

Liver transplantation for hepatocellular carcinoma on cirrhosis: Strategies to avoid tumor recurrence

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Abstract

Hepatocellular carcinoma (HCC) is one of the most frequent neoplasms worldwide and in most cases it is associated with chronic liver disease. Liver transplantation (LT) is potentially the optimal treatment for those patients with HCC who have a poor functional hepatic reserve due to their underlying chronic liver disease. However, due to the limited availability of donors, only those patients whose oncologic profile is favorable can be considered for LT. Despite the careful selection of candidates based on strict rules, 10 to 20% of liver transplant recipients who have HCC in the native cirrhotic liver develop tumor recurrence after transplantation. The selection criteria presently employed to minimize the risk of recurrence are based on gross tumor characteristics defined by imaging techniques; unfortunately, the accuracy of imaging is far from being optimal. Furthermore, microscopic tumor features that are strictly linked with prognosis can not be assessed prior to transplantation. Pre-transplantation tumor downstaging may allow transplantation in patients initially outside the selection criteria and seems to improve the prognosis; it also provides information on tumor biology. The

main peculiarity of the transplantation setting, when this is compared with other modalities of treatment, is the need for pharmacological immunosuppression: this is based on drugs that have been demonstrated to increase the risk of tumor development. As HCC is an aggressive malignancy, immunosuppression has to be handled carefully in patients who have HCC at the time of transplantation and new categories of immunosuppressive agents should be considered. Adjuvant chemotherapy following transplantation has failed to show any significant advantage. The aim of the present study is to review the possible strategies to avoid recurrence of HCC after liver transplantation based on the current clinical evidence and the more recent developments and to discuss possible future directions.

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Key words: Chemotherapy; Hepatocellular carcinoma; Immunosuppression; Liver transplantation; Tumor recurrence

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most frequent neoplasms worldwide with more than 500 000 new cases diagnosed each year. In more than 90% of cases, HCC is associated with chronic liver disease, par-

ticularly disease caused by hepatitis B (HBV) or hepatitis C (HCV) viral infection^[1].

Resective surgery of HCC with curative intent has two main limitations: the impaired functional reserve of the liver in the presence of cirrhosis often contraindicates surgery, while the persistence of the underlying chronic liver disease leads to recurrence of the tumor within the liver in more than 50% of cases in the long-term^[2]. Furthermore, liver cirrhosis is by itself a progressive condition that substantially limits life expectancy.

For these reasons, liver transplantation (LT) theoretically represents the ideal treatment of HCC on cirrhosis as it removes both the tumor and the underlying condition that results in HCC.

However, the initial experience with LT for HCC in the eighties was discouraging, as recurrence rates of more than 50% were reported in many series; the indication for LT in the presence of HCC was therefore questioned^[3-5].

In 1995, Mazzaferro *et al*^[6] published the results of a prospective study where he demonstrated that, by adopting strict selection criteria with regard to the size and number of tumor nodules, it was possible to achieve a satisfactory long-term recurrence-free survival after LT. The criteria established in that study, known as the “Milan criteria” have from then on been the basis for the selection of patients with HCC on cirrhosis for transplantation. Currently, HCC on cirrhosis represents one of the main indications for LT: according to the report of the United Network for Organ Sharing (UNOS), in 2008, 17.5% of 6069 recipients of a liver graft from a deceased donor were HCC carriers, while 10 616 LTs have been performed up to 2009 in Europe on HCC patients according to the data of the European Liver Transplant Registry (ELTR).

Although in absolute terms the present results of LT for HCC are outstanding, considering that we are dealing with a highly aggressive tumor, 10% to 20% of recipients still develop tumor recurrence. This failure rate is of particular relevance in the transplantation field where great effort is made not to waste precious and rare resources such as liver grafts^[7,8].

The purpose of the present review is to analyze possible strategies to avoid HCC recurrence following LT.

