (84). This protects patients against the risk of overstaging of the disease, and we recently transplanted a patient diagnosed with 7 liver nodules typical of HCC only two of which were true HCC on the explanted liver (fully within Milan's criteria). The group in Pisa (Lencioni R, personal communication, 2003) is investigating an approach in which only the lesions with an identical MRI behavior to the index lesion are counted as meaningful, a rational attempt to discriminate between new nodules and intrahepatic metastases.

c) Tumor size and – to a lesser extent – tumor number correlate to microscopic vascular invasion and tumor grading, indeed the only predictor of survival on multivariate analysis in a recent large series (68). Supposedly, histological markers are of limited utility because they are retrospective on the explanted liver, or because they could be obtained only by preoperative biopsy that is subject to complications and to sampling errors. Yet it is possible that even at the cost of a liver biopsy, tumor histology could offer a better prediction of a favorable outcome in patients outside the Milan criteria and prospective evaluation of such a strategy may be warranted.
d) Extrapolation from the available literature of guidelines to expand the criteria should be cautious as most studies refer to histological *post-hoc* criteria in patients that were transplanted intentionally within the traditional criteria (or worse, without known tumors). The biological behavior of these "missed targets" may in fact be different than patients who are known to be outside the criteria from the time of their evaluation. There are two exceptions among these studies. The Mount Sinai group studied prospectively a cohort of patients with expanded criteria, concluding that lesions up to 7 cm without vascular invasion have an acceptable survival rate of approximately 50% at 5 years (76). And we reported on the positive selection effect of TACE when the treatment obtained a reduction of 50% in the size of the tumors (defined as downstaging), with only three recurrences and a 78% 5-year disease-free survival in a group of 19 patients originally outside the Paul Brousse criteria. The latter experience was challenged by the group in Innsbruck who transplanted a group of 10 patients who were downstaged, with poor results. However, the 3 of 5 deaths were not related to the tumor, and no conclusions can be reached on these results. We are presently trying to validate prospectively the concept of downstaging by treating aggressively patients outside the criteria to either within the criteria or to a stage of stable disease where they can benefit form grafts refused otherwise. The rationale for this practice is the assumption that time on the waiting list *and* response to TACE will select the tumors with a more benign biology. The validity of this concept is supported by the analysis of 60 liver nodules after transplantation showing a correlation between complete tumor response and the absence of vascular or capsular invasion, suggesting that TACE is particularly effective in well-differentiated tumors (85). We experienced no recurrences so far in a group of 6 patients, after a median follow up of 3 years.
e) Analysis of the literature offers at least two firm recommendations : i) macroscopic vascular invasion is associated with a poor prognosis, and virtually all patients will recur, with the odd cases of segmental thrombosis that have been censored as surviving, but for whom a longer follow-up may be needed (recurrences have been observed after several years (64,86). ii) tumor differentiation becomes a highly predictive surrogate marker of distant spread in tumors beyond 5 cm in size. Indeed we were not able to find either in the literature or in the experience of transplant colleagues, any patient with a poorly differentiated tumor larger than 5 cm surviving without recurrence beyond 5 years (table 3). The results for poorly differentiated tumors < 5 cm are rather good, with 67% 3-year survival among 9 patients in the series of Tamura (67). Unfortunately case-by case data can be extracted only rarely from published series.

What recommendations can be made ? Enlarged criteria will need defining and prospective validation, in that order. Careful expansion of traditional criteria can be attempted within experimental boundaries, aiming to test strategies that may yield a "reasonable" chance of survival, defined arbitrarily as 50% at 5 years. The Barcelona group included in a prospective protocol patients who fulfill the rule of "7 or symmetric 3s and 5s", representing the size of a solitary nodule, and the number and size of multiple nodules, respectively. In addition they suggested that patients who responded successfully to any form of treatment of HCC to reach the traditional criteria and who did not show signs of progressive disease for 6 months could be included (87). In our center we accept on the main waiting list patients who have reached the traditional criteria after TACE, and consider for transplantation with marginal grafts (for instance from donors with malignant tumors of the central nervous system) patients whose disease has been stabilized with TACE for at least 6 month, or patients who fit in the Barcelona expanded criteria, in whom a liver biopsy does not show a poorly differentiated tumor. The flowchart for the management of potential candidates for liver transplantation in our center is illustrated in figure 4.

