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TOPIC HIGHLIGHT

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Management of "very early" hepatocellular carcinoma on cirrhotic patients

Gonzalo Sapisochin, Elena Fernandez de Sevilla, Juan Echeverri, Ramón Charco

Gonzalo Sapisochin, Elena Fernandez de Sevilla, Juan Echeverri, Ramón Charco, Department of HPB Surgery and Transplantation, Hospital Universitario Vall d'Hebron, Universidad Autónoma de Barcelona, 08035 Barcelona, Spain
Author contributions: All authors contributed to this paper.
Correspondence to: Gonzalo Sapisochin, MD, PhD, Department of HPB Surgery and Transplantation, Hospital Universitario Vall d'Hebron, Universidad Autónoma de Barcelona, Passeig de la Vall d'Hebron 119-129, 08035 Barcelona, Spain. sapisochin@me.com
Telephone: +34-93-2746113 Fax: +34-93-2746112
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Abstract

Due to the advances in screening of cirrhotic patients, hepatocellular carcinoma (HCC) is being diagnosed in earlier stages. For this reason the number of patients diagnosed of very early HCC (single tumors ≤ 2 cm) is continuously increasing. Once a patient has been diagnosed with this condition, treatment strategies include liver resection, local therapies or liver transplantation. The decision on which therapy should the patient undergo depends on the general patients performance status and liver disease. Anyway, even in patients with similar conditions, the best treatment offer is debatable. In this review we analyze the state of the art on the management of very early HCC on cirrhotic patients to address the best treatment strategy for this patient population.

Key words: Hepatocellular carcinoma; Very early; Liver resection; Liver transplantation; Local therapies

Core tip: Very early hepatocellular carcinoma patients are deemed too early for liver transplantation candidacy, known as the best treatment regarding long-term survival and tumor recurrence. Strategies as surgical resection and radiofrequency ablation have gained popularity. Although resection is considered as the first line of treatment, recent studies claim equal results with ablation techniques. Ablation used as a test of time in patients who remain candidates for liver transplantation is attractive. In this review we will analyze in detail the novel strategy repertoire used in the management of these patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, the sixth most common cancer worldwide and the third largest cause of cancer-related deaths[1-3]. The incidence of HCC is increasing in Europe and in the United States[4] and it is currently the leading cause of death among cirrhotic patients[5].

The management of these tumors has significantly improved over the last few years due to a better knowledge of the natural history of the malignancy and the development of staging systems. One of the most reliable and widely adopted methods for staging HCC is the Barcelona Clinic Liver Cancer (BCLC) system[6], that stratifies patients according to the characteristics of the tumor, underlying liver disease and performance status. According to this system, the presence of an asymptomatic single nodule ≤ 2 cm, in the absence of vascular invasion or extrahepatic disease, has been defined as very early stage HCC[7-9].

In recent years, thanks to surveillance programs on the cirrhotic population, more patients are being diagnosed with very early HCC[9-11].

There are basically three potential curative modalities of treatment for patients diagnosed of very early HCC: Liver resection (LR), liver transplantation (LT) and radiofrequency ablation (RFA). Although these patients show excellent outcome in terms of survival and recurrence[12] compared to those with more advanced tumors, the debate regarding what is the best treatment option in that scenario still remains[3,13].

Our aim is to review the current management of very early HCC on cirrhotic patients.

DIAGNOSIS OF VERY EARLY HCC

Hepatocellular carcinoma is frequently diagnosed by imaging criteria based on the contrast enhancement pattern. Early detection by surveillance is the only way to diagnose HCC when curative treatments are feasible, being the optimal profile for this endpoint very early HCC[9,10]. Intense contrast uptake in the arterial phase followed by contrast washout in the venous phase, both on computed tomography or magnetic resonance, is considered diagnostic for HCC > 1 cm[9,14]. Nevertheless, on cirrhotic patients, small lesions may be misdiagnosed as being HCC and can in fact be intrahepatic cholangiocarcinomas (iCCA) or mixed hepatocellular-cholangiocarcinomas (HCC-CC), being their frequency much lower[15,16].

