Liver transplantation according to Milan criteria an overview of the past ten years

Transplante de fígado de acordo com os critérios de Milão: revisão dos últimos 10 anos

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ABSTRACT: Background: Orthotopic liver transplantation (OLT) remains an excellent treatment approach for HCC in well-selected candidates. Milan Criteria (MC) (a single tumor up to 5cm or up to 3 tumors none larger than 3.0 cm) is the most widely used criteria for selection of those patients. Our aim is to study the current situation of the MC focusing on patient survival and tumor recurrence free rate from 1 to 5-yrs after OLT over the past 10 years. Material and Methods: We have reviewed 59 papers published between 2000-2009; from Asia (42.3%), Europe (33.9%) and North America (20.4%). 5.525 patients have undergone OLT within MC. The overall patient survival rate and tumor recurrence free rate from 1 to 5-yrs were analyzed. Results: Overall patient survival rates were 1 year (87.26%), 2 years (81.95%), 3 years (77.47%), 4 years (75.24%) and 5 years (72.41%). We have found tumor recurrence free rate of 80.29% and 71.36% at 1 and 5-yrs, respectively. Conclusion: MC has come to simplify the indication for LT in patients with HCC. The best patient survival rate at 1 and 5 years were in North America (88%) and Asia (76,6%), respectively. On the other hand, Europe had the best tumor recurrence free rate at 5 years (91.8%).

KEYWORDS: Liver transplantation/standards; Carcinoma hepatocelular/terapia; Follow-up-studies.

RESUMO: Introdução: O transplante de fígado (TF) continua sendo o melhor tratamento para pacientes, bem selecionados, portadores de carcinoma hepatocelular. Os critérios de Milão (CM) (tumor único até 5 cm e 3 tumores não maiores que 3 cms) são os critérios mais usados para estes pacientes. Nosso objetivo é avaliar a situação atual dos CM principalmente a sobrevida do paciente e a taxa livre de recorrência tumoral após 1 a 5 anos do TF, nos últimos 10 anos. Material e Métodos: Revisamos 59 trabalhos entre 200-2009; da Asia (42,3%), Europa (33,9%) e da América do Norte (20,4%). 5.525 pacientes submeteram-se ao TF com os CM. A sobrevida total dos pacientes e a taxa livre de recorrência tumoral foram analisados. Resultados: A taxa de sobrevida total dos pacientes foi em 1 ano de (87,26%), 2 anos (81,95%), 3 anos (77,47%), 4 anos (75,24%) e 5 anos (72,41%). A taxa livre de recorrência tumoral foi de 80,29% e 71,36% em 1 e 5 anos, respectivamente. Conclusão: A melhor taxa de sobrevida dos pacientes foi na América do Norte (88%) e na Asia (76,6%), respectivamente. Por outro lado, a Europa teve a melhor taxa livre de recorrência de doença em 5 anos (91,8%).

DESCRITORES: Transplante de fígado/normas; Carcinoma hepatocelular/terapia; Seguimentos.

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INTRODUCTION

The most effective treatment options for hepatocellular carcinoma (HCC) are liver resection (LR) and orthotopic liver transplantion (OLT). However, LR is related with unsatisfactory high recurrence rate due to the fact tha it usually eliminates the tumor but not the underlying liver disease. On the other hand, OLT remains an excellent treatment approach for HCC in well-selected candidates[1,2].

The most widely used criteria for patient selection are those proposed by Mazzaferro et al.[3], the so-called Milan criteria (MC), (a single tumor up to 5cm or up to 3 tumors none larger than 3.0 cm). When MC were applied there was a significant improvement in survival over time mainly for HCC patients undergoing OLT. Currently, the 5-yr patient survival rate with MC is 61.1% contrasting with previously observed rate of 25.3% in 1987.

Our aim is to study the current situation of the MC focusing on patient survival and tumor recurrence free rate from 1 to 5-yrs after OLT over the past 10 years.

MATERIAL AND METHODS

The data collected was based on the online database PUBMED. The key words applied on the search were MC, OLT and HCC limited to the period from 2000 to 2009.

We have found 477 articles in total, out of 59 fulfilled our inclusion criteria: a) Papers that studied patients meeting Milan Criteria (single lesion smaller than 5 cm or up to 3 lesions smaller than 3 cm) and undergoing liver transplantation; b) Papers that reported both overall patient survival and tumor recurrence free rate in 1, 2, 3, 4 or 5 years.

Living donor or donor after cardiac death liver transplantation as well as radiological or pathological analysis, tumor size, gender and age were not considered in our search method.

RESULTS

Review of overall patient survival rate and tumor recurrence free rate on the 1st, 2nd, 3rd, 4th and 5th years in patients undergoing OLT for HCC within Milan Criteria are shown in Table 1.