Living-donor liver transplantation

Only 2 series concentrate specifically on the issue of LDLT for HCC (table 1). On the argument that intention-to-treat results are worsened by a long waiting time,

Table 2. — Selection of recent series of liver transplantation for hepatocellular carcinoma, in which dropout data or intention to treat data are available

Author	Ref	Study	Criteria	Patients (transplanted)	WT (days)	Neoadjuvant treatment	DO Criteria	DO tum	DO LF	DO total	FU (months)	ITT Surv	Comments
Llovet	47	P	Milan	37(29)	242	none	VI/ES	6	2	23%	na 54 (2 years)		No adjuvant treatment
Herrero	66	R		49 (47)	117	TACE 23, PEI 5, RFTA 3	Progression ?	2	na	5	na	na	
Yao	71	R	UCSF	46 (21)	265 med	several	UCSF-	11	2	23%	1	92 73 73*	
Roayaie	76	P	> 5 cm and MS DO :207+-306	80	Tx :142+-168	TACE	MS-	23	4?	46%	55	na	Downstaging 33%
Graziadei	77	P	Milan	48 (41)	178	TACE	progression	0	0	0	35+-20	98/98/94	
			Downstaging +, No VI	15 (10)	254	TACE	progression	3	1	27%	na	93/78/31	Downstaging 42%, 3 non cancer deaths
GLCG	present series	P	Milan+	57 (43)	210	TACE (RF1, PEI 1)	VI/ES	1	6	12	45	91/80/74	drop-out rate increasing recently with increasing waiting time
			Milan -	10 (8)	150			2	0	20		80/80/80	

Statistics : descriptive : mean and standard deviation unless specified. Survival : % patients surviving at 1/3/5 years.
Abbreviations :

CL : contralateral lobe.
DO :droupout.
Downstaging+ : Decrease > 50% in the maximum diameters of the tumors.
LF : because of liver failure or complication of cirrhosis.
MS- : progression outside Mount Sinai criteria.
tum : because of tumor.
VI : vascular invasion.
WT : waiting time.

Table 3. — Selection of recent series of liver transplantation for hepatocellular carcinoma outside the generally accepted criteria for transplantability

Author	Reference	Study	Patients	Definition of cohort	Criteria	FU (months)	Recurrences	Survival	Comments
Majno	63	R	19	> 3 cm	TACE downstaging +	36	16%	84/79/71	3 tumor deaths : 2ps MVI+, 1 with extensive disease
			16		TACE downstaging -		na	56/29729	
Iwatsuki	81	R	196	Grade 1	PRS < 7.5	91 +- 44 months	24%	na/na/100	Incidental tumors included. Survival is tumor-free
			45	Grade 2	PRS 7.5-10.9			na/na/61	
			34	Grade 3	PRS 11-14,9			na/na/40	
			43	Grade 4	PRS > 15			na/na/5	
			26	Grade 5	LN+ or Mets +			0,0E+01	
Tamura	67	R	8	size : 6.25 median 5.5-15 range	> 5 well-mod differentiated	38 d months	25%	na/62/na	
“			6		> 5 poorly diff		83%	0/-/-	
Steinmuller	81	R	10	ldlt	Iwatsuki 2-4	10	2%	80	Short FU (median 10 months) precludes conclusions on criteria
Yao	81	R	60	UCSF+	s < 6.5, < 3t < 4.5, < 8cm sum		7%	90/82/75	33% incidental
			10	UCSF-			40%	50/50	
Roayaie	76	P	43	5.8 +-2.7	MS	55 months	40%	na/na/44	Dropout 46%
			na	subgroup	MS and < 7 cm and no PVT		29%	na/na/55	
Graziadei	77	P	10	TACE Downstaging +	Downstaging +, no VI		30%	82/55/41	High non-tumor related mortality
Kaihara	72		25	Beyond Milan	No PVT/distant spread	13 months (for disease free)	40%	na	25% postoperative mortality
GLCG	present series	P	6	Beyond Milan	Tace downstaging +	24	0	100	

Statistics : descriptive : median and range unless specified. Survival : % patients surviving at 1/3/5 years.
Abbreviations :