If the lesion does not show the typical HCC pattern on imaging, biopsy is mandatory[10]. A prospective study including 89 cases with liver nodules between 0.5 and 2 cm reported that non-invasive criteria had a sensitivity of 30%, being necessary a biopsy for their diagnosis[17]. However, pathological diagnosis is particularly complex for nodules < 2 cm, being difficult the distinction between high-grade dysplastic nodules, intrahepatic cholangiocarcinomas (iCCA) and HCC[17]. It is currently considered that a positive tumor biopsy is clinically useful to diagnose an HCC, while a negative biopsy cannot rule out malignancy[18,19].

Anyway, despite the misdiagnosis of small nodules, current data has shown interesting results on the outcome of patients diagnosed of "very early" iCCA and HCC-CC at pathology. These studies demonstrated excellent post-transplant survival for patients with such tumors on pathology. Nevertheless, future studies must be conducted to confirm these results[15,16].

LIVER RESECTION

Liver resection constitutes the first-line treatment option for patients with very early HCC and compensated cirrhosis in most centers[3,11,20]. As indicated by the BCLC, this is especially true when patients are potential candidates for LT[21,22] as we will analyze later in detail.

Partial LR in cirrhotic patients must be addressed under two contradictory principles: to be a curative resection and to preserve as much liver parenchyma volume as possible to avoid postoperative liver failure[1]. Thanks to recent advances in surgical technique and immediate postoperative care, the modern standards for resection of HCC in cirrhotic patients have improved and include a perioperative mortality less than 1%, blood transfusion requirements below 10% and 5-year survival rates of at least 50%[20]. Anyway, major resections are not recommended even in compensated cirrhotic patients because of the risk of post operative liver failure due to an insufficient remnant liver, which can lead to death[9]. Nevertheless and thanks to the advance in several techniques such as portal vein embolization, some groups perform major hepatectomies for HCC after portal vein embolization if there is a sufficient growth of the liver remnant[23,24].

The discussion between anatomic *vs* non anatomic resection still remains. Most studies defend anatomic resection as a method to avoid or ameliorate local recurrence[25,26]. Other studies have not been able to confirm this[27]. If the invasive phenotype is minor, as in the case of very early HCC, the spread beyond the segment may be low and anatomic resection may provide a benefit[9]. Basically the recommendation would be to perform an anatomic resection whenever possible and safe.

One of the main contraindications for LR in cirrhotic patients is the presence of portal hypertension. The BCLC group identified the absence of clinically relevant portal hypertension and normal bilirubin as the key variables to make a safe selection of candidates for LR. An hepatic venous pressure gradient ≥ 10 mmHg was shown to be a predictor of unresolved hepatic decompensation and, consequently, of poor long-term outcome in Child-Pugh A cirrhotic patients after surgery[14,28]. The presence of esophageal varices detectable at endoscopy, splenomegaly and/or a platelet count less than 100000 were considered indirect signs of portal hypertension[29]. The value of portal hypertension assessment in predicting prognosis has been confirmed also by japanese groups[30]. However, some authors have reported good results for patients resected with portal hypertension. Cucchetti *et al*[31], found in 2009 after one-to-one matching, that the only predictors of postoperative liver failure were model of end-stage liver disease (MELD) score and the extent of hepatectomy and so, did not found portal hypertension as a risk factor[31]. Ruzzenente *et al*[32], also concluded that portal hypertension is not an absolute contraindication to liver resection in Child-Pugh class A cirrhotic patients but noted a worse survival in patients who were resected two or more segments if portal hypertension was present probably showing the higher risk of more extended hepatectomies in the cirrhotic population[32]. Anyhow, most centers would only perform LR if portal hypertension is not present, and so, despite the results of some retrospective studies[33], prospective multicenter studies should be conducted to assess the safety of LR in the presence of portal hypertension. Even though the presence of portal hypertension may not be considered an absolute contraindication for LR, it will significantly affect patients early and late outcome after resection.

One of the principal advantages of LR over other

treatments like local therapies is the pathological examination of resected tumors. Indeed, this may represent a very useful tool to predict the risk of recurrence and to select patients with HCC who are likely to obtain the maximum benefit from LT[1,34]. Accordingly, the BCLC recommend LR in cirrhotic patients with very early HCC who are candidates for LT. Histological features on the LR specimen have been proposed as a guide for selection of LT candidates and as a tool for optimization of the donor pool. In selected cases and according to characteristics in specimen aggressiveness, resection may be considered as a bridge to transplantation[35].

Cillo *et al*[36] reported tumor differentiation as a direct marker of biologic tumor aggressiveness, providing interesting information about the risk of recurrence[36].

The BCLC and other groups have proposed a policy of listing patients for LT without evident HCC based on pathological risk of recurrence after resection, characterized by the presence of vascular invasion and/or satellitosis. They have given the name "ab initio" indication, also known as "de principe" LT[34,36-39]. Both parameters, presence of microvascular invasion and additional nodules, could be used to stratify resected patients in two categories: patients with low risk of recurrence and patients with high risk of recurrence[30,40]. The rate of microvascular invasion increases according to the tumor size and it is present in 20%-25% of HCC less than 2 cm[14,41]. Sala *et al*[34] reported in 2004 the efficacy of this strategy in 6 patients who were transplanted after being diagnosed with high risk recurrence (according to gross and microscopic examination after LR) with good results[34]. Scatton *et al*[35] published a retrospective cohort study in 2008, in which de principe LT was proposed to 6 patients because of poor prognosis histological findings on the resected specimen, reporting that all these patients were alive at the time of publication, with a mean follow-up of 55 mo[35]. On the other hand, other authors have proposed that patients who exceed Milan criteria and present poor histological findings at the time of resection, should be precluded from LT because of the high risk of recurrence, while patients exceeding Milan criteria but with good histological prognostic factors may benefit from de principe LT[34,35].

Some recent studies have proposed a molecular signature to define the level of risk due to the oncogenicity of the cirrhotic liver. This concept still has to be validated in clinical practice[9], but looks very promising.

Recurrence after LR

The main problem after LR for HCC is the high rate of tumor recurrence[1,13,42]. There are several reports indicating that the 5-year recurrence rate is up to 80%-100%[43-46].

The most common site of post-resection recurrence is the remaining cirrhotic liver[47], as the persistent underlying liver disease (main risk factor for the development of HCC) is associated with high rates of intrahepatic recurrence[48]. Basically, two types of tumor recurrence after LR have been described: local recurrence, which usually happens in the first 2 years after resection and may be the result of inadequate R1 resection or secondary to the progression of microscopic vascular invasion and "de novo" recurrence, which happens more than 2 years after resection and constitutes the development of a new tumor due to the presence of underlying cirrhosis[49].

Patients with very early HCC can achieve 5-year survival rates around 90% after resection and extremely low 3-year recurrence rates have been described (around 8%)[3,50]. Other published studies reported similar survival but the disease free survival was around 40% at five years[50,51]. The largest retrospective experience on the outcomes of LR in very early HCC was reported by Ikai *et al*[52] analyzing 2320 patients and finding a 3- and 5-year survival of 84% and 66% respectively. Lee *et al*[53] also reported similar outcomes, with a 3-year survival of 82.5%. None of these studies specified on the recurrence rate after very early HCC.

Treatment of HCC recurrence after LR is currently based on several strategies that include the use of antineoplasic drugs, RFA, chemoembolization, alcoholization, re-resection and liver transplantation; being the most curative therapies the last two[54].

Re-resection: The applicability of re-resection will be determined by the patient general performance status and liver function at the time of recurrence. Some authors have described a low applicability rate (10%-25%) for re-resection and argue that it should ideally be restricted to "*de novo*" cases and not "local recurrences"[55,56]. Several studies have demonstrated good results after re-resection. Poon *et al*[57] reported a 5-year survival rate after re-hepatectomy of 69.3% and Sugimachi *et al*[56] concluded in another study that despite patients with recurrence treated with re-hepatectomy having a better prognosis compared to patients with recurrence who did not have a repeat hepatectomy, re-resection must be performed in selected patients[56]. Anyhow, whenever possible, re-resection should be considered at the time of recurrence and analyzed in a patient to patients basis.