PATIENT SELECTION

Although they provide excellent results, the selection criteria introduced by Mazzaferro result in the exclusion of a great number of possible LT candidates whose tumor slightly exceeds the limits. In addition, in the original article the Milan criteria were verified by pathology of the explanted liver, while in the clinical setting HCC is staged by imaging techniques. The accuracy of imaging in preoperative staging is far from optimal and ranges between 14% and 80%^[9-12] (Table 1).

Since 1996, attention has been focused on the possibility of recruiting a larger number of LT candidates whose tumor is beyond the Milan criteria but still within

Table 1 Accuracy of imaging techniques in the pre-transplant staging of hepatocellular carcinoma

Author, yr, center	No. of pts	Accuracy in detecting No. of nodules (%)	Accuracy in detecting diameter of nodules (%)	Accuracy in assessing Milan criteria (%)
Yao FY, 2001, San Francisco	70	75	62-80	nr
Sotiropoulos GC, 2005, Essen	70	34	14	60
Shah SA, 2006, Toronto	118	75	78	57
Grasso A, 2006, London	74	80	80	nr

pts: Patients; nr: Not reported.

Table 2 Proposed criteria for liver transplantation in patients with hepatocellular carcinoma

Author, yr, center	No. of pts	Selection criteria	Survival
Mazzaferro V, 1996, Milan	48	1 nodule \leq 5 cm or \leq 3 nodules \leq 3 cm	83% (4-yr RF)
Yao FY, 2001, San Francisco	70	1 HCC \leq 6.5 cm or \leq 3 HCC \leq 4.5 cm with cumulative diameter \leq 8 cm	75.2% (5-yr overall)
Toso C, 2008, Edmonton	288	Total HCC volume \leq 115 cm ³	80% (5-yr overall)
Mazzaferro V, 2009, multicenter study	1556	No. of HCC nodules + maximum diameter (cm) \leq 7	71% (5-yr overall) if MVI absent

pts: Patients; RF: Recurrence-free; HCC: Hepatocellular carcinoma; MVI: Microvascular tumor invasion.

a safety zone in terms of likelihood of recurrence. Several proposals for revision of the Milan criteria have been made over the years, the most popular of which are summarized in Table 2^[6,9,13,14]. The latest of these proposals is from Mazzaferro *et al*^[14] and is known as the “up-to-seven” rule: the sum of the number of tumor nodule(s) and the maximum diameter of the nodule(s) must not exceed the value of seven.

A system has also been developed to predict the survival probability of a LT candidate with HCC as a function of size and number of tumor nodules; using freely accessible software it is possible to calculate the probability of survival linked to given tumor features. This software, called the Metroticket Calculator takes into account another parameter, the presence of microvascular tumor invasion (MVI) that has been shown to be intimately related to the biology of the tumor^[15]. The importance of MVI as a determinant of recurrence has been known for years; histological grading has also been associated with tumor recurrence in several reports^[16-17]. Unfortunately, MVI and histological grading can not be precisely assessed prior to transplantation; percutaneous biopsy of the tumor nodule can miss the area of the tumor where MVI is present or may fall in an area of the nodule where the tumor is more differentiated. In fact, grading varies within the same nodule and is eventually defined by the area where the highest degree of undifferentiation is found^[18].

The main bias of all the selection systems currently in use is that they are based on the gross pathological features of the tumor. Apart from the difficulty of cor-

rectly staging the tumor at imaging, size and number of nodules are not always related to the effective biology of the tumor. Esnaola showed that MVI is certainly more frequent in multiple and large tumors; however, 53% of patients with multiple nodules and 50% of patients with nodules larger than 4 cm in diameter did not display MVI at histology^[19]. Jonas *et al*^[20] has recently proposed an index based on DNA cytometry in tumor tissue that can establish the relative risk of recurrence; unfortunately, this index can not be evaluated prior to transplantation. Fiorentino *et al*^[21] a few years ago demonstrated that biological markers such as membrane expression of E-cadherin and β -catenin, and nuclear expression of β -catenin were predictors of prognosis. These markers could be assessed on preoperative biopsy; however, the value of these markers has never been tested prospectively.

