CURRENT TREND

Natural history and therapeutic management of recurrent hepatocellular carcinoma after liver transplantation

Histoire naturelle et traitement de la récidive du carcinome hépatocellulaire après transplantation hépatique

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Summary While the natural history and appropriate diagnostic and management practices are relatively well defined for hepatocellular carcinoma (HCC), data are scarce concerning the characteristic features and treatment modalities for recurrent HCC after liver transplantation. The time of recurrence appears to impact survival more significantly than localization, but to date, guidelines for therapeutic management of recurrent HCC have not been established. Data in the literature shows that late and unifocal recurrence has a better prognosis when treated by surgery or radiofrequency. In the event of early recurrence, surgery cannot be recommended due to the lack of evidence and the high risk of advanced disease. Systemic therapy can be discussed in a situation of multifocal recurrence. Proliferative signal inhibitors exhibit both immunosuppressive and antiproliferative properties and liver transplantation teams tend to introduce such treatment despite the lack of extensive data.

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Résumé Alors que l’histoire naturelle et la prise en charge thérapeutique du carcinome hépatocellulaire (CHC) sont mieux codifiées, il existe peu de données sur les caractéristiques et le traitement de la récidive du CHC après transplantation hépatique. Le délai de récidive semble plus influencer la survie que sa localisation et il n’existe actuellement pas de recommandation précise sur la prise en charge thérapeutique de la récidive du CHC post-transplantation hépatique. La récidive unifocale et tardive apparaît de meilleur prognostic si une résection chirurgicale ou une radiofréquence peuvent être proposées. En cas de récidive tumorale précoce, il ne semble pas licite de proposer la chirurgie d’emblée compte tenu du fort risque de
Introduction

Hepatocellular carcinoma (HCC) is the commonest primary malignant disease of the liver. Worldwide, it is the sixth leading cause of cancer and the third leading cause of cancer death [1]. Incidence has risen steadily in Europe, doubling in France in the last two decades [2].

Liver transplantation is the ideal treatment for HCC in cirrhosis because in addition to resection of the tumor, any malignant and/or pre-malignant foci, which could be present but not necessarily visible in the adjacent parenchyma, are removed. Until the early 1990s, the rate of disease recurrence following liver transplantation was high because transplantation was proposed for any stage of tumor dissemination. Indicators predictive of recurrence were then rapidly identified enabling an evidence-based selection of candidates with a low probability of recurrence. Using the Milan criteria, widely applied in Europe, the overall probability of survival at five years is relatively close to that observed for cirrhosis without HCC.

In France, the number of HCC patients waiting for liver transplantation has doubled in the last five years (135 candidates in 2002 and 323 in 2007). This indication is becoming one of the more prominent for liver transplantation (12.8% of the activity at enrolment in 2002 and 24% in 2007). At the present time, the rate of recurrence five years after liver transplantation is to the order of 10% to 20%[3,4]. As the activity level for this indication increases, transplantation teams will be called upon to provide care for a growing number of patients with recurrent HCC. While the natural history and appropriate diagnostic and management practices are relatively well defined for HCC [5], data are scarce concerning the characteristic features and treatment modalities for recurrent HCC after liver transplantation.

Natural history of recurrence

Evolving risk of recurrence

In the past, the rates of recurrence after liver transplantation have varied greatly, depending on the series reported, but with a steady trend toward lower rates in recent years (Table 1). Before 1993, reported rates were high, to the order of 50%, and had a direct impact on survival. This situation arose because liver transplantation was proposed for patients with large or diffuse non-resectable tumors [6,7]. As early as 1993, sensitivity analysis focusing on sub-groups of patients with small tumors enabled the identification of populations with a recurrence-free survival rate to the order of 75% [8]. In 1996, Mazzaferro et al. demonstrated the usefulness of selecting candidates with a unique tumor measuring ≤ 5 cm or at most three nodules all measuring ≤ 3 cm on the preoperative images [9]. When the liver explant met these criteria, which was not the case for 73% of transplant recipients, the prognosis was excellent with a 4-year actuarial survival of 85% and recurrence-free survival of 92%. These criteria came to be known as the Milan criteria and were widely adopted by liver transplantation teams worldwide. An analysis of liver transplantation activity in France over a period of 10 years showed that the rate of recurrence at five years was 21% in patients who, for two-thirds, fulfilled the Milan criteria [10]. Currently, the 5-year recurrence risk is 15% [5].

