

ORIGINAL ARTICLE

The estimated number of patients with hepatocellular carcinoma selected for liver transplantation using expanded selection criteria

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Summary

Recently, several groups have introduced expanded criteria for selection of patients with hepatocellular carcinoma (HCC) prior to transplant, but the exact number of potential newly recruited patients remains unclear. This registry-based study assessed 270 patients diagnosed with HCC. The potential number of transplant candidates was based on age (≤ 65 years), absence of metastases and macro-vascular invasion, and on 12 previously published, expanded selection criteria. A wide range of increase in the number of transplant candidates was observed (12–63% when compared with the number of such candidates who would have been selected solely based on the Milan criteria). The most conservative criteria were Seoul (Kwon, 2007; increase of 12%), Valencia (Silva, 2008; 16%), total tumor volume/alpha-fetoprotein (Toso, 2009; 20%) and UCSF (Yao, 2007; 20%). This data will assist Centers and policy agencies in predicting the need for resources linked to an expansion of criteria.

Introduction

Since the publication of the Milan criteria in 1996, transplantation has been recognized as the best treatment for patients with small non resectable hepatocellular carcinoma (HCCs) [1]. If strictly adhered to these criteria, excellent outcomes can be achieved with 5-year survival rates between 70% and 90%, and most centers have adopted this score to select transplant candidates [1–17].

Several studies however have now demonstrated that the Milan criteria are too restrictive and that favorable outcomes can be achieved following more liberal selection policies [11,18]. The group at the University of California, San Francisco (UCSF), was the first to propose expanded criteria [2]. While validated by other centers [4,19–21], the UCSF criteria have failed to gain unanimous recognition, possibly because they exclude patients with more than three HCCs (even when of small size and with expected favorable outcomes) and include patients with large tumors (up to 6.5 cm in diameter), which have

been associated with decreased post-transplant outcomes [22–24]. In addition, a large multicenter study has suggested decreased post-transplant outcomes in patients selected based on the Milan criteria and the UCSF expanded criteria [20]. As a consequence, many other groups have proposed alternative morphologic scores to select transplant candidates (Table 1) [3,5–15,17]. The backbone of most of these scores is a combination of HCC size and number, with or without the addition of alpha-fetoprotein (AFP) or tumor grade. We recently introduced the concept of total tumor volume (TTV ≤ 115 cm³) for patient selection, and demonstrated similar outcomes to Milan and UCSF criteria, but with the inclusion of more patients [15,17].

The acceptance of new and modified expanded selection criteria should be based on the observation that the newly recruited patients (beyond Milan, but within the new score) have stable and acceptable post-transplant outcomes when compared with those within Milan criteria. Beside this, it is important for Centers and policy

Table 1. Selected transplant criteria.

Original author (year), abbreviation	Criteria	Reported 5-year patient survival (no. patients)	Reference
Mazzaferro (1996), Milan	1 HCC \leq 5 cm or \leq 3 HCC \leq 3 cm	85%* (35)	[1]
Yao (2001), UCSF	1 HCC \leq 6.5 cm or \leq 3 HCC \leq 4.5 cm with cumulated diameter \leq 8 cm	Milan: 72% (46) EC: 73% (14)	[2]
Herrero (2001), CUN	1 HCC \leq 6 cm or \leq 3 HCC \leq 5 cm	Milan: 70% (59) EC: 73% (26)	[3,10]
Yao (2007), UCSF	Same as Yao (2001)	Milan: 80%† (130) EC: 82%† (38)	[4]
Onaca (2007), Dallas	1 HCC \leq 6 cm or \leq 4 HCC \leq 5 cm	Milan: 62%† (628) EC: NA (130)	[5]
Kwon (2007), Seoul	HCC \leq 5 cm without # restriction and AFP \leq 400 ng/ml	Milan: 80% (99) EC: NA	[6]
Sugawara (2007), Tokyo	\leq 5 HCC \leq 5 cm	Milan: 94%‡ (68) EC: NA (4)	[7]
Takada (2007), Ito (2007), Kyoto	\leq 10 HCC \leq 5 cm	Milan: 73% (74) EC: NA (33)	[8,9]
Zheng (2008), Hangzhou	Total tumor diameter \leq 8 cm or HCC grade I or II and AFP \leq 400 ng/ml	Milan: 76% (152) EC: NA (22)	[12]
Lee (2008), Asan	\leq 6 HCC \leq 5 cm	Milan: 78.3% (72) EC: NA (26)	[13]
Silva (2008), Valencia	\leq 3 HCC \leq 5 cm with cumulated diameter \leq 10 cm	Milan: 62% (231) EC: NA (26)	[14]
Toso (2008), TTV	TTV \leq 115 cm ³	Milan: 78% (157) EC: 72% (94)	[15]
Mazzaferro (2009), Up-to-seven	Number + maximum size of HCC = 7	Milan: 73% (444) EC: 71% (283)	[16]
Toso (2009), TTV/AFP	TTV \leq 115 cm ³ and AFP \leq 400 ng/ml	Milan: 71%‡ (6268) EC: 65%‡ (169)	[17]