Serum alpha fetoprotein level at the time of LT is also linked to prognosis^[22-24]; however, it is not considered in the more widely used selection systems for LT candidates.

PRE-TRANSPLANT DOWNSTAGING

Neo-adjuvant therapy prior to LT has been proposed mainly to slow the progression of HCC while the patient is on the waiting list, to avoid drop-out^[25]. Other authors have proposed downstaging, within the Milan criteria, of tumors that were initially beyond the criteria, thus allowing transplantation^[26,27]. Among the possible techniques used to downstage HCC, the most widely used is transarterial chemoembolization (TACE), followed by radiofrequency ablation (RFA)^[28]. In 2008, Yao *et al*^[29] reported the results of a prospective trial of downstaging that included 61 patients originally outside the Milan criteria; in the majority of cases, TACE was used for downstaging however, some patients were also treated with RFA or surgical resection. No tumor recurrences were observed at a median follow-up of 25 mo in the 35 patients who underwent LT following downstaging. There is some evidence that response to downstaging can be used as a prognostic factor to select patients with best prognosis after LT; in particular, it has been observed that the degree of tumor necrosis after TACE is linked to prognosis^[30,31].

ADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy has historically failed to show any advantage after resection of HCC^[32]. In the setting of liver transplantation, the first relevant report on adjuvant chemotherapy was published by Olthoff and colleagues in 1995; a series of 25 LT recipients with HCC received intravenous fluorouracil, doxorubicin, and cisplatin for 6 mo after LT. Many of these patients had tumors well beyond the Milan criteria, 6 patients did not complete the treatment because of severe side-effects and a 3-year tumor-free survival of 46% was reported; the authors concluded that this result was satisfactory

when compared to that achieved in an historical series of 17 patients transplanted between 1984 and 1988 whose tumor-free survival was worse^[33].

In 2002, Roayaie published the results of a prospective study carried out on 43 patients who had tumors larger than 5 cm in diameter at the time of LT and were administered 6 cycles of systemic doxorubicin after surgery. In 11 of these 42 patients, adjuvant treatment was discontinued, mainly due to side-effects; recurrence-free survival was 48%^[34].

In more recent years, two different prospective randomized trials showed no significant advantage of adjuvant therapy with systemic doxorubicin administered after LT^[35,36].

Another recent report on adjuvant therapy with cisplatin and adriamycin on a series of 12 LT recipients with poor prognostic factors again failed to show any advantage^[37].

Although promising preliminary results have been reported with the use of targeted molecular drugs such as sorafenib in advanced HCC, the use of these agents in the transplantation field has not yet been assessed^[38].

PHARMACOLOGICAL IMMUNOSUPPRESSION

Some 20 years ago, Yokoyama *et al*^[39] from the Pittsburgh group noticed that the doubling time of HCCs that recurred after LT was significantly shorter than that observed in HCCs that arose in non-transplanted patients. The authors concluded that the accelerated growth rate of HCC in LT recipients was due to pharmacological immunosuppression.

Indirect evidence of a favoring effect of immunosuppression on tumor genesis comes from the observation that the incidence of malignancies is significantly higher in organ recipients than in the general population^[40].

The cornerstone of pharmacological immunosuppression in organ transplantation is represented by the calcineurin inhibitors (CNIs), namely cyclosporine and tacrolimus. These agents affect T-cell recognition of alloantigen and signal transduction *via* the calcium-dependent calcineurin pathway. Besides inhibiting interleukin (IL)-2 expression, they increase transforming growth factor (TGF)- β 1, a potent inhibitor of IL-2-stimulated T-cell proliferation; unfortunately, TGF- β 1 depresses the natural killer cell-mediated anti-tumor immune response, and is implicated in the development of the metastatic process^[41-43].

