

LIVER TRANSPLANTATION AND EXPANDED MILAN CRITERIA.

Does it really work?

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ABSTRACT – *Context* - Orthotopic liver transplantation is an excellent treatment approach for hepatocellular carcinoma in well-selected candidates. Nowadays some institutions tend to Expand the Milan Criteria including tumor with more than 5 cm and also associate with multiple tumors none larger than 3 cm in order to benefit more patients with the orthotopic liver transplantation. *Methods* - The data collected were based on the online database PubMed. The key words applied on the search were “expanded Milan criteria” limited to the period from 2000 to 2009. We excluded 19 papers due to: irrelevance of the subject, lack of information and incompatibility of the language (English only). We compiled patient survival and tumor recurrence free rate from 1 to 5-years in patients with hepatocellular carcinoma submitted to orthotopic liver transplantation according to expanded the Milan criteria from different centers. *Results* - Review compiled data from 23 articles. Fourteen different criteria were found and they are also described in detail, however the University of California – San Francisco was the most studied one among them. *Conclusion* - Expanded the Milan criteria is a useful attempt for widening the preexistent protocol for patients with hepatocellular carcinoma in waiting-list for orthotopic liver transplantation. However there is no significant difference in patient survival rate and tumor recurrence free rate from those patients that followed the Milan criteria.

HEADINGS – Liver transplantation. Carcinoma, hepatocellular. Patient selection. Expanded Milan criteria.

INTRODUCTION

Orthotopic liver transplantation (OLT) is an excellent approach for hepatocellular carcinoma (HCC) in well-selected candidates^(8, 47). The most widely used criteria for patient selection are those proposed by Mazzaferro et al.⁽³⁹⁾, the so-called Milan criteria (MC), (a single tumor up to 5 cm or up to 3 tumors none larger than 3,0 cm).

When MC were applied there was a significant improvement in survival over time for HCC patients undergoing OLT with a 5-year survival of 61,1% contrasting with previously observed 5-year survival rate of 25,3% in 1987.

In recent years, however, some groups have argued that the MC are too restrictive, and exclude some HCC-patients from OLT despite the possibility of benefit. Expanded criteria can be defined by the use of OLT in recipients with tumors beyond the MC. The first description was published in 2001 by the group of the University of California⁽⁶³⁾. In their study, 70 HCC-patients who underwent OLT were retrospectively evaluated on the basis of explants analysis, not pre-transplant

radiology. In the 60 cases with either a single nodule up to 6.5 cm, or up to three nodules none larger than 4.5 cm, and total tumor diameter no more than 8 cm the 5-years overall survival was 75.2%. Forty-six out of the 60 patients (76%) had tumors that were within the MC and these had a 5-year survival of 72%.

Subsequently, in the past 10 years, some major new criteria was created expanding Milan criteria (EMC) such as: University of California, San Francisco (UCSF) Criteria⁽⁶³⁾, Kyoto⁽⁵⁷⁾, Asian⁽²⁶⁾, Shanghai⁽¹³⁾, and others.

Our aim is to study the current situation of these several EMC proposed in order to clarify both this debate through a critical analysis of available data and addressed discussion of further parameters beyond number and size of tumors, focusing on patient survival rate and tumor recurrence free rate from 1 to 5-years after OLT.

METHODS

A systematic search of Medline (PubMed) database was performed to identify studies evaluating

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expanded criteria for patients with HCC submitted to liver transplantation. The search was restricted to papers written in English and published from 2000 to 2009. The keywords used were hepatocellular carcinoma, liver transplantation, expanded criteria, the UCSF criteria, Milan Criteria, and others. Only papers reporting cadaveric liver donors that evaluated expanded criteria on the basis of tumor number and size were selected. This search resulted in a total of 39 studies. Additionally, a full manual search from bibliographies of papers describing aspects beyond tumor number and size, and reports of consensus conference was also performed. Nineteen papers were excluded due to: irrelevance of subject, lack of information and incompatibility of language.

We compiled data focusing on patient survival rate and tumor recurrence free rate from 1 to 5-years. We also compared results between MC and EMC. A $P < 0.05$ was considered statistic significant.

RESULTS

Twenty-three papers including centers from North and South America, Europe and Asia were compiled. Fourteen different EMC were found; however UCSF was the most studied^(10, 11, 13, 26, 57, 63). The patient survival rate and tumor recurrence-free rates from 1 to 5-years were shown in Table 1.