Recent studies suggest these criteria could be expanded without significantly impacting long-term survival. The transplantation team in San Francisco reported 88% 5-year recurrence-free survival in a cohort of patients whose liver explant presented one tumor measuring ≤ 6.5 cm or two to three nodules with the largest lesion measuring ≤ 4.5 cm and a total tumor diameter of ≤ 8 cm, defining the San Francisco (UCSF) criteria [11]. A retrospective analysis of recurrence and survival conducted in French transplant recipients identified three sub-groups on the basis of the preoperative tumor properties: the first sub-group fulfilled the Milan criteria (Milan+), the second exceeded the Milan criteria but fulfilled the San Francisco criteria (Milan− UCSF +) and the third exceeded the Milan and UCSF criteria (Milan− UCSF −) [10]. The risk of recurrent HCC five years after transplantation was significantly different between the Milan+ or Milan− UCSF + patients (20.2% and 27.1% respectively) and the Milan − UCSF − patients (52.6%) (p=0.0025). The difference between the Milan+ and the Milan UCSF + groups was not significant, suggesting the selection criteria for transplantation could be expanded without increasing the risk of recurrence.

Characteristic features of the recurrence

HCC recurrence after liver transplantation usually develops early, with a median delay of 12 months [10,12−15]. The large majority of these recurrences develop within the first two years following transplantation, and for 20%, after three years [13−15]. Very late recurrences (greater than six years) have also been reported [16]. Post-recurrence survival would be significantly better when the recurrence develops more than 12 months after transplantation [17]. The time to recurrence is shorter for larger, multifocal, poorly differentiated tumors with vascular involvement [13].

A wide spectrum of localizations is reported (Table 2) and can involve the liver graft, lungs, bones, lymph nodes, adrenal glands, skin, peritoneum, or the brain. Extra-hepatic and multiple-organ recurrences are common (30%−70% of cases). An isolated recurrence within the graft is seen in only 20% of cases (Table 2). This type of recurrence, which could be accessible to local treatment, appears to develop more frequently with well-differentiated tumors [15].

**Table 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Recurrence Rate (5 years) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milan+</td>
<td>21</td>
</tr>
<tr>
<td>Milan− UCSF +</td>
<td>20.2</td>
</tr>
<tr>
<td>Milan− UCSF −</td>
<td>52.6</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Localization</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver graft</td>
<td>Graft recurrence</td>
</tr>
<tr>
<td>Lungs</td>
<td>Pulmonary metastasis</td>
</tr>
<tr>
<td>Bones</td>
<td>Bone metastasis</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Lymph nodal metastasis</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>Adrenal gland metastasis</td>
</tr>
<tr>
<td>Skin</td>
<td>Skin metastasis</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>Peritoneal metastasis</td>
</tr>
<tr>
<td>Brain</td>
<td>Brain metastasis</td>
</tr>
</tbody>
</table>
Impact of recurrence on survival

Unlike post-transplantation survival in general, the specific question of survival after post-transplantation recurrence has not been extensively studied. It is known that recurrent HCC is associated with shorter survival, with death occurring 5.6 to nine months after diagnosis [14,15,18,19]. Tumor size, early recurrence, undifferentiated histology, and presence of bone metastases have been found predictive of mortality in multivariate analysis while access to surgical treatment would enable longer survival [14]. Late (greater than one year) or very late (greater than six years) recurrence would have a better prognosis with survival greater than three years [16]. Post-recurrence survival would depend more on time since transplantation than tumor localization [17].

Factors predictive of recurrence

It is important to identify factors predictive of post-transplantation recurrence of HCC in order to select patients eligible for liver transplantation whose risk of recurrence is low or who could be expected to benefit from adjuvant treatment and/or specific immunosuppressive strategies. Two categories of predictive factors can be considered:

- preoperative factors used to assess the candidate's transplantability;
- postoperative markers which could impact surveillance, the immunosuppression scheme or the indication for adjuvant treatment.