A study published in the Lancet by Dantal *et al*^[44] in 1998, showed that there was a significant relationship between the dosage of cyclosporine administered to kidney transplant recipients and the development of posttransplant *de novo* malignancies, while Freise *et al*^[45] demonstrated in an animal model that cyclosporine has an adverse effect on recurrence of hepatoma after liver transplantation.

In 2002, the group of Bologna first demonstrated that there was a direct relationship between the cumulative dosage of cyclosporine administered in the first year

after LT and HCC recurrence-free survival: the higher the dosage of cyclosporine given, the lower the recurrence-free survival^[46]. This observation was confirmed by a subsequent study from the same group, where exposure to cyclosporine was shown to be an independent determinant of recurrence-free survival^[47]. A later report published in 2008, showed that both tacrolimus and cyclosporine exposure were independently associated with HCC recurrence together with MVI and tumor histological grading^[48].

A newer category of immunosuppressant drugs called m-TOR (mammalian target of rapamycin) inhibitors have raised a high degree of interest. These drugs are associated with strong immunosuppressant activity, due to the blocking of IL-2 stimulation of lymphocyte proliferation, and have a potential anti-cancer effect which has been demonstrated in the experimental setting. The anti-cancer effect is mainly related to the impairment of vascular endothelial growth factor (VEGF) production and the blockage of VEGF-induced vascular endothelial cell stimulation^[41]. Several reports are available in the literature that seem to indicate that m-TOR inhibitors have some efficacy in reducing the incidence of *de novo* malignancies, or even arresting the progression of aggressive neoplasms after organ transplantation^[49-56].

In the clinical setting, m-TOR inhibitors, namely sirolimus and everolimus, have been initially tested in association with CNIs to reduce renal damage associated with the use of these latter agents.

However, a report by Knetemann *et al*^[57] published in 2004, showed that by minimizing the use of CNIs through the use of m-TOR inhibitors it was possible to achieve a satisfactory disease-free survival when transplanting patients whose HCC was beyond the Milan criteria.

Since then several centers have employed m-TOR inhibitors in patients with HCC; unfortunately, this has been done outside controlled multicentric trials.

Few reports have compared the results of LT for HCC in patients under CNIs-based immunosuppression to those observed under m-Tor inhibitor-based immunosuppression. The first of these reports comes from Bologna: in a matched case-control study where the clinical and pathological risk factors were identical in the two groups, the 3-year recurrence-free survival was 30% higher in patients who received sirolimus as part of their immunosuppressive schedule than in those who remained on standard treatment based on tacrolimus^[58].

Some confirmation of this finding has been provided by Toso *et al*^[59], who analyzed the Scientific Registry of Transplant Recipients in the United States to ascertain whether survival after LT in HCC patients was influenced by type of immunosuppression: the author concluded that sirolimus-based maintenance therapy was associated with improved survival.

CONCLUSION

Of the possible strategies to avoid tumor recurrence after LT in HCC patients, the careful selection of candidates

based on macroscopic tumor findings is a cornerstone that seems to have been exploited to the maximum. Thus, better characterization of tumor biology is necessary; the main problem in this field is outlining markers assessable on tumor biopsy.

While there is no evidence of the efficacy of adjuvant chemotherapy, more research on immunosuppressive agents is warranted. It is reasonable to suggest that CNIs should be administered at their effective minimum in HCC LT recipients. Although definitive evidence is not yet available, there are enough data to support the use of m-TOR inhibitors in association with CNIs for immunosuppression, or when the risk of tumor recurrence is high, due to the presence of poor prognostic factors, as the main immunosuppressants in a CNI-sparing regimen.

Further prospective studies on large numbers of patients are warranted to confirm the efficacy of this strategy and to quantify the extent of the possible gain in terms of recurrence-free survival.