We have shown the UCSF patient survival and tumor recurrence-free rates from 1 to 5-years comparing them with MC in Table 2. No significance difference was found between the two groups.

DISCUSSION

HCC is a major health problem worldwide⁽³¹⁾. In the West 30%-40% of HCC cases are detected at early stages and treated with intention to cure, a figure that reaches 60% of the cases

TABLE 1. Comparison of patient survival rate and tumor recurrence free rate among different expanded Milan criteria in the literature

Author	Year	N	Criteria	1y	3y	5y	Staging
Mazzaferro et al. ⁽³⁸⁾	2009	283	Up-to-seven: in the absence of microvascular invasion, fulfilled the so-called up-to-seven criteria, with seven being the result of the sum of size (in cm) and number of tumors for any given hepatocellular carcinoma		77.7%	71.2%	P
Fan J, et al. ⁽¹³⁾	2009	176	Single tumor ≤ 9 cm in diameter, 2-3 tumors with the largest ≤ 5 cm, a total tumor diameter ≤ 9 cm without macrovascular invasion, lymph node invasion and extrahepatic metastasis	82.7% / 51.2% ²	-	75.9% / 46.1% ²	P
Li J, et al. ⁽²⁷⁾	2009	25	Total tumor size ≤ 9 cm and who were without macrovascular invasion or extrahepatic metastases, regardless of the number of tumor lesions	85,2% / 95.0% ²	-	48,4% / 70.4% ²	P
Takada Y, et al. ⁽⁵⁸⁾	2010	23	Diameter ≤ 5 cm; number of lesions ≤ 10 ; PIVKA-II ≤ 400 mAU/mL	-	-	95% ²	R
Boin, et al. ⁽⁵⁾	2008	19	Any tumor beyond Milan Criteria	-	-	47.4% (10y)	P
Lee SG, et al. ⁽²⁶⁾	2008	22	Largest tumor diameter ≤ 5 cm, HCC number ≤ 6 , no gross vascular invasion	100%	88.9%	80%	P
Majeed, et al. ⁽³⁵⁾	2008	23	No extrahepatic evidences of spread on abdomen computed tomography (CT) and chest	-	50% - 70%	-	NA
Silva, et al. ⁽⁵³⁾	2008	26 / 46*	Up to 3 nodules, with none larger than 5 cm, and a cumulative tumor burden ≤ 10 cm	92% / 74%*	79% / 55%*	69% / 40%*	R / P
Herrero, et al. ⁽¹⁹⁾	2008	24	Any tumor beyond Milan Criteria	92%	78%	73%	R
Onaca, et al. ⁽⁴²⁾	2007	130	2-4 tumors with the largest ≤ 5 cm or a single tumor up to 6 cm	-	-	64.6% ² / NA	P
Soejima, et al. ⁽⁵⁴⁾	2007	40	Without extrahepatic spread or macroscopic vascular invasion. The size and number of HCC nodules were not limited	83% ²	74% ²	-	R
Todo, et al. ⁽⁶¹⁾	2007	272	Any tumor beyond Milan Criteria	-	-	66.4% ²	P
Takada, et al. ⁽⁵⁷⁾	2007	33	≤ 10 tumors and all ≤ 5 cm	-	-	93% ²	R
Hwang, et al. ⁽²⁰⁾	2005	62	Any tumor beyond Milan Criteria	-	62.6%	-	P
Kneteman, et al. ⁽²⁵⁾	2004	21	1 nodule < 7.5 cm any number < 5 cm	90.5%	-	83% (4y)	R
Todo, et al. ⁽⁶¹⁾	2007	171	Any tumor beyond Milan Criteria	75% / 64.9% ²	60.4% / 52.6% ²	-	NA
Roayaie, et al. ⁽⁴⁵⁾	2002	32	1 or more nodules 5 to 7 cm	-	-	55% ²	R

n = number of patients transplanted during each study

Staging refers to the method used for tumor staging = P = pretransplant radiology; R = explant tumor pathology; NA = not available

* pathology based // ² Recurrence free rate

TABLE 2. Comparison of patient survival rate and tumor recurrence free rate between University of California San Francisco (UCSF) and Milan Criteria