Preoperative factors

Univariate analysis identifies several factors predictive of outcome, but only selected items exhibiting an independent link with survival and/or post-transplantation recurrence. Most are morphological features of the HCC recognized during the pretransplantation work-up: number and size of tumor(s) [10,18,20], gross vascular invasion [18], bilobar involvement [21].

Tumor differentiation, determined on the preoperative biopsy sample or the liver explant, is also an independent factor predictive of recurrence after liver transplantation [22,23] which is inversely correlated with gross vascular invasion [24]. Preoperative liver biopsy is however not routine practice in most transplantation centers due to the presence of ascites, coagulation disorders, or risk of tumor dissemination [25–30]. Furthermore, because of potential sampling bias, the differentiation described from a preoperative biopsy sample is not necessarily in agreement

### Table 1: Rate of recurrent hepatocellular carcinoma and 5-year recurrence-free survival in liver transplant recipients.

<table>
<thead>
<tr>
<th>First author [ref]</th>
<th>Study period</th>
<th>Number of patients</th>
<th>Recurrence (%)</th>
<th>5-year recurrence-free survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ringe et al. [7]</td>
<td>74–88</td>
<td>61</td>
<td>Na</td>
<td>15</td>
</tr>
<tr>
<td>Iwatsuki et al. 1991 [6]</td>
<td>80–89</td>
<td>105</td>
<td>42.9</td>
<td>36</td>
</tr>
<tr>
<td>Bismuth et al. [8]</td>
<td>80–91</td>
<td>60</td>
<td>54</td>
<td>Na</td>
</tr>
<tr>
<td>Schlitt et al. [15]</td>
<td>72–94</td>
<td>69</td>
<td>57</td>
<td>Na</td>
</tr>
<tr>
<td>Mazzafacco et al. [9]</td>
<td>91–94</td>
<td>48</td>
<td>17a</td>
<td>74a</td>
</tr>
<tr>
<td>Dechaes et al. [10]</td>
<td>85–98</td>
<td>467</td>
<td>27</td>
<td>52.1</td>
</tr>
<tr>
<td>Yoa et al. [11]</td>
<td>88–00</td>
<td>70</td>
<td>11.4</td>
<td>72.4</td>
</tr>
<tr>
<td>Jonas et al. [22]</td>
<td>89–00</td>
<td>120</td>
<td>16.7</td>
<td>71</td>
</tr>
<tr>
<td>Roayaie et al. [14]</td>
<td>88–02</td>
<td>311</td>
<td>18.3</td>
<td>Na</td>
</tr>
<tr>
<td>Kim et al. [18]</td>
<td>96–05</td>
<td>119</td>
<td>23.4</td>
<td>Na</td>
</tr>
<tr>
<td>Dharancy et al. [17]</td>
<td>95–05</td>
<td>68</td>
<td>20</td>
<td>73</td>
</tr>
</tbody>
</table>

Na: not available.

### Table 2: Localization and type of recurrent hepatocellular carcinoma after liver transplantation.

<table>
<thead>
<tr>
<th>Localization of recurrence</th>
<th>Type of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (%)</td>
<td>Lung (%)</td>
</tr>
<tr>
<td>-----------</td>
<td>----------</td>
</tr>
<tr>
<td>Roayaie et al. [14]</td>
<td>47</td>
</tr>
<tr>
<td>Schlitt et al. [15]</td>
<td>62</td>
</tr>
<tr>
<td>Regalia et al. [13]</td>
<td>Na</td>
</tr>
<tr>
<td>Kim [18]</td>
<td>68.8</td>
</tr>
<tr>
<td>Dharancy et al. [17]</td>
<td>49.1</td>
</tr>
</tbody>
</table>

Na: not available.
with the histological analysis of the whole liver explant [31].

Post-transplantation factors

The gold standard for evaluating factors predictive of recurrence, i.e. analysis of the hepatic explant, cannot be included in the transplantation waiting list inscription algorithm. Certain studies have identified an important risk of underestimation (50%) and poor agreement (15%–20%), in terms of tumor size and number, between preoperative morphology studies and final pathology results [32–37].