REFERENCES

- 1 Nordenstedt H, White DL, El-Serag HB. The changing pattern of epidemiology in hepatocellular carcinoma. *Dig Liver Dis* 2010; **42** Suppl 3: S206-S214
- 2 Poon RT. Optimal initial treatment for early hepatocellular carcinoma in patients with preserved liver function: transplantation or resection? *Ann Surg Oncol* 2007; **14**: 541-547
- 3 Iwatsuki S, Gordon RD, Shaw BW, Starzl TE. Role of liver transplantation in cancer therapy. *Ann Surg* 1985; **202**: 401-407
- 4 O'Grady JG, Polson RJ, Rolles K, Calne RY, Williams R. Liver transplantation for malignant disease. Results in 93 consecutive patients. *Ann Surg* 1988; **207**: 373-379
- 5 Ringe B, Pichlmayr R, Wittekind C, Tusch G. Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. *World J Surg* 1991; **15**: 270-285
- 6 Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699
- 7 Bruix J, Fuster J, Llovet JM. Liver transplantation for hepatocellular carcinoma: Foucault pendulum versus evidence-based decision. *Liver Transpl* 2003; **9**: 700-702
- 8 Bartlett A, Heaton N. Hepatocellular carcinoma: defining the place of surgery in an era of organ shortage. *World J Gastroenterol* 2008; **14**: 4445-4453
- 9 Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; **33**: 1394-1403
- 10 Sotiropoulos GC, Malagó M, Molmenti E, Paul A, Nadalin S, Brokalaki E, Kühl H, Dirsch O, Lang H, Broelsch CE. Liver transplantation for hepatocellular carcinoma in cirrhosis: is clinical tumor classification before transplantation realistic? *Transplantation* 2005; **79**: 483-487
- 11 Shah SA, Tan JC, McGilvray ID, Cattral MS, Cleary SP, Levy GA, Greig PD, Grant DR. Accuracy of staging as a predictor for recurrence after liver transplantation for hepatocellular carcinoma. *Transplantation* 2006; **81**: 1633-1639
- 12 Grasso A, Stigliano R, Morisco F, Martines H, Quaglia A, Dhillon AP, Patch D, Davidson BR, Rolles K, Burroughs AK. Liver transplantation and recurrent hepatocellular carcinoma: predictive value of nodule size in a retrospective and