*Four-year survival; †recurrence-free survival; ‡3-year survival.

EC, beyond Milan and within expanded criteria; TTV, total tumor volume; AFP, alpha fetoprotein; NA, not available.

agencies to be able to predict the need for resources linked to an expansion of criteria, as this has the potential to impact the work load as well as the need for alternative sources of organs, including live donors or donors after cardiac death. This study examined the estimated impact of various previously proposed expanded criteria on the number of newly recruited transplant candidates.

Methods

This study was based on data from the Alberta Cancer Registry (ACR), which is a population-based registry, which records and maintains data on all new cancer cases and deaths occurring within the province of Alberta, Canada. It is operated by the Alberta Cancer Board's Division of Population Health and Information and is mandated by the Cancer Programs Act of Alberta. It is mandatory for all physicians in Alberta to contribute complete data on all cancer patients to the database. The ACR has met the Gold Standard for Registry Certification for the years included in the study, representing the high-

est North American Association for Central Cancer Registries standard for complete, accurate, and timely data (including completeness of data of 95% or higher, <http://www.naacrr.org>). This study has been reviewed and approved by the Health Research Ethics Board at the University of Alberta.

All patients, diagnosed with HCC between January 2003 and December 2006 in Northern Alberta (Edmonton area, 1.6 million inhabitants in 2006) were included. Data from the ACR included basic demographic (identifier, gender, date of birth, date of death) and cancer-related information (date of HCC diagnosis, modality of diagnosis including radiology, histology or postmortem, and histologic grade when available). The registry database was completed by a chart review assembling data on the cause of underlying liver disease, size and number of HCCs, AFP level and administration of a local HCC treatment, including surgical resection, transarterial chemoembolization (TACE), ethanol injection or radiofrequency ablation (RFA). Charts were available on all patients.

The morphologic staging was assessed from reports of ultrasound, contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging. A lesion was considered an HCC, when it demonstrated an arterial enhancement with wash-out on delayed images, or when significant increase in size was documented. A stable, non enhancing small lesion was not considered as HCC. Morphologic and AFP data were recorded from the time of diagnosis to the end of follow-up (defined as death or September 2008). A successful down-staging after local HCC treatment was defined as the absence of enhancement around the site of ablation for at least 3 months, as described by Yao *et al.* [11,25]. Of note, the policy in place in the region was to offer local HCC treatment any time tumor characteristics and general patient condition allowed.

Potential candidates for transplantation were defined as ≤ 65 years of age and without metastases or large liver vessel tumor invasion. Following this preliminary candidate selection, further assessments were performed according to previously proposed selection criteria summarized in Table 1. We first included all potential candidates in the analysis. In a subsequent model, we excluded patients with preserved hepatocellular function, who have undergone HCC resection, assuming that they would be better treated by this modality (resection was the first choice when feasible). The impact of down-staging was also further estimated.

Results were provided as mean \pm standard deviation. Categorical tables and Chi-squared tests were used to compare criteria. Standard alpha level of 0.05 indicated statistical significance. Analyses were conducted using SPSS 15.0 (SPSS, Chicago, IL, USA).