If the liver explant is also taken into account, certain pretransplantation findings (tumor size and number) can be recognized as predictive of HCC recurrence [38]. Moreover, the explant provides complementary information about micro-vascular invasion which appears to be critical for predicting recurrence. Independently of this micro-vascular invasion element, tumor size > 3 cm [38], presence of microsatellites nodules [39], allelic imbalance [40,41], or expression of certain genes [42,43] have been described as independent factors predictive of tumor recurrence. Thus pathology scores have been developed to help determine the risk of recurrence [38,44]. The development of these new recurrence scores should enable individualized surveillance schemes after liver transplantation [45].

Role of immunosuppression

Immunosuppressive treatment, known to favor cell proliferation and metastatic spread, was rapidly incriminated as the causal element for recurrent HCC after liver transplantation [46,47]. There are several arguments suggesting that the intensity of the immunosuppressive protocol impacts the risk of recurrence: a retrospective multicentric analysis of 412 HCC liver transplant recipients in France showed that use of anti-lymphocyte and anti-CD3 antibodies was independent factors predictive of recurrent HCC [19]. The level of exposure to anticalcineurins was identified as independent factors predictive of tumor recurrence: the intensity of the immunosuppressive protocol impacts the risk of recurrence [46,47]. There are several arguments suggesting that the causal element for recurrent HCC after liver transplantation to prevent tumor recurrence [50,51]. The first study noted that among 11 patients, only one case of recurrence developed one year after transplantation for advanced-stage HCC. The second study compared 45 patients given anticalcineurins and sirolimus with a group of 52 patients not given mTOR inhibitors. An improvement in the overall 1- and 5-year survival rates was observed after transplantation in the group given both sirolimus and anticalcineurins (95.5% versus 83% and 78.8% versus 62% respectively). These data suggest that the Milan criteria could be expanded without increasing the risk of recurrence for patients given this class of immunosuppressive drugs [52,53]. These data were not obtained in a controlled trial and require further confirmation.

Therapeutic management of recurrence

Adjuvant/neoadjuvant chemotherapy

Several adjuvant/neoadjuvant chemotherapy protocols, adjusted to the real stage of HCC dissemination found on the liver explant, offer attractive therapeutic potential. Considering the low rate of recurrence observed in recent series, it would be logical to propose such protocols for selected sub-populations with a high risk of recurrence. The main problem with this attitude is the safety aspect related to the cumulative toxicity of immunosuppressive and chemotherapy drugs.

Licartin, a monoclonal antibody (IgG1 HAb18mAb) labeled with 131-iodine which binds to tumor cells, was recently used in a randomized controlled trial versus placebo in 60 patients with a high risk of recurrence (TNM III and IV documented on the explant). At one year, the results were in favor of the Licartin group which showed a significantly lower risk of recurrence (26.7% versus 57.1%) and an improved survival (82.5% versus 62%). The safety profile was good since no adverse effects were reported (including allergic reactions, fever, nausea, diarrhea, abdominal pain). Further work in a larger group is needed to confirm these results [54].

Doxorubicin has been given alone in two studies, one with a controlled design [55,56]. The first non-controlled study tested the 20 mg/m² per week dose for 20 weeks in 10 patients with a high risk of recurrence (TNM IV A and III). Sixty percent of the patients were recurrence-free at mean 28 months follow-up. The safety study disclosed two discontinuations for nephrotoxicity and bone marrow failure, and one fatal pneumopathy [55]. The second controlled study combined neoadjuvant and adjuvant treatments in 34 patients compared with 28 controls treated with liver transplantation alone. The 5-year analysis was unable to identify any significant difference in recurrence-free survival [56].

The Los Angeles team also tested an adjuvant chemotherapy combination in a non-controlled study. They delivered fluorouracil, doxorubicin, and cisplatin for six months after liver transplantation in 25 patients including eight who had vascular invasion and five who had an invaded capsule. At three years, 46% of the patients were recurrence-free despite these factors favoring recurrence [57]. The gemcitabine + cisplatin combination was studied in 17 patients who did not meet the Milan criteria in comparison with 13 controls; there was a trend in favor of the chemotherapy for recurrence-free survival at two years and for overall survival at three years [58].