Table 1. Review of overall patient survival rate and tumor recurrence free rate on the 1st, 2nd, 3rd, 4th and 5th years in patients undergoing OLT for HCC within Milan criteria

					Patient Survival Rate (%)					Tumor Reccurrence Free Rate (%)				
Ref	Author	Year		N	1st	2nd	3rd	4th	5th	1st	2nd	3rd	4th	5th
1	Jonas et al.	2001	Europe	120	**90**	NR	NR	NR	**71**	NR	NR	NR	NR	NR
2	Parolin et al.	2001	South America	8	NR	NR	NR	NR	NR	**75**	**37,5**	NR	NR	NR
3	Yao FY et al.	2002	North America	46	**91**	**81**	NR	NR	**72**	NR	NR	NR	NR	NR
4	Khakhar A et al.	2003	North America	22	**89,1**	NR	**80,2**	NR	**70,2**	NR	NR	NR	NR	NR
5	Fernández JA et al.	2003	North America	33	**82**	NR	NR	NR	**68**	NR	NR	NR	NR	NR
6	Kaihara S et al.	2003	Asia	31	NR	**87,4**	NR	NR	NR	NR	NR	NR	NR	NR
7	Kneteman NM et al.	2004	North America	19	**94.1**	NR	NR	**87.4**	NR	NR	NR	NR	NR	NR
8	Sun PL et al.	2004	Asia	12	NR	NR	NR	NR	NR	**92**	**73**	NR	NR	NR
9	Todo S et al.	2004	Asia	138	**81.2**	NR	**78.7**	NR	NR	NR	NR	NR	NR	NR
10	Santoyo J et al.	2005	Europe	30	**80**	NR	**70**	NR	**70**	NR	NR	NR	NR	NR
11	Merli M et al.	2005	Europe	49	**90**	**85**	NR	NR	NR	NR	NR	NR	NR	NR
12	Herber S et al.	2005	Europe	17	NR	NR	NR	NR	NR	**93,3**	NR	**82,5**	NR	**82,5**
13	Tanaka H et al.	2005	Asia	279	NR	NR	NR	NR	NR	**84**	**62**	**49**	NR	**29**
14	Cheng YF et al.	2005	Asia	12	NR	NR	**79**	NR	NR	NR	NR	NR	NR	NR
15	Malago M et al.	2006	Europe	17	NR	**70**	NR	NR	NR	NR	NR	NR	NR	NR
16	Yokoi H et al.	2006	Asia	11	**83**	**72**	NR	NR	NR	NR	NR	NR	NR	NR
17	Shah SA et al.	2006	North America	118*	NR	NR	NR	NR	NR	NR	NR	NR	NR	**78**
17	Shah SA et al.	2006	North America	67**	NR	NR	NR	NR	NR	**95**	**88**	**88**	**85**	**85**
18	Wai CT et al.	2006	Asia	22	**91**	NR	**76**	NR	NR	NR	NR	NR	NR	NR
19	Kishi Y et al.	2006	Asia	29	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
20	Decaens T et al.	2006	Europe	279	**87**	**82**	**78**	**72**	**70**	NR	NR	NR	NR	NR
21	Yang SH et al.	2006	Asia	26	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
22	Kim DY et al.	2006	Asia	57	**86**	NR	**72**	NR	**67**	NR	NR	NR	NR	NR
23	Oya H et al.	2006	Asia	8	NR	NR	NR	NR	NR	**50**	**50**	**50**	NR	NR

Continua

Table 1. Review of overall patient survival rate and tumor recurrence free rate on the 1st, 2nd, 3rd, 4th and 5th years in patients undergoing OLT for HCC within Milan criteria *Continuação*