Salvage LT: As previously stated, LR constitutes the first-line therapy for very early HCC on potential candidates for LT with compensated liver cirrhosis. In these regards, surgeons may have in mind that patients can be transplanted at the time of recurrence[58]. This strategy of secondary LT is called salvage transplantation[27]. Poon *et al*[59] published that 80% of patients with recurrence after a LR for HCC remain eligible for LT. Although some authors have published similar results regarding the applicability of salvage transplantation[60], in clinical practice the real applicability of this policy is low, only 10%-20% of cases, as it has been shown in several studies[61,62]. In a previous study from our department, we reported a series of 17 potential candidates for salvage LT, but could only be performed in 6 patients. Age at the time of recurrence was the main reason for contraindicating LT. In spite of that, we found that results of salvage transplantation were similar to those of primary LT[63]. The main problem with this strategy is related to a high drop out of resected patients

from LT, due to a non-transplantable recurrence, tumor progression during the waiting time or life-threatening complication of underlying cirrhosis, and so, the feasibility of salvage transplantation will be closely related to a strict surveillance after resection and the consequent early diagnosis of intrahepatic recurrence[62]. Although there is conflicting results when comparing primary LT and salvage transplantation and there is a concern on the higher risk of complications in patients that receive a transplant after LR, most studies showed no differences when comparing biliary leaks, vascular complications, re-operation or re-transplantation rates[64,65]. Nevertheless, operative mortality and bleeding have been described to be significantly higher after salvage transplantation in some series[62]. As no randomized controlled trials are feasible in this regard, and methodological pitfalls of current data exist, comparable outcomes are still a matter of debate.

A determining factor when including a patient in the waiting list for salvage transplantation is the time from LR to recurrence. Early recurrence (before 1 year) after LR has been found to be a risk factor for poor outcome after transplant probably indicating the tumors aggressiveness[54].

In patients with very early HCC or small single tumors (< 3 cm), salvage transplantation may be more applicable as recurrence of these tumors can be more limited. This may explain the excellent 10-year survival when comparing patients diagnosed with a very early HCC that are transplanted or resected[13,66].

LOCAL THERAPIES

In the last decade RFA has become one of the standard treatments of very early HCC on cirrhotics[67,68]. This treatment can be included basically in 2 strategies: intended as a definitive curative treatment or as a bridge to LT.

According to the European Association for the Study of the Liver (EASL) and the European Organization for Research and Treatment of Cancer, percutaneous ethanol injection (PEI) and RFA are considered as the standard of care for HCC patients with very early HCC not suitable for surgery[16]. According to the American Association for the Study of Liver Diseases (AASLD), PEI was initially suggested as the standard against which any percutaneous therapy should be compared[22]. However, recent studies demonstrate that RFA has better local control for HCC > 2 cm. In tumors < 2 cm RFA and PEI have equal results[69]. Patients with very early HCC do not afford any priority points on the waiting list and generally have low MELD scores, the probability of attracting an organ is very low[70,71]. Accordingly the debate arises on to what is the best option for these patients: immediate ablation or wait until the tumor grows and then patients afford exception points and have real options of attracting an organ[71].

Several studies have shown the efficacy of local therapies on very early HCC[72-76]. Sala *et al*[77] reported a 50% survival at 5 years in Child A patients and treatment response in 70% of nodules < 3 cm and 50% in nodules > 3 cm or multi-nodularity, achieving results that could almost be equal to surgical resection in selected patients. Livraghi *et al*[78], conducted a multicenter study enrolling cirrhotic patients with HCC < 2 cm undergoing RFA, of whom 46% where initial candidates for surgery. The estimated 3-year and 5-year survival rates were 76% and 55%, respectively and 65% in the subgroup that could potentially have been resected; thus achieving a 5-year survival rate similar to that achieved after surgical resection[78]. The advantages of RFA over surgery were less invasiveness, complications, hospital stay, blood transfusions and treatment costs. N'Kontchou *et al*[79] evaluated long term outcomes of RFA as the first line treatment and prognostic variables in patients with early-stage HCC defined as tumors < 5 cm and less than 3 tumors. They had a complete radiological ablation in 94.7% of their cohort with estimated overall 3 and 5-year survival rates of 60% and 40% respectively. The estimated 3 and 5-year recurrence-free survival rates were 37% and 18% respectively, with a median recurrence-free survival of 23 mo. The size of the tumor was found to be a predictor of local recurrence, but not of overall or tumor-free survival rates. Recurrences where limited and ablated by additional RFA sessions[80]. RFA has been suggested, according to these studies, as an adequate treatment for small HCC, having less side effects and in case of recurrence, multiple RFA sessions could control the disease without comprising survival.

As previously stated, RFA has emerged as the first line treatment for patients with very early HCC non candidates for LT and as a curative-intent treatment for HCC in some centers, as patients will not be afforded with exception points and then wait very long times for a graft[80-82]. The most important limiting factor to this strategy includes post RFA recurrence of 50%-80% at 5 years. Emergence of new tumors rather than local tumor progression seems to be responsible for these results[77-80,83]. A two-step strategy comprises performing RFA to LT candidates with HCC, leaving transplantation as definite therapy only if recurrence or liver failure occurs. A previous "test of time" would identify those patients with aggressive tumor biology who would carry a high risk of recurrence post LT, thus optimizing the scarce resource of organ donors and reducing the burden of HCC patients on the waiting list[4,79]. As stated in a recent editorial by Yao, patients selected for this strategy should be those who have a high probability of long-term cure with a low risk of recurrence[68]. Limitations to this strategy, include the uncertainty for those patients who do not remain as candidates for salvage transplantation according to the size and number of recurrent tumors. Tsuchiya *et al*[84] published a retrospective analysis of 323 patients undergoing RFA as initial treatment of which 60% of patients suffered recurrence beyond transplantation criteria and only 30% of these patients were eligible for salvage LT. Predictors of HCC recurrence were AFP > 100 ng/mL, tumor size > 2 cm, and early recurrence within 1 year[84]. This has raised the question if the "ablate and wait" strategy may result in a percentage of patients with recur-

rence out of transplantable criteria and then loose the opportunity for LT. N'Kontchou *et al*[79] reported promising results with the "two step" strategy, using RFA as first line treatment in patients eligible for LT. The 3- and 5-year overall recurrence rates were 50% and 58%, respectively. For Child A patients, survival rates at 5 years were comparable to that of patients who were offered LT as first line therapy[79].

We believe that the best candidates for RFA as first line treatment would be those Child A patients with solitary lesions ⩽ 2 cm who fail to recruit enough exception points on the waiting list as this patients achieve the best long term survival and best complete initial response[68,78,79]. Anyway, these patients should undergo strict follow-up to diagnose recurrence in an early manner.

LIVER RESECTION *VS* RADIOFREQUENCY ABLATION

According to the clinical guidelines by the AASLD and the EASL, surgical resection is the first line treatment for patients with small solitary HCC Child A cirrhosis and no portal hypertension[22]. RFA is an optional treatment for small HCC, obtaining similar results regarding long-term survival compared to surgical resection. Several meta-analysis have tried to assess the advantages and disadvantages of RFA compared to surgical resection. Conflicting data has been obtained from these studies regarding overall survival and disease free survival due to the retrospective nature of the studies involving heterogeneous cohorts. Moreover most of these studies have not analyzed patients with very early HCC in detail[85,86].