- explant study. *Transplantation* 2006; **81**: 1532-1541
- 13 **Toso C**, Trotter J, Wei A, Bigam DL, Shah S, Lancaster J, Grant DR, Greig PD, Shapiro AM, Kneteman NM. Total tumor volume predicts risk of recurrence following liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl* 2008; **14**: 1107-1115
 - 14 **Mazzaferro V**, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, Adam R, Neuhaus P, Salizzoni M, Bruix J, Forner A, De Carlis L, Cillo U, Burroughs AK, Troisi R, Rossi M, Gerunda GE, Lerut J, Belghiti J, Boin I, Gugenheim J, Rochling F, Van Hoek B, Majno P. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; **10**: 35-43
 - 15 **Mazzaferro V**, Chun YS, Poon RT, Schwartz ME, Yao FY, Marsh JW, Bhoori S, Lee SG. Liver transplantation for hepatocellular carcinoma. *Ann Surg Oncol* 2008; **15**: 1001-1007
 - 16 **Jonas S**, Bechstein WO, Steinmüller T, Herrmann M, Radke C, Berg T, Settmacher U, Neuhaus P. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology* 2001; **33**: 1080-1086
 - 17 **Cillo U**, Vitale A, Bassanello M, Boccagni P, Brolese A, Zanusi G, Burra P, Fagiuoli S, Farinati F, Rugge M, D'Amico DF. Liver transplantation for the treatment of moderately or well-differentiated hepatocellular carcinoma. *Ann Surg* 2004; **239**: 150-159
 - 18 **Edmondson Ha**, Steiner Pe. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. *Cancer* 1954; **7**: 462-503
 - 19 **Esnaola NF**, Lauwers GY, Mirza NQ, Nagorney DM, Doherty D, Ikai I, Yamaoka Y, Regimbeau JM, Belghiti J, Curley SA, Ellis LM, Vauthey JN. Predictors of microvascular invasion in patients with hepatocellular carcinoma who are candidates for orthotopic liver transplantation. *J Gastrointest Surg* 2002; **6**: 224-232; discussion 232
 - 20 **Jonas S**, Al-Abadi H, Benckert C, Thelen A, Hippler-Benschel M, Saribeyoglu K, Radtke B, Pratschke J, Neuhaus P. Prognostic significance of the DNA-index in liver transplantation for hepatocellular carcinoma in cirrhosis. *Ann Surg* 2009; **250**: 1008-1013
 - 21 **Fiorentino M**, Altamari A, Ravaioli M, Gruppioni E, Gabusi E, Corti B, Vivarelli M, Bringui PP, Scoazec JY, Grigioni WF, D'Errico-Grigioni A. Predictive value of biological markers for hepatocellular carcinoma patients treated with orthotopic liver transplantation. *Clin Cancer Res* 2004; **10**: 1789-1795
 - 22 **Sotiropoulos GC**, Lang H, Nadalin S, Neuhaus M, Molmenti EP, Baba HA, Paul A, Saner FH, Weber F, Hilgard P, Frilling A, Broelsch CE, Malagó M. Liver transplantation for hepatocellular carcinoma: University Hospital Essen experience and metaanalysis of prognostic factors. *J Am Coll Surg* 2007; **205**: 661-675
 - 23 **Yang SH**, Suh KS, Lee HW, Cho EH, Cho JY, Cho YB, Kim IH, Yi NJ, Lee KU. A revised scoring system utilizing serum alphafetoprotein levels to expand candidates for living donor transplantation in hepatocellular carcinoma. *Surgery* 2007; **141**: 598-609
 - 24 **Vibert E**, Azoulay D, Hoti E, Iacopinelli S, Samuel D, Saloum C, Lemoine A, Bismuth H, Castaing D, Adam R. Progression of alphafetoprotein before liver transplantation for hepatocellular carcinoma in cirrhotic patients: a critical factor. *Am J Transplant* 2010; **10**: 129-137
 - 25 **Schwartz M**, Roayaie S, Uva P. Treatment of HCC in patients awaiting liver transplantation. *Am J Transplant* 2007; **7**: 1875-1881
 - 26 **Chapman WC**, Majella Doyle MB, Stuart JE, Vachharajani N, Crippin JS, Anderson CD, Lowell JA, Shenoy S, Darcy MD, Brown DB. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. *Ann Surg* 2008; **248**: 617-625