Downstaging+ : Decrease > 50% in the maximum diameters of the tumors.
VI : Vascular invasion.
CL : contralateral lobe.
GLCG : Geneva Liver Cancer Group.
Milan : Milan criteria : single tumor < 5 cm or 3 tumors up to 3 cm, no vascular invasion, no lymph nodes, no distant spread.
MS : Mount Sinai criteria : tumor involves < 75% of liver; main portal vein free, if bilateral tumors, smallest tumor < 5 cm, no lymph nodes, no distant spread.
Paul Brousse : pauld Brousse criteria : up to 3 tumors, up to 3 cm, no vascular invasion, no lymph nodes, no distant spread.
UCSF : University of California San Francisco criteria :single tumor < 6.5 cm, up to 3umors < 4.5 cm, sum of all tumors < 8 cm.

it would be reasonable to assume that the results of LDLT would be better than of cadaveric liver transplantation. Unfortunately no series addresses the issue of intention to treat results, and follow-up is too short to extrapolate data on recurrences or overall survival. In theory, recurrences may be as high or higher than with cadaveric liver transplantation, for two reasons. The first is that LDLT frees the teams from the duty to optimize the use of a public commodity, and patients outside the traditional criteria can be transplanted. The second is that LDLT allows transplanting borderline patients quickly, without the natural selection offered by seeing how the disease evolves during the time on the waiting list – with or without treatment. It is therefore possible that LDLT transforms some would-be early dropouts into recurrences. The latter concern is apparently not supported – at least within Milan's criteria - by the experience of the Kyoto group showing only 1 recurrence among 20 patients (72). The follow-up of the series, however, was very short, and so far it is not possible to state whether LDLT is better or worse than cadaveric liver transplantation for the treatment of HCC. Only theoretical models are available to guide counseling and clinical choices. We investigated the potential advantages of LDLT for HCC in a decision analytic approach (88). Assuming a drop-out rate of 4% per month (the only one published that far), and a success rate of LDLT equal to average results of cadaveric liver transplantation for HCC (70% 5-year survival in a 60 year-old patient) we concluded that LDLT offered an appreciable advantage on cadaveric liver transplantation for waiting times in the region of 6-12 months. Better post-transplantation outcomes and higher dropout rates increased the advantage on favor of LDLT. One of the interesting point of the analysis was that for survival rates lower than 50% at 5 years, the conventional target of a cost-effective procedure (50 000 $ for year of life saved) was never reached. Although the results of the analysis may change according to the value of the different parameters, the low cost-effectiveness argue against accepting patients with extended criteria and an anticipated survival in the LDLT program. In our team, each case is discussed on its own right, and the group takes a consensual decision. Overall, we prefer to transplant patients who are outside the criteria with a marginal graft rather than resorting to LDLT, because the potential adverse long-term psychological consequences of unsuccessful recipient outcome on the donor are still unknown. Also, we believe that to some extent even LDLT should be considered as a public resource, as the community will judge the results and the maturity of the transplant teams on the ground of long-term results and overall satisfaction. On the whole, this seems also to be the position of the European transplant community, as the preliminary figures of the ELTR show excellent figures for liver transplantation for HCC (R. Adam, personal communication 2003).

When multiple options are open : resection vs. transplantation or primary resection and salvage transplantation

Several series have tried to compare the results of liver resection and of liver transplantation for HCC (23,47,89,90,91). The retrospective nature of the studies and the different clinical characteristic of patients for resection and patients for transplantation introduce insoluble biases that render the conclusions of these studies of little use. The merit of these series is to have highlighted the main problems concerning each treatment, namely that resection can be offered only to a minority patients and that recurrences are almost universal, and that liver transplantation is limited by the scarcity of grafts. Other crucial issues, such as of quality of life, long-term survival and hepatitis C virus recurrence have yet to be addressed. Similarly to what was said for the choice between resection and RFTA, however, in daily practice of the specialized clinic, the question is more theoretical than practical : while the answer may be uncertain for a given tumor, once the whole clinical context of the patient and the availability of a graft is taken into account, the answer of the best treatment is generally obvious. Rather than on the direct comparison between resection and transplantation, therefore, our group focused on whether a strategy of primary resection and salvage liver transplantation could be applied (92). In other words, whether when offering liver resection to a patient – a sub-optimal choice in terms of disease-free survival – liver transplantation could be offered as a viable rescue option in case of recurrence. The strategy would reconcile resection and transplantation not as opposing alternatives but as non-exclusive options for patients in whom both would be available. The decision analysis allowed to integrate the strength and weaknesses of the two treatments – primary transplantation and primary resection and salvage transplantation- for several practical scenarios taking into account different waiting times, recurrence rates and transplantability at the time of recurrence. We concluded that primary resection and salvage transplantation was a reasonable strategy, provided that at least 60% of recurrences could be detected at a stage when they are still transplantable, and that the outcome of transplantation is not more than 10% inferior to primary liver transplantation. Leading groups analyzed their experience in this context, and the option appears viable, with figures of transplantability at recurrence and survival after transplantation similar or better than the ones that we had estimated (74,93) despite the Paul Brousse group reporting inferior results for salvage transplantation (73), a result possibly affected by the high mortality, recurrence rate and low transplantability of earlier patients (table 1). Despite the dry and theoretical flavor of decision analysis, the advantage of the method is that it is easier to estimate probabilities of dropout, transplantability and recurrence for individual patients than

for whole series and that this can help to customize clinical choices better than a pre-defined attitude. For instance, in our group, primary transplantation is the favored option with long life expectancy and quality of life after transplantation, and a high recurrence rate after resection (the extreme would be a young hepatitis B patient with a single small tumor but multiple dysplastic nodules), while resection would be the preferred option for a relatively old weaned alcoholic cirrhosis with normal transaminases and preserved hepatic function (low recurrence rate after resection), or for a blood-group O hepatitis C virus patient with a large tumor, in whom the chances of dropping out on the waiting list are high.

Palliative treatments

Transarterial chemoembolization

The consensus conference could not find sufficient evidence to include TACE into the accepted therapeutic modalities for HCC, and one of the main advances in the past three years was the confirmation that in a carefully defined group of patients – Child A with intermediate disease – TACE has a favorable effect on survival. These results must be credited to two well-designed prospective randomized studies (17,18) that reproduced the scenario of the main negative investigation on TACE that showed an anti-tumor effect but no significant survival benefit (79), and a of a thorough meta-analyisis (94). The reasons of the differences between the negative studies and the most recent ones have been attributed to better patient selection and in the absence of treatment-related deaths. More useful for clinical practice, and somehow underestimated in the meta-analysis, is that both recent studies (and modern TACE in most centers) involved *selective* catheterization of the tumoral vessels, or of the vessels of the segment involved by the tumor, rather than embolization in the main branches of the hepatic artery. With this technique, in our unit TACE is being offered with minimal morbidity and no mortality in selected child B patients with multifocal disease not amenable to percutaneous treatment. The potential benefit in survival and the cost-effectiveness of widening the indications of TACE are being investigated.

Hormonal manipulations and systemic chemotherapy for advanced HCC

A recent meta-analysis has confirmed that Tamoxifen confers no survival advantage in patients with advanced HCC (94). No definitive data are yet available for medroxiprogesterone acetate, for which preliminary reports had suggested a potential effect. A small randomized study on the advantages of somatostatin (95) has not been confirmed on a wider trial published recently (96) and in a large multicentric European investigation (in press). Traditional chemotherapeutic regimens have been tried with no success other than in anecdotal reports, and their use is complicated by the presence of (decompensated) cirrhosis. Also, anecdotal reports have illustrated dramatic responses to combined immunotherapy-chemotherapy regimens (97). These studies await confirmation in prospective protocols, and no regimen can be recommended at present.

Future prospects

The field of HCC is changing rapidly, and new markers for HCC at a pre-clinical stage, or for differentiation and distant spread of known tumors, are being explored, including the use of sophisticated techniques from DNA microsatellites analysis (98), to polymerase-chain-reaction detection of HCC cells in the circulation or in the bone marrow (99). Despite the intensive efforts of many investigators, however, none of these studies has yet given results useful in clinical practice. The problem is compounded by the focal nature, in the same tumor, of the progression towards de-differentiation and aggressive behavior. This feature, common in many cancers, is particularly evident in HCC with areas of good differentiation and areas of poor differentiation and aggressive behavior co-existing in the same tumor, making it difficult to interpret correctly preoperative biopsies or more refined molecular biology markers. Because less subject to sampling errors, it is possible that new imaging techniques, some of which will include metabolic information such as it is already the case for some hepatocytic MRI contrast media (100), will be the first to fill the need for better screening, staging and prognostication of the disease.

Conclusions

At the dawn of the third millennium, the treatment of HCC has rapidly evolved from a field of doom and inactivity, to an exciting and rewarding practice, at the crossroad of hepatology, radiology, liver surgery and transplantation, and health resource management. While the correct treatment of individual patients remains difficult, therapies are effective, the choice among them rests on evidence-based medicine, and the framework is set for clinical research to solve some crucial issues, such as expansion of the criteria for liver transplantation.

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