Multimodal schemes have also been proposed combining radiation therapy and neoadjuvant chemotherapy followed by adjuvant chemotherapy. The Mount Sinai Medical Center in New York reported encouraging results with superselective chemoembolization using mitomycin, cisplatin and doxorubicin delivered before liver transplantation and followed by six cycles of systemic chemotherapy after transplantation using doxorubicin alone every three weeks. The 5-year survival in 43 patients with a HCC measuring at least 5 cm along the largest diameter was 48% [59].
To date however, there has not been any trial formally demonstrating the usefulness of administering neoadjuvant/adjuvant treatment before and after liver transplantation. Excepting therapeutic trials, no evidence is available clearly favoring neoadjuvant / adjuvant treatment.

**Curative treatments**

Despite the absence of underlying cirrhosis, the multifactorial nature of recurrence is the main limiting factor for potentially curative surgery (R0). Curative treatment is thus a valid option in only a very few patients. A unique intrahepatic focus or a unique metastasis in the lungs or adrenals are the better indications for surgical resection.

The team at the Mount Sinai Hospital reported their experience with 18 cases of recurrent disease (32% of their reported series) treated surgically: hepatectomy ($N = 5$), lung resection ($N = 7$), radiofrequency surgery ($N = 3$), adrenalectomy ($N = 2$), wall resection after post biopsy recurrence ($N = 1$). Surgery was an independent factor predictive of survival (47% versus 10% at five years) [14]. Similarly, the Milan team reported a series of seven patients who underwent potentially curative surgery. Surgical resection was found to be an independent factor predictive of survival (57% versus 14% at four years in the surgery group and in the non-resectable HCC group respectively [13].

Focal resection of a pulmonary tumor or lobe has been proposed in patients with a unique pulmonary metastasis because these tumors often arise late and are generally accessible to R0 surgery. A series from New Orleans had five cases of pulmonary tumors which developed on average 16.5 months after liver transplantation and could be treated by surgical resection. Mean survival after resection was 27.5 months [60].

Summarizing, surgical resection can be considered the standard treatment for focal HCC recurrence. There have been anecdotal cases of retransplantation for recurrent HCC [15].

**Targeted therapy**

Sorafenib (Nexavar®) is a multikinase inhibitor exhibiting antitumor and antiangiogenic activity that targets receptor tyrosine kinases (c-KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR-β) and Raf kinase (serine/threonine kinase). The SHARP trial, was a randomized phase III trial versus placebo conducted in patients with metastatic or locally advanced HCC on Child cirrhosis which demonstrated a benefit in terms of overall survival (10 versus 7.9 months for sorafenib versus placebo) and radiological progression-free survival (5.5 months versus 2.8 months) [61]. In the situation of post-transplantation recurrence, preliminary data from a French case-control study show less satisfactory tolerance for sorafenib in terms of grade 3/4 skin and gastrointestinal adverse effects compared with non-transplanted patients. This greater toxicity led to earlier dose reduction, only one-third of the patients were able to tolerate the full dose. Drug interactions with immunosuppressive treatments would probably explain, at least in part, this difference. These data will have to be clarified with a larger-scale cohort [62].

**Systemic chemotherapy**

Theoretically, systemic chemotherapy would be an attractive alternative due to the high proportion of extrahepatic recurrence in multiple localizations. To our knowledge, there have not been any published studies examining the usefulness of systemic chemotherapy for palliative recurrence of HCC after liver transplantation. By analogy with the non-transplanted patient, one might expect rather disappointing results since all studies reported to date in this population have had a low rate of objective response and significant bone marrow toxicity. Administration of doxorubicin, the most widely studied drug, has enabled objective response rates to the order of 10% [45]. More aggressive protocols such as PIAF (cisplatin, interferon alpha-2b, doxorubicin, fluorouracil) have produced response rates above that observed with doxorubicin alone (20.8% versus 10.5%) in one phase II trial which included 188 patients, but with no significant difference in survival and with greater myelotoxicity [63].