 - 27 **Ravaioli M**, Grazi GL, Piscaglia F, Trevisani F, Cescon M, Ercolani G, Vivarelli M, Golfieri R, D'Errico Grigioni A, Panzini I, Morelli C, Bernardi M, Bolondi L, Pinna AD. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. *Am J Transplant* 2008; **8**: 2547-2557
 - 28 **Toso C**, Mentha G, Kneteman NM, Majno P. The place of downstaging for hepatocellular carcinoma. *J Hepatol* 2010; **52**: 930-936
 - 29 **Yao FY**, Kerlan RK, Hirose R, Davern TJ, Bass NM, Feng S, Peters M, Terrault N, Freise CE, Ascher NL, Roberts JP. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. *Hepatology* 2008; **48**: 819-827
 - 30 **Otto G**, Herber S, Heise M, Lohse AW, Mönch C, Bittinger F, Hoppe-Lotichius M, Schuchmann M, Victor A, Pitton M. Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. *Liver Transpl* 2006; **12**: 1260-1267
 - 31 **Millonig G**, Graziadei IW, Freund MC, Jaschke W, Stadlmann S, Ladurner R, Margreiter R, Vogel W. Response to preoperative chemoembolization correlates with outcome after liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl* 2007; **13**: 272-279
 - 32 **Samuel M**, Chow PK, Chan Shih-Yen E, Machin D, Soo KC. Neoadjuvant and adjuvant therapy for surgical resection of hepatocellular carcinoma. *Cochrane Database Syst Rev* 2009; CD001199
 - 33 **Olthoff KM**, Rosove MH, Shackleton CR, Imagawa DK, Farmer DG, Northcross P, Pakrasi AL, Martin P, Goldstein LI, Shaked A. Adjuvant chemotherapy improves survival after liver transplantation for hepatocellular carcinoma. *Ann Surg* 1995; **221**: 734-741; discussion 731-743
 - 34 **Roayaie S**, Frischer JS, Emre SH, Fishbein TM, Sheiner PA, Sung M, Miller CM, Schwartz ME. Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 centimeters. *Ann Surg* 2002; **235**: 533-539
 - 35 **Pokorny H**, Gnant M, Rasoul-Rockenschaub S, Gollackner B, Steiner B, Steger G, Steininger R, Mühlbacher F. Does additional doxorubicin chemotherapy improve outcome in patients with hepatocellular carcinoma treated by liver transplantation? *Am J Transplant* 2005; **5**: 788-794
 - 36 **Söderdahl G**, Bäckman L, Isoniemi H, Cahlin C, Höckerstedt K, Broomé U, Mäkitalo H, Friman S, Ericzon BG. A prospective, randomized, multi-centre trial of systemic adjuvant chemotherapy versus no additional treatment in liver transplantation for hepatocellular carcinoma. *Transpl Int* 2006; **19**: 288-294
 - 37 **Bernal E**, Montero JL, Delgado M, Fraga E, Costán G, Barrera P, López-Vallejos P, Solórzano G, Rufián S, Briceño J, Padillo J, López-Cillero P, Marchal T, Muntané J, de la Mata M. Adjuvant chemotherapy for prevention of recurrence of invasive hepatocellular carcinoma after orthotopic liver transplantation. *Transplant Proc* 2006; **38**: 2495-2498
 - 38 **Alves RC**, Alves D, Guz B, Matos C, Viana M, Harriiz M, Terrabuio D, Kondo M, Gampel O, Polletti P. Advanced hepatocellular carcinoma. Review of targeted molecular drugs. *Ann Hepatol* 2011; **10**: 21-27
 - 39 **Yokoyama I**, Carr B, Saito H, Iwatsuki S, Starzl TE. Accelerated growth rates of recurrent hepatocellular carcinoma after liver transplantation. *Cancer* 1991; **68**: 2095-2100
 - 40 **Fung JJ**, Jain A, Kwak EJ, Kusne S, Dvorchik I, Eghtesad B. De novo malignancies after liver transplantation: a major cause of late death. *Liver Transpl* 2001; **7**: S109-S118
 - 41 **Guba M**, Graeb C, Jauch KW, Geissler EK. Pro- and anti-cancer effects of immunosuppressive agents used in organ transplantation. *Transplantation* 2004; **77**: 1777-1782