Some randomized controlled trials have been performed to assess this issue; none of them strictly analyzes the subgroup of patients with very early HCC. Huang *et al*[87] assessed, in an intention to treat analysis, overall survival, recurrence free survival and overall recurrence comparing 115 RFA patients with 115 surgical resected patients, (both groups had tumors within the Milan criteria). After a 5-year follow-up, overall survival rates of RFA and surgical resection were 54.78% and 75.65%, respectively. Overall survival and recurrence-free survival were significantly higher in the surgical resection group than in the RFA group. Once stratifying by tumor size, surgical resection still offered an advantage over RFA in patients with early HCC (defined as tumors < 3 cm). RFA had an advantage in terms of less hospital stay and less adverse events[87]. Feng *et al*[88] evaluated survival and recurrence undergoing a randomized controlled trial in an intention to treat basis comparing RFA *vs* surgical resection. Early HCC was defined as tumors with a maximum diameter of 4 cm and up to 2 nodules. The 1, 2, and 3-year overall survival rates were 96.0%, 87.6%, 74.8% and 93.1%, 83.1%, 67.2% for the surgical resection and RFA groups, respectively. Recurrence-free survival was 90.6%, 76.7%, 61.1% for the surgical resection group and 86.2%, 66.6%, 49.6% for the RFA group. No significant differences were seen between the two groups regarding overall and recurrence-free survival. No stratified analysis regarding tumor size and outcomes on both groups was presented. Again, patients that underwent RFA had less hospitalization stay and less blood transfusion rates. Chen *et al*[89] evaluated a cohort of 90 patients who underwent surgical resection compared to 90 patients who underwent RFA. Early HCC was defined as a solitary lesion less than 5 cm. There were no differences in the overall and disease free survival rates. Stratified analyses of both therapeutic interventions for lesions less than 3 cm revealed no differences[89]. The information from the randomized controlled trials on the outcomes of RFA *vs* LR for very early HCC is not clear and the outcomes comparing these therapies still require further investigations.

On the other hand, several observational retrospective studies do make emphasis on very early HCC and outcomes after RFA and surgical resection, however, they lack randomization and may be biased by covariate distribution[90,91]. Hung *et al*[90] analyzed a cohort of patients with very early HCC that included 66 patients in the RFA group and 50 in the surgical resection group. There were no statistically significant differences in terms of overall survival and recurrence but both groups were heterogeneous[90]. Peng *et al*[92] compared retrospectively the effects of RFA and surgical resection in patients with resectable HCC < 2 cm. Seventy-one patients treated with RFA were compared with 74 surgically treated. Overall survival rates at 1, 3, and 5-years were 98.5%, 87.7%, and 71.9% in the RFA group compared to 90.5%, 70.9%, and 62.1% in the surgical resection group. No differences were found regarding disease-free survival between groups. The main problem with this study was its retrospective nature that leads to several selection bias[92]. Wang *et al*[51] compared in a cohort of very early HCC patients, 51 patients undergoing RFA *vs* 91 patients undergoing surgical resection. There was no significant difference in overall survival between groups; however, patients treated by surgical resection had a better disease free survival than those in the RFA group. They suggested that surgical resection should be the preferred modality in very early HCC when liver transplantation is not feasible[51]. Finally, Takayama *et al*[91] published a large Japanese multicenter study analyzing RFA *vs* surgical resection in a cohort of 2550 patients. Basically half of the patients were treated with RFA and half were operated. Disease free survival was significantly better in the surgical resection group compared to RFA. Overall survival in both groups showed no differences. Again, due to the retrospective nature of their study, several selection bias were found. Percutaneous ablation was more prominent in Child B patients who had more hepatic dysfunction compared to those who underwent resection[91].

Surgical resection continues to be the first line treatment for patients with early HCC suitable for surgical therapy; however, many patients cannot be offered resection because of liver dysfunction at the time of diagnosis. RFA seems to be a suitable modality of treatment for these patients, achieving similar results regarding disease free survival and overall survival according to the available

information. The decision on whether to perform RFA or resection of patients with very early HCC will depend on the type of resection required, the general performance status of the patients and their liver function.

LIVER TRANSPLANTATION

Liver transplantation is accepted as the best treatment modality for HCC, as it efficiently removes the tumor within the liver and the remaining oncogenic cirrhotic tissue caused by the underlying pathology[9,93]. Despite the efforts for assuring transplantability for HCC patients according to the Milan Criteria and expansion of these parameters by the University of California, San Francisco criteria, scarcity of organ donors and the increased number of patients on the waiting list renders patients to undergo other treatment modalities[94-98]. According to the principle of utility, ablation and resection in tumors ⩽ 2 cm avoids futile transplantation in these patients[75,95,99,100].

In patients with tumors ⩽ 2 cm LT is not considered as first line treatment as these patients are deemed "too early" for transplantation and may not be listed with exception points. Three strategies for management may be considered; RFA, surgical resection or waiting for tumor progression with subsequent listing once the tumor exceeds 2 cm.

The wait and not ablate strategy considers waiting for tumors to exceed 2 cm and then seek exception points for LT. With this strategy 9% of patients progress from T1 to directly beyond T2 before listing, drop-out rates once on the waiting list account for 7%-10% of patients, and 3-year survival rates with transplantation achieve 75%[70,71].

Although LT is the best strategy for the treatment of HCC regarding survival and recurrence, in the setting of very early HCC, RFA and surgical resection continue to be first line treatments. The wait and not ablate strategy seems to have good results, however, robust evidence is still lacking as to how and when to apply it considering patients eligible for other ablative techniques[70].

Nowadays, LT remains as a second line treatment for patients with very early HCC and low MELD scores. The main benefit of LT is the treatment of recurrence after LR or RFA. Anyhow, this statement must be taken with caution as some patients may loose their opportunity to be transplanted if recurrence exceeds each centers transplantation criteria.

LIVER RESECTION *VS* LIVER TRANSPLANTATION

Many publications have compared the results of LR and LT for HCC, in general, they have found similar patient survival with better disease-free survival in patients undergoing LT[48,101-105]. However, there are not many publications that focus on the outcomes of very early HCC.

Bismuth *et al*[103] published in a retrospective study that in case of small uninodular or binodular tumors smaller than 3 cm, LT had much better results than resection, showing a disease free survival of 83% *vs* 18% in resected patients[103].

Cha *et al*[101] concluded that partial hepatectomy in patients with early HCC who are otherwise eligible for LT can be performed with minimal morbidity and can achieve comparable 5-year survival to that reported for LT. They stated that resection should be considered the standard therapy for patients with HCC who have an adequate liver reserve[101].

Another publication by Margarit *et al*[63], comparing outcomes of LR and LT in a retrospective study with 259 patients, found no significant differences in overall actuarial survival, with a median survival of 85 mo in both groups. They reported that HCC recurrence was significantly higher after LR (59%) than LT (11%). However, this study included all the patients who presented tumors smaller than 5 cm and the mean tumor size was 3 cm[63].

The publications listed above did not report longer 5-year follow-up, nor did they distinguish between very early and early HCC.

There are two studies (recently published) that tried to assess the long-term outcome (10 years) for patients resected and transplanted. Adam *et al*[62] compared results of HCC < 5 cm after LR or LT under the policy to prioritize Child A patients with peripheral lesions for resection rather than transplantation, finding better results for transplanted patients. For single HCC smaller than 3 cm, they found that LR achieved comparable 10-year overall survival[13]. In another study published by our department, the outcomes were similar to Adam's paper. We compared patients with HCC < 5 cm who underwent LT or LR, finding a higher tumor recurrence rate in resected patients and better survival in patients who were transplanted. However, when we analyzed those tumors < 2 cm, no significant differences were observed in 1-, 5- and 10-year survival between the two groups[66].

The good outcomes of these publications could be justified because the recurrences in very early HCC are easier to treat, whether by re-resection or especially by salvage transplantation, allowing LR to be the treatment of choice for these tumors.

CONCLUSION

The best approach for cirrhotic patients diagnosed of very early HCC is still debatable as there is a lack of sufficient data. With the available information LR is the best treatment option in the case the patients liver function and performance status permits such approach. Moreover, the location of the tumor will also be part of the algorithm when making a decision on resecting the tumor. Ablative therapies such as RFA are an excellent alternative with good outcomes in case of very early HCC. The main counterpart to these treatments is the high rate of tumor recurrence. In this scenario (recurrence after primary treatment) LT can play an important role in the treatment of very early HCC. With the current allocation systems, patients with these tumors don't get exception

points and another interesting approach would be to wait and not treat until the tumor grows to get exception points. Further investigations on the best management of cirrhotic patients diagnosed of very early HCC are needed.

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