**Proliferation signal inhibitors**

Proliferation signal inhibitors constitute a new class of immunosuppressive drugs belonging to the family of mTOR inhibitors. Two compounds (sirolimus, everolimus) are currently used for the prevention of rejection in organ transplant recipients [64–68]. Proliferation signal inhibitors also exhibit antiproliferative and antiangiogenic properties in vitro and in vivo, leading to their evaluation in several oncology therapeutic trials [69–75]. The use of proliferation signal inhibitors is also associated with a significant decrease in the risk of de novo cancer after kidney transplantation [76]. Proliferation signal inhibitors inhibit the PI(3)K/Akt/mTOR pathway dysregulated by the process of hepatic carcinogenesis [77]. Experimentally and clinically, there would probably be a rationale for evaluating the effect of proliferation signal inhibitors for the prevention and/or treatment of recurrent HCC after liver transplantation.

The evidence available suggests a potential decline in the risk of recurrence and of post-recurrence tumor progression and/or a survival benefit in patients transplanted for HCC [50–52]. In a recent study, outcome in 97 recipients transplanted for HCC was analyzed as a function of their immunosuppressive treatment. Forty-five patients given a proliferation signal inhibitor in combination with anticalcineurins were matched with 52 patients given mofetil mycophenolate, anticalcineurins and corticosteroids. The 1- and 5-year recurrence-free survival rates were significantly better in the group, which received proliferation signal inhibitors (93% and 78.8% in the sirolimus group versus 75% and 54% in the control group; odds ratio 0.622 [95% confidence interval: 0.385–0.954]) [51]. An international multicenter prospective study (SILVER) is currently being conducted to determine the survival benefit and the antitumor effect of an immunosuppression scheme using a proliferation signal inhibitor introduced early (one month
after liver transplantation). Although data are lacking on the usefulness of this treatment of recurrence by proliferation signal inhibitors, most liver transplantation centers propose proliferation signal inhibitors introduced in addition to or in replacement of anticalcineurins. This strategy should be evaluated. A pilot study has provided evidence in favor of this attitude, showing that sirolimus would enable a higher objective response rate of 36% in patients with advanced HCC (excepting transplant recipients) using a weekly dose of 30 mg [78].

**Decision-making algorithm**

Precise guidelines for therapeutic management of post-transplantation recurrent HCC have not been established. The evidence-based algorithm we present in Fig. 1 takes into account all available data.

Unifocal late recurrence (after 12 months) would have a better prognosis if surgical resection (hepatectomy, pulmonary resection, adrenalectomy) or radiofrequency treatment can be proposed. In the event of an early tumor recurrence (lesser than 12 months), surgery would probably not be licit, excepting a cutaneous localization, because of the high risk of dissemination. A new evaluation three months later with complete search for extension would be useful to avoid proposing surgery outside a situation of focal recurrence for potentially curative treatment. The prognosis is poor with bone involvement, but radiation therapy can be useful for pain relief.

Systemic treatment can be discussed for patients with multifocal recurrence. At the present time, proliferation signal inhibitors offer the advantage of exhibiting, although available data are scarce, both immunosuppressive and antiproliferative activity. Liver transplantation teams have readily introduced this new therapeutic class, targeting the upper level of exposure [79,80]. Finally, very preliminary data would suggest the feasibility of targeted therapies, possibly at the cost of dose adjustment.

**Conclusion**

Within five years after their liver transplantation for HCC, 10% to 20% of the recipients will develop recurrent HCC. The overall prognosis of recurrent HCC is poor with fatal outcome within one year of diagnosis. An analysis of the natural history of recurrent HCC identifies several sub-populations with a better prognosis, defined more on the basis of time from liver transplantation to recurrence than on tumor localization. Expressed in terms of survival, the best prognosis is achieved with surgical resection, when possible. Multimodal schemes associating for example neoadjuvant and adjuvant chemotherapy have given encouraging preliminary results and may offer attractive therapeutic perspectives. A precise analysis of the explanted liver and the development of new molecular tools should enable an earlier and more precise identification of sub-populations with a high risk of recurrence.

**Conflict of interests**

None.
References