Results

During the 4-year study-period, 270 patients were diagnosed with HCC in Northern Alberta, representing an incidence of 4.2/100 000 inhabitant-year. Of them, 129 (48%) were >65 years of age and were not considered potential transplant candidates (Fig. 1). Of the remaining 141 patients, 14 (10%) had radiologic evidence of major vascular invasion, six (4%) had metastases and two (1.5%) had both macro-vascular invasion and metastases. In addition, 11 patients had incomplete data, attributable to either very advanced tumors and/or death directly after diagnosis, and therefore were not included in the analysis. Of note, they would not have been transplant candidates.

The remaining 108 patients with HCC, with complete data, were further considered for transplantation (Table 2). This group comprised 81% male patients, with a mean age of 55 ± 5 years. The most frequent cause of underlying liver disease was related to hepatitis C virus

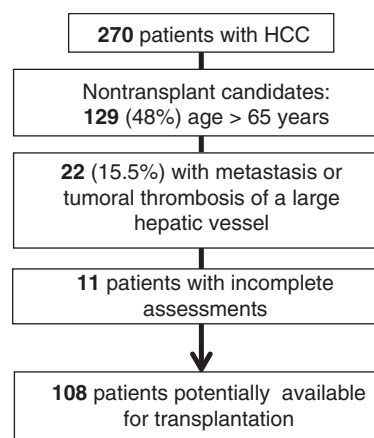


Figure 1 Selection of potential transplant candidates with hepatocellular carcinoma (HCC).

Table 2. Characteristics of potential transplant candidates.

Patients (number)	108
Mean age (years)	55 ± 5
Gender	Female:20/male:88
Cause of liver disease (%)	
HCV (\pm alcohol, \pm HBV)	62 (57)
Alcohol	12 (11)
HBV	14 (13)
Cryptogenic	8 (7.5)
NASH	1 (1)
Primary biliary cirrhosis	1 (1)
Hemochromatosis	2 (2)
Other	8 (7.5)
Local HCC treatment (%)	
Surgical resection	19 (16.5)
TACE	17 (15)
Ethanol injection	11 (9.5)
Radiofrequency ablation	8 (7)
None	60 (52)
Mean number of tumors (#)	2 ± 2
Mean diameter of the largest tumors (cm)	5 ± 4
Mean total diameter (cm)	7 ± 6
Mean total tumor volume (cm ³)	294 ± 904
Mean serum alpha fetoprotein level (ng/ml)	542 ± 1067
Serum alpha fetoprotein level >400 (%)	23 (21)

HCV, hepatitis C virus infection; HBV, hepatitis B virus infection; TACE, transarterial chemo-embolization.

infection (57%). The mean number of HCC was 2 ± 2 (range 1–9), mean diameter of the largest HCC 5 ± 4 cm (0.6–21) and mean TTV 294 ± 904 cm³ (0.11–7239). AFP demonstrated a wide range from 1 to 4500 ng/ml (mean 542 ± 1067 ng/ml).

Of the remaining 108 patients with HCC, 49 (45%) fulfilled Milan criteria. These potential transplant candidates within this criteria represented 18% of all patients diagnosed with HCC during the study period (49/270).

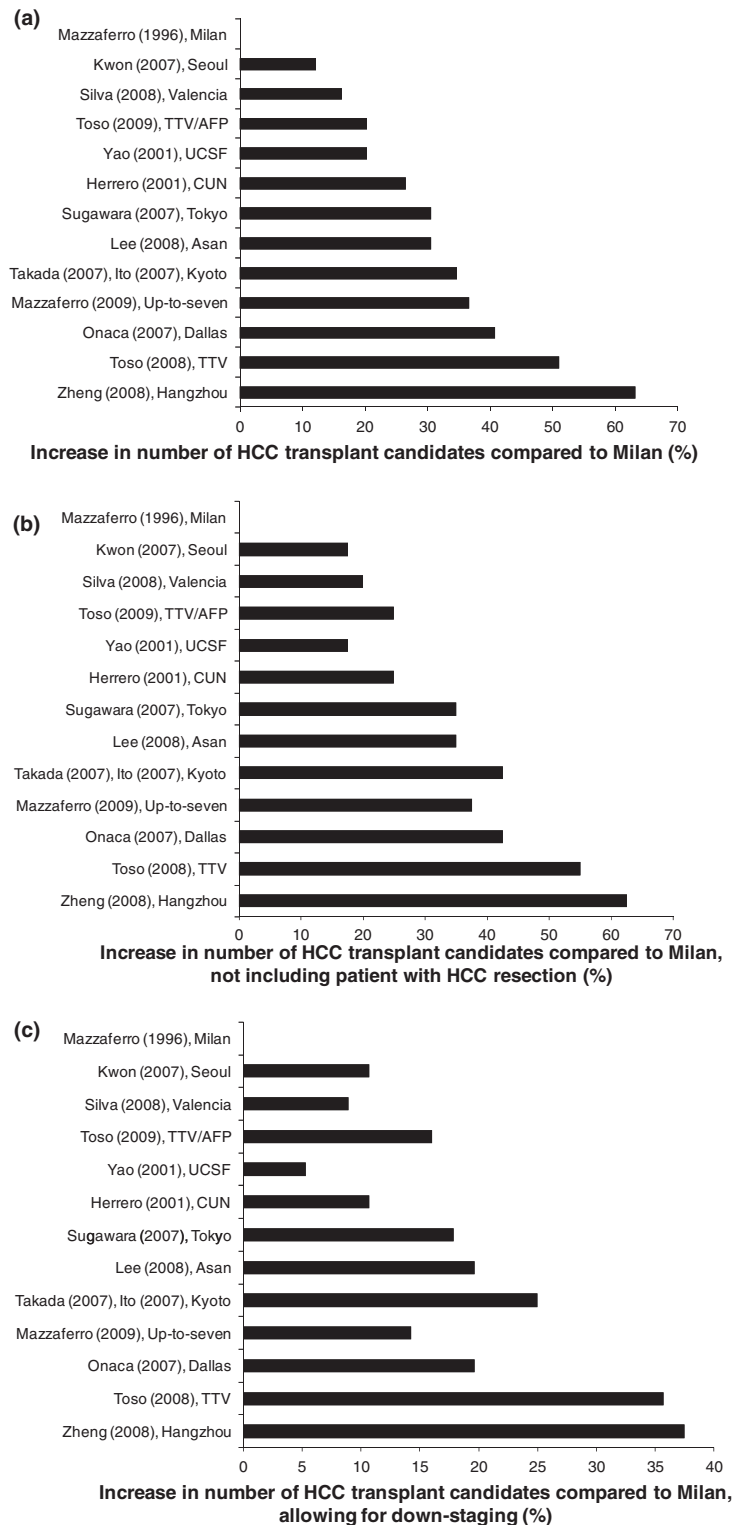


Figure 2 Estimated increase in the number of transplant candidates with hepatocellular carcinoma (HCC) as compared with the number of patients within the Milan criteria. The analysis described in (a) was performed using all patients with HCC, ≤65 year old and without evidence of macro-vascular invasion or metastases. The analysis in (b) excluded patients with preserved hepatocellular function, who had undergone HCC resection, assuming that they had attained cure by this modality. The estimate described in (c) allowed down-staging, defined as the absence of enhancement around the site of ablation for at least 3 months.

By applying the range of proposed modified expanded selection criteria, the number of potential transplant candidates increased by 12–63% when compared with the number of those who would have been selected under the application of the Milan criteria exclusively (Fig. 2a). The most conservative selections were performed with Seoul (increase of 12% compared with Milan), Valencia (16%), TTV/AFP (20%) and UCSF (20%) criteria.

In a subsequent analysis, patients who had undergone surgical resection of HCC were presumed to have been cured and were no longer considered for transplant (Fig. 2b). Once again, a wide range of increase was observed compared with the Milan criteria (17.5–62.5%) and the most conservative were the Seoul (17.5%), Valencia (20%), TTV/AFP (25%) and UCSF (17.5%) criteria.

Forty-eight patients (44%) underwent local HCC treatment. The impact of the expanded selection criteria was assessed allowing down-staging to any criteria (Fig. 2c). Seven patients were successfully down-staged to within the Milan criteria and remained stable for more than 3 months, increasing the number of potential candidates within the Milan criteria to 56. After down-staging, the number of potential transplant candidates was expanded by 5–38% compared with Milan. Once again, the most conservative were Seoul (5%), Valencia (7%), TTV/AFP (9%) and UCSF (5%) criteria.

In order to better understand the observed wide range of expansion in the number of potential transplant candidates, we plotted the allowed number of tumors and diameter for each criterion (Fig. 3). While the allowed

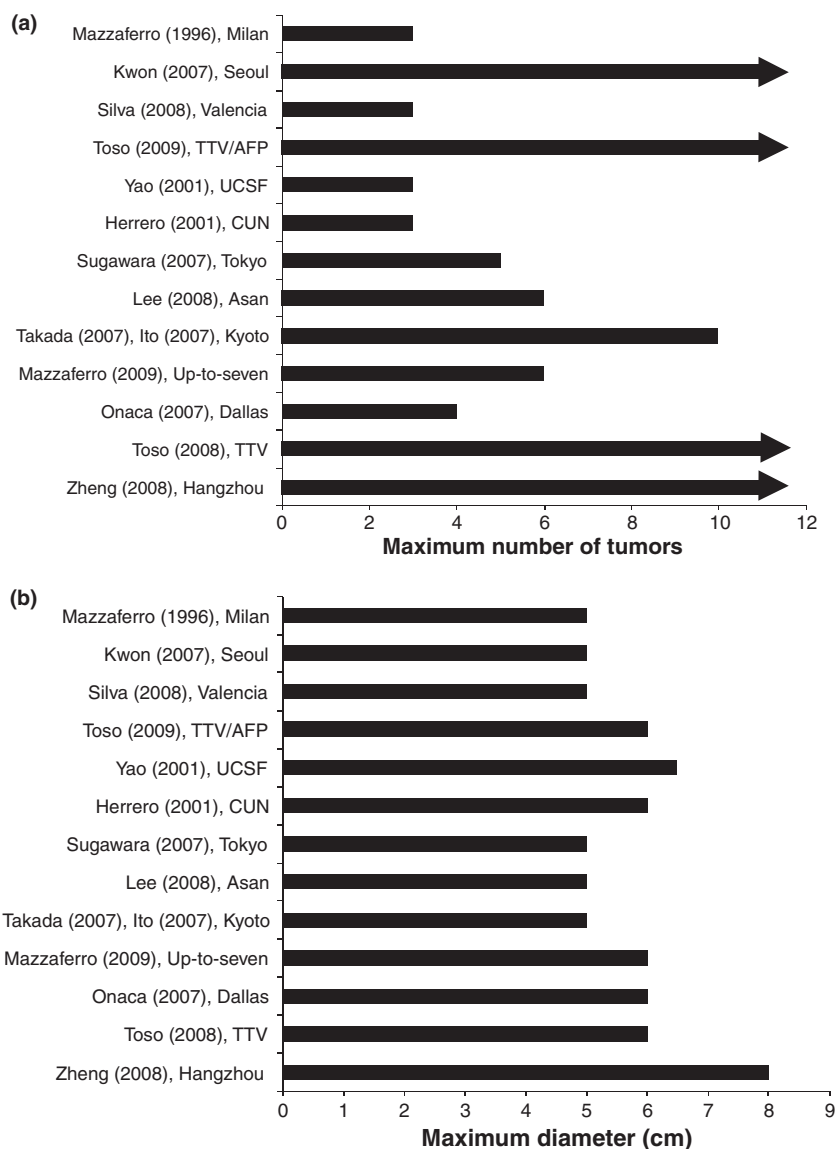


Figure 3 Allowed maximum number (a) of hepatocellular carcinoma (HCC) and HCC diameter (b) for the various studied criteria. The criteria were put in the same order as in Fig. 1. