Should we biopsy each liver mass suspicious for HCC before liver transplantation?–No, please don't

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Liver transplantation (LT) is curative therapy in selected cases of hepatocellular carcinoma (HCC), as it removes both the tumour and the premalignant cirrhotic liver [1–3]. In Europe, 10% of LT were performed for HCC from 1988 to 1997 [4].

Two groups of patients with HCC are considered for transplant [2]. One has HCC with a background of decompensated cirrhosis. The indication for transplantation is as much the failing liver as the HCC. The presence of HCC gives the patient a higher priority for transplantation, to shorten waiting times as much as possible so as to prevent growth of tumour, as well as to prevent drop out from the waiting list [2,3,5]. Biopsy of the suspected HCC nodule, or largest nodule if multiple ones exist (providing the number and size are within current criteria for liver transplantation [2–4]), would not change the indication for transplantation, and therefore, biopsy is unnecessary. The second group is formed by patients with HCC and well-compensated cirrhosis, thus not needing a liver transplant in the short term for cirrhosis per se. These patients usually have HCC diagnosed during surveillance programs [10]. The progress in imaging methods will most likely increase the discovery of potentially malignant but small liver nodules in such patients. If one were to transplant such patients and find no HCC, the patient would have a 10% risk of mortality within a year [4], in respect of transplantation being performed earlier than necessary. Thus, the clinical problem of whether to biopsy or not occurs in this group.

With nodules of 2 cm diameter or more, a diagnosis of HCC complicating cirrhosis can be made by two imaging techniques [ultrasound (US), Computed Tomography (CT) or Magnetic resonance imaging (MRI), or hepatic arteriography] both showing increased vascularity characteristics of HCC or one technique associated with αFP> 400 ng/mL. This practice was advocated by a European panel of experts [5], and has been recently reviewed in the EASL-AASLD-JSH meeting in Barcelona 2005. The panel has now considered the concept of 'washout' in the portal venous phase of a CT scan as defined as a hypoattenuating area that was hypervascular in the arterial phase [6]. This finding is specific for HCC [7,8]. The improvement in the accuracy of contrast-enhanced harmonic ultrasonography was also acknowledged, and thus this imaging technique was considered as a robust diagnostic tool [8]. Finally, it was stated that AFP levels are only specific for HCC diagnosis in the context of a liver mass with typical radiological characteristics [9]. Thus, the non-invasive criteria for HCC in cirrhotic patients have been re-defined as follows: (1) in nodules between 1 and 2 cm, two coincidental imaging techniques showing hypervascularization of the nodule in the arterial phase and 'washout' of the contrast in the venous or late phase are required. (2) In tumours >2 cm in diameter only one of such imaging techniques is required, or two coincidental imaging techniques showing arterial hypervascularization.

Heterogeneous imaging, due to absence or less developed characteristic hypervascularity usually only occurs in nodules less than 2 cm diameter. In these cases, liver biopsy is advocated for diagnosis [5], but still the question is: is it necessary to biopsy before liver transplantation? We do not believe so, for two main reasons. The first is that histological diagnosis of small diameter tumours does not have sufficient diagnostic accuracy, a fact commonly forgotten, as histology has always been reckoned to be the gold standard. The two major areas of diagnostic difficulty are differentiation of both benign tumours and non-neoplastic hepatic nodules from well differentiated HCC, and secondly identification of malignant cells as HCC and not due to other tumours [11].

Needle core biopsy (NCB) has been the standard procedure for histological diagnosis of hepatic lesions for more than 50 years. In recent years, fine needle aspiration cytology (FNAC) has emerged as a minimally invasive, relatively inexpensive and a rapid method of pathologic evaluation of primary or metastatic hepatic masses. Although, the specificity and the positive predictive value of FNAC for focal liver lesions is very high, the

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Abbreviations: HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; NCB, needle core biopsy; FNAC, fine needle aspiration cytology; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation.

sensitivity ranges widely between 67 and 93% [12–15] and thus diagnostic accuracy is less than for histology. Herzeny et al reported a sensitivity of 93% for a group of nodules whose mean diameter was 3.4 cm ± 1.9 for a series of nodules whose sensitivity was 93% [14]; Durand et al reported a sensitivity of 90% for a group of nodules whose mean diameter was 7.4 ± 4.7. The remnant study did not specify the size of nodules. In addition, NCB is no better than the diagnostic accuracy of radiological investigations which have up to 91% sensitivity using Hispeed Advantage helical CT scan and Horizon 1.5T MR system with a phased-array multicoil system MRI [16].