Author (year), <i>Institute</i>	n		Staging (P)	3-year				5-year			
				UCSF		Milan		UCSF		Milan	
	UCSF	Milan		PS	RR	PS	RR	PS	RR	PS	RR
Yao, et al. (2001) ⁽⁶³⁾	14	46	-	-	-	-	-	73%	-	72%	-
Decaens T, et al. (2006) ⁽¹⁰⁾	44	279	R (0.10) ^{ITT} / (0.14) ²	-	-	-	-	45.60% ^{ITT}	47.80%	60.10% ^{ITT}	60.40%
	39	184	P (0.33) ¥/(0.26) ²	-	-	-	-	63.60%	62.70%	70.40%	70.20%
Yao, et al. (2007) ⁽⁶⁶⁾	38	130	R (0.58) ²	-	-	-	-	82%	93.60%	80%	90.10%
Duffy, et al. (2007) ⁽¹¹⁾	185	173	R (0.061)	74%	-	-	-	64%	-	79%	-
	208	126	P (0.057)	83%	-	-	-	71%	-	86%	-
Lee SG, et al. (2008) ⁽²⁶⁾	10	152	P (0.953)	90%	-	-	-	78.80%	-	76%	-
Xiao L, et al. (2009) ⁽⁶²⁾	32	68	P (0.058) ¥/ (0.103) ²	55.2%	40%	88.40%	81.80%	-	-	-	-

ITT = intention to treat

¥ = patient survival (PS)

² = recurrence free rate (RR)

Staging refers to the method used for tumor staging. P = pretransplant radiology; R = explant tumor pathology; NA = not available

in Japan⁽³¹⁾. Surgical treatments are accepted as the standard of care for early tumors because they provide survival rates consistently better than their untreated counterparts (5-years survival rates of 40%-70% vs < 20%)^(6, 31, 33, 34). Resection of single tumors in patients with well-preserved liver function lead to remarkable outcomes (5-years survival exceeds 50%-60%)⁽³⁴⁾. Early results after OLT in unselected patients with cirrhosis and HCC were poor, with early recurrence rates and 5-year survival of only 18%-49%^(15, 21, 30, 37, 41, 43, 44, 46). Several small studies in the early 1990s suggested that recurrence-free survival could be improved by restricting transplantation to patients with two-three nodules or a single tumor < 3-5 cm in diameter^(1, 14, 51). Two large retrospective studies^(21, 24) confirmed that tumors > 5 cm had a high rate of post-transplantation recurrence, largely because of the association with vascular invasion and poor differentiation.

The MC is considered the gold standard for selection of the best HCC candidates for OLT after numerous external validations of the seminal proposed⁽³⁹⁾. In fact, the MC as a restriction selection for patients with HCC have been confirmed as consistent by several other groups among more than 1,000 patients^(2, 22, 29). The MC were subsequently used by the United Network for Organ Sharing to assign the listing priority of patients presenting HCC.

On the other hand, some studies have recently suggested that the MC might be too restrictive, with relatively good results achieved when different proposals are used (Table 1).

There are essential aspects that should be considered when treatments related to HCC are evaluate: (1) treatments that achieve survival rates higher than 50% in 5-years are considered effective therapies, given the fact that studies have demonstrated the 3-years survival of early HCC to be about 50%^(5, 32); (2) the deleterious impact of the progressive increase in the waiting list time has to be considered when the efficacy of OLT as a treatment for HCC is evaluated because of the risk of tumor progression and death during this period^(33, 63),

and (3) it is well known that preoperative imaging techniques underestimated HCC staging in about 20% of cases, and thus the extrapolation of the histopathologic data to the preoperative scenario might be misleading⁽⁷⁾.

Yao et al.⁽⁶⁴⁾ from UCSF, reported a 5-year survival of 75% in patients with single tumor as large as 6.5 cm or a maximum of three tumors up to 4.5 cm and a cumulative tumor burden < 8 cm. With mostly retrospective data, some groups have independently tested these criteria^(10, 11, 37). These results have, however, been challenged because of the use of explants pathology, rather than preoperative imaging, as a determinant for the definition of the tumor stage.

The UCSF proposal is the approach mostly tested; however, it has been challenged because of the use of explants pathology. Duffy et al.⁽¹¹⁾ and Yao et al.⁽⁶⁴⁾ recently published their results analyzing the survival rates and recurrence probabilities on the basis of the pre-OLT radiologic assessment.