					Patient Survival Rate (%)					Tumor Reccurrence Free Rate (%)				
Ref	**Author**	**Year**		**N**	**1st**	**2nd**	**3rd**	**4th**	**5th**	**1st**	**2nd**	**3rd**	**4th**	**5th**
24	de Luque DP et al.	2006	Europe	81	**80**	NR	**67**	NR	**61**	**60**	**30**	**10**	**10**	**10**
25	Toso C et al.	2007	North America	34	**85**	NR	NR	**73**	NR	**85**	NR	NR	**73**	NR
26	Soejima Y et al.	2007	Asia	20	NR	NR	NR	NR	NR	**100**	**100**	**100**	NR	NR
27	Shah AS et al.	2007	North America	155	**87**	NR	**74**	NR	**65**	NR	NR	NR	NR	NR
28	Parfitt JR et al.	2007	North America	50	NR	NR	**83**	NR	**83**	NR	NR	NR	NR	NR
29	Cillo U et al.	2007	Europe	60	**95**	NR	**85**	NR	NR	NR	NR	NR	NR	NR
30	Poon RT et al.	2007	Asia	43	NR	NR	NR	NR	**81**	NR	NR	NR	NR	**84**
31	Onaca N et al.	2007	North America	631	NR	NR	NR	NR	NR	**84,7**	NR	NR	NR	**61,8**
32	Shah AS et al.	2007	North America	110	**90**	NR	**70**	NR	**64**	NR	NR	NR	NR	**79**
33	Shen ZY et al.	2007	Asia	97	**92**	**87,2**	**86,4**	**86,4**	**86,4**	NR	NR	NR	NR	NR
34	Hwang S et al.	2007	Asia	3	NR	**33**	NR	NR	NR	NR	NR	NR	NR	NR
35	Baccarani U et al.	2007	Europe	48	NR	NR	**79**	NR	**74**	NR	NR	**74**	NR	**74**
36	Bozorgzadeh A et al.	2007	North America	37	**81,1**	NR	**57,04**	NR	**49,3**	NR	NR	NR	NR	NR
37	Facciuto ME et al.	2008	North America	66	**92**	NR	NR	**62**	NR	NR	NR	NR	NR	NR
38	Castroagudín JF et al.	2008	Europe	98	**85,1**	NR	**78,3**	NR	**70,1**	NR	NR	NR	NR	NR
39	Silva M et al.	2008	Europe	231	**85**	NR	**74**	NR	**72**	NR	NR	NR	NR	NR
40	Andorno E et al.	2008	Europe	108	**87,02**	NR	**74,53**	NR	**65,93**	NR	NR	NR	NR	NR
41	Lee SG et al.	2008	Asia	164	**86,6**	NR	**79,4**	NR	**76**	NR	NR	NR	NR	NR
42	Zheng SS et al.	2008	Asia	72	**94,3**	NR	**78,3**	NR	**78,3**	**87,3**	NR	**74**	NR	**69,7**
43	Ravaioli M et al	2008	Europe	88	**86**	NR	**77**	NR	**72**	NR	NR	NR	NR	NR
44	Li J et al.	2009	Asia	24	NR	**88,5**	NR	NR	**88,5**	NR	NR	NR	NR	NR
45	Chen JW et al.	2009	Oceania	112	**88,4**	NR	**79,5**	NR	**74,3**	NR	NR	NR	NR	NR
46	Vakili K et al.	2009	Asia	21	NR	NR	NR	NR	**87,1**	NR	NR	NR	NR	NR
47	Kuo WT et al.	2009	Asia	14	**92,9**	NR	**92,9**	NR	NR	NR	NR	NR	NR	NR
48	Jang JW et al.	2009	Europe	37	**89,2**	**70,3**	NR	NR	**54,6**	NR	NR	NR	NR	NR
49	Scatton O et al.	2009	Asia	279	NR	NR	NR	NR	**70**	NR	NR	NR	NR	NR
50	Takada Y et al.	2009	Asia	74	NR	NR	NR	NR	**75**	NR	NR	NR	NR	NR
51	Fujiki M el al.	2009	Asia	79	NR	NR	NR	NR	**77**	NR	NR	NR	NR	NR
52	Xiao L et al.	2009	Asia	68	NR	NR	**88,4**	NR	NR	NR	NR	**85,3**	NR	NR
53	Muscari F et al.	2009	Europe	73	NR	NR	NR	NR	**79**	NR	NR	NR	NR	NR
54	Di Sandro S et al.	2009	Europe	126	NR	NR	**81,93**	NR	**75,43**	NR	NR	**91,29**	NR	**90,37**
55	Fan J et al.	2009	Asia	394	**86,6**	NR	NR	NR	**78,8**	**65,2**	NR	NR	NR	**55,7**
56	Sánchez Antolín G et al.	2009	Europe	42	NR	NR	NR	**88,1**	NR	NR	NR	NR	NR	NR
57	Santoyo J et al.	2009	Europe	144	NR	NR	NR	NR	**65**	NR	NR	NR	NR	NR
58	Qasim A et al.	2009	Europe	15	**96**	NR	NR	NR	**84**	NR	NR	NR	NR	NR
59	Mazzaferro V et al.	2009	Europe	444	NR	NR	NR	NR	**73,3**	NR	NR	NR	NR	**94,5**

OLT: orthotopic liver transplantation; HCC: hepatocellular carcinoma; Ref: Reference; NR: Not Reported, *Radiological Criteria; **Patological Criteria

From 2000 to 2009, 5525 patients have undergone liver transplantation within MC. Europe (38.1%) and Asia (35.8%) contributed with more than 70% of these patients while the others 30% have came from North America (23.9%) and Oceania (2%), Figure 1.

One year global overall patient survival rates was 87.2%, 2nd year- 81.9%, 3rd year- 77.4%, 4th year- 75.2% and 5th year -72.4%, Figure 2.

One year patient survival rates were similar in North America, Europe, Asia and Oceania, while five year overall patient survival rate was slightly better in Asia (76.6%), Figure 3.

Europe had the best one and five years overall patient survival rates 86.7% and 70.9% respectively, Figure 3. North America had the best one year tumor recurrence free rate (85.6%) whereas Europe had the best five years tumor recurrence free rate (91.8%), Figure 4.

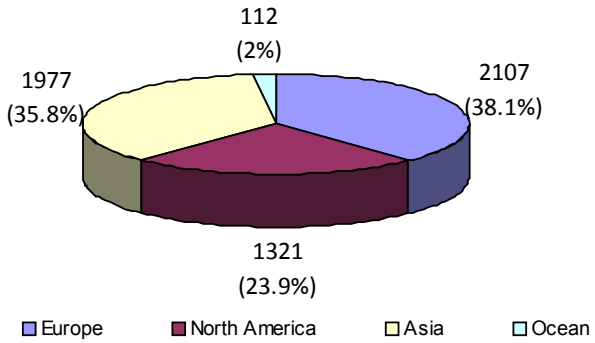

Figure 1. Number of patients by continent: Europe (2107), North America (1321), Asia (1977), and Oceania (112)

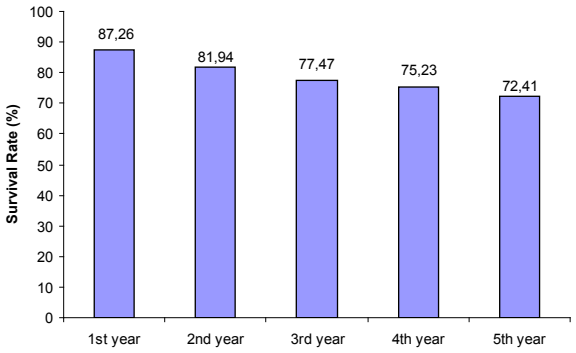

Figure 2. Global patient survival rate: 1 year (87.26%), 2 year (81.94%), 3 year (77.4%), 4 year (75,23%) e 5 year (72,41%)

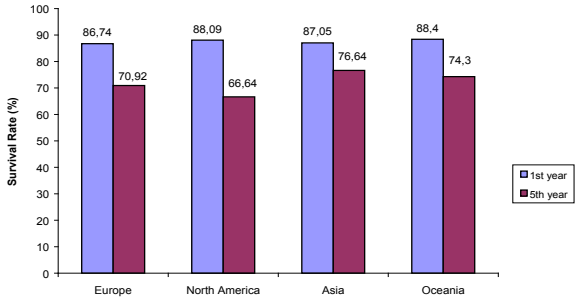

Figure 3. Overall patient survival rates from 1 to 5 year (by continent)

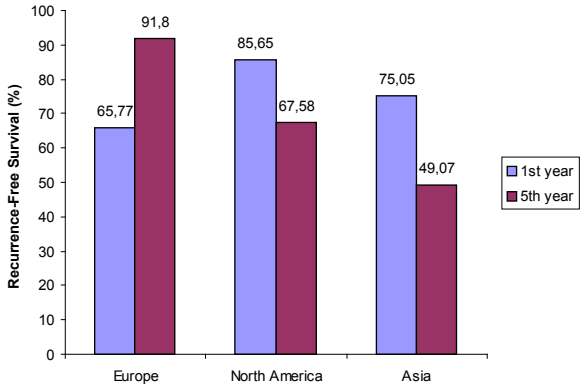

Figure 4. Tumor recurrence free survival rates from 1 to 5 year (by continent)

DISCUSSION

HCC is a major health problem worldwide[4]. 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 in Japan[4]. Surgical treatments are accepted as the standard of care for early tumors because they provide survival rates consistently better than their untreated counterparts (5-yrs survival rates of 40-70% vs. < 20%)[4,5,6,7].

Resection of single tumors in patients with well-preserved liver function lead to remarkable outcomes (5-yrs survival exceeds 50-60%)[28]. 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%[8-16]. Several small studies in the early 1990s suggested that tumor recurrence-free survival could be improved by restricting transplantation to patients with 2-3 nodules or a single tumor < 3-5 cm in diameter[17-19]. Two large retrospective studies confirmed that tumors > 5 cm had a high rate of post-transplantation recurrence, largely because of the association with vascular invasion and poor differention[15,20].

The MC is considered the gold standard for selection of the best HCC candidates for OLT after numerous external validations of the seminal proposed[3]. 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[21-23]. The MC were subsequently used by the United Network for Organ Sharing to assign the listing priority of patients presenting HCC.

CONCLUSION

MC has come to simplify the indication for LT in patients with HCC. The best patient survival rate at 1 and 5 years were in North America (88%) and Asia (76.6%), respectively. On the other hand, Europe had the best tumor recurrence free rate at 5 years (91.8%).

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