- 42 **Fung J**, Kelly D, Kadry Z, Patel-Tom K, Eghtesad B. Immunosuppression in liver transplantation: beyond calcineurin inhibitors. *Liver Transpl* 2005; **11**: 267-280
- 43 **Yang L**. TGFbeta, a potent regulator of tumor microenvironment and host immune response, implication for therapy. *Curr Mol Med* 2010; **10**: 374-380
- 44 **Dantal J**, Hourmant M, Cantarovich D, Giral M, Blanche G, Dreno B, Souillou JP. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. *Lancet* 1998; **351**: 623-628
- 45 **Freise CE**, Ferrell L, Liu T, Ascher NL, Roberts JP. Effect of systemic cyclosporine on tumor recurrence after liver transplantation in a model of hepatocellular carcinoma. *Transplantation* 1999; **67**: 510-513
- 46 **Vivarelli M**, Bellusci R, Cucchetti A, Cavrini G, De Ruvo N, Aden AA, La Barba G, Brilli S, Cavallari A. Low recurrence rate of hepatocellular carcinoma after liver transplantation: better patient selection or lower immunosuppression? *Transplantation* 2002; **74**: 1746-1751
- 47 **Vivarelli M**, Cucchetti A, Piscaglia F, La Barba G, Bolondi L, Cavallari A, Pinna AD. Analysis of risk factors for tumor recurrence after liver transplantation for hepatocellular carcinoma: key role of immunosuppression. *Liver Transpl* 2005; **11**: 497-503
- 48 **Vivarelli M**, Cucchetti A, La Barba G, Ravaioli M, Del Gaudio M, Lauro A, Grazi GL, Pinna AD. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence. *Ann Surg* 2008; **248**: 857-862
- 49 **Boffa DJ**, Luan F, Thomas D, Yang H, Sharma VK, Lagman M, Suthanthiran M. Rapamycin inhibits the growth and metastatic progression of non-small cell lung cancer. *Clin Cancer Res* 2004; **10**: 293-300
- 50 **Euvrard S**, Ulrich C, Lefrançois N. Immunosuppressants and skin cancer in transplant patients: focus on rapamycin. *Dermatol Surg* 2004; **30**: 628-633
- 51 **Stallone G**, Schena A, Infante B, Di Paolo S, Loverre A, Maggio G, Ranieri E, Gesualdo L, Schena FP, Grandaliano G. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 2005; **352**: 1317-1323
- 52 **Kauffman HM**, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation* 2005; **80**: 883-889
- 53 **Rizell M**, Cahlin C, Friman S, Hafström L, Lönn L, Olausson M, Lindner P. Impressive regression of primary liver cancer after treatment with sirolimus. *Acta Oncol* 2005; **44**: 496
- 54 **Stippel DL**, Kasper HU, Schleimer K, Töx U, Bangard C, Hölscher AH, Beckurts KT. Successful use of sirolimus in a patient with bulky ovarian metastasis of hepatocellular carcinoma after liver transplantation. *Transplant Proc* 2005; **37**: 2185-2187
- 55 **Elsharkawi M**, Staib L, Henne-Bruns D, Mayer J. Complete remission of postransplant lung metastases from hepatocellular carcinoma under therapy with sirolimus and mycophenolate mofetil. *Transplantation* 2005; **79**: 855-857
- 56 **Campistol JM**, Eris J, Oberbauer R, Friend P, Hutchison B, Morales JM, Claesson K, Stallone G, Russ G, Rostaing L, Kreis H, Burke JT, Braut Y, Scarola JA, Neylan JF. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *J Am Soc Nephrol* 2006; **17**: 581-589
- 57 **Kneteman NM**, Oberholzer J, Al Saghi M, Meeberg GA, Blitz M, Ma MM, Wong WW, Gutfreund K, Mason AL, Jewell LD, Shapiro AM, Bain VG, Bigam DL. Sirolimus-based immunosuppression for liver transplantation in the presence of extended criteria for hepatocellular carcinoma. *Liver Transpl* 2004; **10**: 1301-1311
- 58 **Vivarelli M**, Dazzi A, Zanello M, Cucchetti A, Cescon M, Ravaioli M, Del Gaudio M, Lauro A, Grazi GL, Pinna AD. Effect of different immunosuppressive schedules on recurrence-free survival after liver transplantation for hepatocellular carcinoma. *Transplantation* 2010; **89**: 227-231
- 59 **Toso C**, Merani S, Bigam DL, Shapiro AM, Kneteman NM. Sirolimus-based immunosuppression is associated with increased survival after liver transplantation for hepatocellular carcinoma. *Hepatology* 2010; **51**: 1237-1243

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