Expansion of tumor criteria for transplantation risks including patients with higher-grade tumors or microvascular invasion who might have a higher risk of recurrence. Indeed, as observed in previous reports, we found that tumors that exceeded the MC criteria were more likely to have evidence of vascular invasion in the explants^(21, 24). However, interestingly, this finding only affected recurrence-free survival when there were > five tumors or a single tumor > 6 cm. Thus, this may reflect tumor mass and the degree of vascular invasion rather than the presence of vascular invasion itself.

Several studies have shown that some tumor patients transplanted outside of the UNOS and MC survive longer^(9, 12, 16, 17, 18, 36, 44, 52) and as consequence, several proposals have been made to expand the HCC inclusion criteria^(18, 28, 63, 64, 65). However, the criteria proposed by the University of Pittsburgh and some groups in Europe are based, at least in part, on pathological features (nodal invasion, grade, vascular invasion) that are not usually available before transplantation^(9, 21, 50, 68). By contrast, the MC, UCSF and Onaca et al.⁽⁴²⁾ proposal rely on factors (tu-

mor size and number) that can be determined by preoperative imaging, however, such criteria must consider the limitations of imaging studies^(7, 23, 48, 55, 56, 59, 60). The continued improvement in imaging techniques may decrease the gap between imaging and pathology of HCC, although some understanding will certainly continue to exist⁽⁵³⁾.

Silva et al.⁽⁵⁴⁾ reported 281 cases of HCC in cirrhotic livers treated by OLT using a new criteria (up to three tumors, each no larger than 5 cm, and a cumulative tumor burden < 10 cm) with a 5-year survival rate of 57% based on the intention-to-treat principle. The 5-year survival rate was 63% among transplanted patients.

No difference in survival or in recurrence were found between cases within and beyond the UCSF criteria and others. Although these results suggest that this expansion does not result in an impaired outcome, we understand that they need validation, given the relatively small number of patients. Microvascular invasion was the only factor that predicted poor survival in the multivariate analysis. Indeed, several studies have shown that the differentiation degree and microvascular

invasion represent direct indicators of the biologic progression of HCC, being associated with tumor recurrence and poor long-term survival^(9, 11, 18, 39, 40, 45).

Expansion of transplantation inclusion criteria should be made cautiously. Listing criteria for HCC should reflect the minimum acceptable recurrence-free survival rate and must reflect a consensus of transplantation community. Furthermore, the results need to be confirmed prospectively if criteria were liberalized to ensure that an unrecognized selection bias did not influence the results themselves. Finally, the societal benefit of expanding tumor criteria needs to be weighed against a relatively fixed donor organ supply and a growing demand for OLT for other indications, such as decompensated cirrhosis due to chronic hepatitis C, where long-term survival may be better.

In conclusion, the EMC is useful attempt for widening the preexistent protocol for patients with HCC in the waiting-list for OLT, however there is no significant difference in patient survival rate and tumor recurrence free rate from those patients that followed the MC.

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RESUMO – *Contexto* - Em pacientes bem selecionados, o transplante ortotópico de fígado é um excelente tratamento para pacientes com carcinoma hepatocelular. Algumas instituições atualmente tendem a expandir os critérios de Milão. São os chamados Critérios de Milão Expandidos, que incluem tumores maiores do que 5 cm e também aqueles associados com múltiplos tumores, não maiores do que 3 cm, a fim de beneficiar o maior número possível de pacientes submetidos ao transplante ortotópico de fígado. *Métodos* - Os dados foram coletados na base de dados do PubMed. A palavra-chave para procura foi Critérios de Milão expandidos, no período de 2000 a 2009. Foram excluídos 19 trabalhos devido à falta de dados de sobrevida e à recorrência tumoral, não compatíveis com a língua inglesa e fora do assunto em questão. Foram analisadas a sobrevida do paciente e a taxa de recorrência do tumor de 1 a 5 anos de pacientes submetidos ao transplante hepático com critérios de Milão expandidos em diferentes centros internacionais. *Resultados* - Esta revisão agregou 23 trabalhos. Catorze diferentes critérios foram encontrados e descritos em detalhes. No entanto, os critérios da Universidade da Califórnia em São Francisco foram os mais estudados entre todos os analisados. *Conclusão* - Os Critérios de Milão Expandidos são úteis para ampliar os protocolos para adesão de doentes na lista de espera para transplante de fígado, não havendo diferença significativa na sobrevida do doente e nem na taxa livre de recorrência tumoral quando comparados aos critérios de Milão.

DESCRITORES – Transplante de fígado. Carcinoma hepatocelular. Seleção de pacientes. Critério de Milão expandido.

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