Combining analysis of cytologic and histologic specimens, the sensitivity of ultrasound-guided FNAC for diagnosis of liver tumours improves, with a slightly higher sensitivity for fine needle biopsy (FNB) [14,15,17], in one study 88% compared to 78% for either used alone [18]. The lower diagnostic accuracy of cytology alone resulted mainly from its reduced ability to distinguish well-differentiated HCC from benign lesions [12,15], for which it performs less well than histology. Moreover, cytology is less able to distinguish malignant from non-malignant nodules when the nodule is 2 cm or less [18,19]. In a recent series of fine needle biopsy, for HCC nodules 2 cm or less in diameter, the diagnostic accuracy decreased with diminishing size of nodules (88.6% for nodules with diameters ≤10 mm; 86.2% for nodules with diameters of 11–15 mm, and 91.3% for nodules measuring 16–20 mm). The false negative cases were 10.6% and the specimen was inadequate for diagnosis in 2.9%. However, this study may be optimistic in its diagnostic accuracy as it has a low rate of dysplastic nodules (5.4%) compared to others which are as high as 39% [20,21]. It is well recognized that these preneoplastic lesions are prevalent amongst nodules less than 1 cm [20,22]. When a well differentiated HCC reaches a size about 1–1.5 cm in diameter, less differentiated cancer cells with greater proliferative activity evolve within it. Such a phenomenon is often appreciated grossly and/or histologically as a ‘nodule-in-nodule’ appearance [22]. Subsequently, moderately to poorly differentiated HCC tissue gradually replaces the initial surrounding HCC. This replacement of well differentiated HCC tissue is completed when the tumour reaches a size of about 2–3 cm. Therefore, the biopsy of such smaller nodules gives more false negatives than larger nodules. False negative biopsies are well recognised even when a repeat biopsy is performed the diagnosis remains in doubt in two thirds of cases [23], even disregarding error in targeting small lesions in difficult locations such as posterior and superior segments of the liver [13].

The second reason for not biopsying masses suspicious of HCC before liver transplantation, even if the tumours are small, is the issue of seeding. In a mouse model Ryd et al. [24] showed that fine-needle aspiration, considered less invasive than biopsy, induced the implantation of between 1000 and 100,000 cells along the needle tract. Leakage of tumour cells along the needle track may result in local tumour implantation, and extravasation of tumour cells into the blood stream and lymphatics may cause distant metastases. Dissemination of liver cells detected by mRNA expression of alphafetoprotein in the blood stream is recognised after liver biopsy: in nine of 20 patients (with various cancers of the liver) in comparison to liver resection, in which it is found more frequently (14 of 16). Although the clinical significance of finding these cells (in HCC patients they are potentially malignant) is not known, it is clear that even needle biopsy can lead to haematogeneous as well as local dissemination [25].

Malignant seeding is a well known complication of both diagnostic and therapeutic procedures in patients with HCC. This must be considered in potential candidates for LT, when percutaneous therapeutic approaches are used, as seeding has even been described after liver transplantation, secondary just to pre transplant biopsy [26,27]. So what is the risk of seeding? Unfortunately, there are no published prospective studies, but only several case reports and small series. The real incidence of seeding with HCC is difficult to assess precisely. Against this background it should be said that some [28] feel that there is a systematic underestimation of the risk of metastasis during needle biopsy, and it is possible that several seedings are not diagnosed or not reported.

In view of the apparently rare occurrence of needle tract seeding, it has been assumed that most tumour cells released by needle biopsy are destroyed by host immune response [29] or that it only occurs with more aggressive tumours. However, this is not true, a fact evident following a search of both English and non-English literature for reports of seeding of HCC: 64 cases after biopsy with an average of two passes [1–3] (39 references), 40 cases after PEI (22 references), 13 cases after RFA (9 references), 6 cases after microwave treatment (4 references) and 64 after surgery (5 references). The median interval to diagnosis of seeding after biopsy was 10 months (3 weeks–48 months).

There are nine retrospective studies [13,19,30–36] shown in Table 1, and two case reports [26,37] which relate the number of seedings to consecutive cohorts of patients whose HCC was biopsied. Thus, there is a denominator to estimate the frequency of seeding. It ranges from 0 to 5.1% with a median 2.67% (amalgating cohorts, 34 cases of seeding in 1729 patients (0.0196%). However, it is clear that HCC are particularly prone to seeding, as these are higher rates (0–5.1%) of seeding (even when using FNAC), compared to seeding rates of 0.003–0.017% with pancreatic tumours and 0–0.03% [38,39] with other abdominal tumours.

Numerous factors have been related to the risk of neoplastic dissemination after invasive procedures: larger diameter needles [40]; more passes [40]; superficial location of the tumour in the liver; intrinsic metastatic property of the

Table 1
Reports of seeding after percutaneous biopsy in series of HCC patients in which the size of the cohort biopsied is reported

	Author (reference)	Year	Total number of patients	Number with seeding	%
1	Huang [19]	1996	420	8	1.9
2	Chapoutot [30]	1999	150	4	2.7
3	Kim [31]	2000	205	7	3.4
4	Takamory [35]	2000	59	3	5.1
5	Durand [13]	2001	122	2	1.6
6	Kosugi [32]	2004	31	1	3.2
7	Ng [33]	2004	91	1	1.0
8	Shuto [34]	2004	480	5	1.0
9	Wang [36]	2005	90	0	0
10*	Kanematsu [37]	1997	50	2	4
11*	Dumortier [26]	2000	31	1	3.2

*Case report where the denominator is specified.

tumour [41] related to either or both tumour size or aggressivity; patients' immunodepression [29].

Evaluating the literature in relation to these factors, the risk of metastasis grows exponentially with worsening of these risk factors. For example, increasing the needle diameter by a factor of two, increased the seeding by a factor 60, without improving diagnostic efficiency [12,42] for primary and secondary liver tumours.

From 64 cases of seeding following biopsy alone, only 28 describe the characteristics of the biopsy needle: 14 aspiration and 14 cutting needles. In only 33 was histology well described: 70% occurred with well-differentiated tumours. The size of nodules was reported in 36 cases; nine were $\leq$20 mm diameter, and six of these were $\leq$20 mm diameter. In these nine small HCC, six were well differentiated. Thus, small size and better differentiation may not diminish the risk of seeding.

The consequences of seeding can be devastating. Surgery may no longer be feasible because of the spread of neoplastic disease, reported in three cases [43–45] or seeding may occur after potentially definitive therapy including liver transplantation [26,27].

Some clinicians have advocated using percutnaeous ethanol injection (PEI) after a biopsy to minimize the risk of seeding. However, this involves multiple passes thus increasing the risk and indeed seeding has been reported following PEI, despite the use of a smaller needle and injecting alcohol down the track. After PEI seeding occurs between 0.13 and 1.15%[46–50] in five series in which the denominator is documented (Table 2). The risk during PEI has been calculated as 0.08% per session [46], but this is without concomitant biopsy. Conversely, one cannot exclude that seeding might have been due to previous percutaneous biopsy rather than to PEI when biopsy was performed as in some case reports.

Thus PEI may reduce the frequency of seeding, due to the smaller needle, the effect of alcohol, and perhaps smaller nodules [12,41,42,48,51]. Location may not materially diminish the risk of seeding as Di Stasi et al. [46] reported seven cases after PEI following biopsy of deeply located HCC, as well as following biopsy of small HCC. No

Table 2
Reports of seeding after percutaneous ethanol injection (PEI) or radiofrequency (RFA) for HCC in cirrhotics in which the size of the cohort biopsied is reported

	Author (reference)	Year	Procedure	Total number of patients	Number with seeding	%
1	Livraghi [48]	1995	PEI	746	1	0.13
2	Di Stasi [46]	1997	PEI	1066	7	0.66
3	Ishii [47]	1998	PEI	348	4	1.15
4	Livraghi [49]	1998	PEI	108	1	0.9
5	Riccardi [50]	2004	PEI	29	2	6.8
1	Llovet [53]	2001	RFA	32	4	12.5
2	Goldberg [54]	2001	RFA	450	1	0.2
3	Livraghi [56]	2001	RFA	330	2	0.6
4	Liu [55]	2003	RFA	33	1	3.0
5	Livraghi [65]	2003	RFA	1610	4+?^	
6	Buscarini [57]	2004	RFA	114	1	0.9

In this series 12 cases of seeding were reported in 2320 focal liver lesions; 4 seedings were definitely following biopsy of HCC.

Table 3
Summary of reasons not to biopsy lesions suspicious for HCC prior to OLT

1	Biopsy will not change the indication for transplantation for HCC when it is diagnosed on the background of decompensated cirrhosis
2	Biopsy has a 10% rate of false negative diagnosis and the smaller nodule particularly $\leq$2 cm diameter or less, in a less secure histological diagnosis
3	A single small ($\leq$2 cm) HCC and well compensated cirrhosis can be monitored by imaging before a decision on liver transplantation needs to take place
4	Error sampling for small nodules and for location
5	Risk of seeding is underestimate currently among the available cohorts it has a median value of 2.67%

correlation between seeding and HCC cytology could be made. Tumour seeding has been reported after PEI for poorly differentiated HCCs [46], as well as for well differentiated ones (Table 3).

Whether larger volumes of ethanol injected during each session or the use of another agent, such as acetic acid would reduce the risk of seeding is not known. Parietal peritoneal seeding has been also reported in one of 108 patients after a single session PEI with large HCC [52].

An important study is a prospective one by Riccardi et al. [50] who assessed the rate of seeding after local percutaneous ablation followed by alcohol injection of the track, using ultrasound follow-up at the point of puncture (marked with a tattoo) and reported two cases of seeding in 29 (6.8%) within 12 months; there was a biopsy with the initial PEI. This could represent an accurate estimate when PEI follows a liver biopsy of a suspicious nodule subsequently confirmed to be HCC.

Radiofrequency ablation rather than PEI could follow a biopsy of a suspicious nodule. Theoretically, it could be better than PEI in reducing or removing the risk of seeding, as it results in a larger margin of destruction of normal parenchyma around the HCC nodule. However, this potential advantage might be lost, due to the larger needles used, as the risk of seeding is not substantially different from PEI. Even discounting the high rate of 12.5% reported by Llovet et al. [53] because of superficial position of the nodules biopsied, the rates are 0.22–3% [54–58] again in five series which report the denominator (Table 2). This could be an under-estimate as the technique is increasingly used in well compensated cirrhotics, who will survive longer as thus be at risk for longer for seeding to be diagnosed.

In a recent review [59], several mechanisms are suggested as contributing to seeding after percutaneous RFA. Viable tumour cells may adhere to a biopsy needle or to electrode during its retraction. Tumour cells may also be carried into the track with a little bleeding. Furthermore, cells may be forced into the track by sudden increase in intratumoral pressure, which is frequently encountered during RFA. Finally, cells may be driven in, when saline is injected during or before RFA. Seeding has also been reported following laparoscopic surgery and microwave ablation [60], the latter reporting a 10% seeding rate in 20 patients.

We believe the risk of seeding always needs to be considered, as at present it outweighs any improvement in diagnostic accuracy for the confirmation of HCC, which in any case may be small [11,13,61,62], compared to optimal imaging techniques. For well compensated cirrhotics with small 2 cm diameter or less nodules without characteristic diagnostic imaging (i.e. no hypervascularity), a delayed wait for liver transplantation (e.g. 3–4 months) with the possibility of re-imaging can be entertained. During this interval, some patients with HCC will achieve these diagnostic imaging criteria and this will eliminate them from consideration of a biopsy. These patients, providing the nodule is single, or less than three nodules $\leq$3 cm diameter are present, will be at almost zero risk of recurrence following liver transplantation [63]. This would be a safer strategy than to biopsy, if there were uncertainty. Tumours larger than 2 cm diameter with characteristic hypervascularity in cirrhotic patients do not need a biopsy before liver transplantation, as data on imaging criteria, are very sound and will improve.

There are recommendations, if one is compelled to biopsy [64] which are the following: (1) the needle biopsies of solid masses should be performed by trained teams; (2) only when taking decisions about the patient's management; (3) through normal parenchyma, whenever possible, respecting anatomical boundaries as to ensure that the needle track is resected with the metastases; (4) always with a fine non cutting needle; (5) the sampling has to be done under suction, which must be maintained when withdrawing the needle; (6) the sample quality has to be checked later to keep the number of passes to the very minimum. However, these are difficult to achieve in cirrhotic patients, and have not been validated as substantially reducing the risk of seeding of HCC.

Whether in the future, tissue markers will improve the diagnosis of HCC and/or give sufficiently reliable information on the potential invasiveness of the tumour (thus leading to semiurgent transplantation, if an allocation system allows it), remains to be determined. At present microvascular invasion, although associated with greater likelihood of recurrence, is not a contraindication for liver transplantation. This kind of information can only be collected in prospective studies. Randomized studies should be performed in which the information obtained from a biopsy leads to a different therapeutic outcome e.g. transplantation is not offered if no HCC diagnosis is made, or early transplantation is planned on the basis of the biopsy. Patients will need to know about the risk of seeding when a biopsy is proposed in such a study and weigh up the risk of participating. Another possibility is to formally evaluate the value of a biopsy for HCC in centres

which currently routinely biopsy nodules before liver transplantation (presumably having no experience of seeding, or an extremely low risk).

In conclusion, the number of patients in whom a liver biospy of a nodule suspicious for HCC in a cirrhotic liver will change the decision for liver transplantation is fortunately very small. Other strategies, apart from biopsy, such as evaluating new imaging techniques for more precise pre-transplant diagnosis (against explant histology), or simply waiting for a defined period with repeated imaging, may also be effective. These strategies also need to be tested formally, just as a putative policy of liver biopsy of suspected HCC nodule before liver transplantation. Until such time that any of these strategies clearly indicates their value, liver biopsy of HCC must be considered potentially hazardous due the risk of seeding, and also limited in its diagnostic accuracy, especially when the suspicious nodule is ≤ 2 cm diameter. Please don't do it!

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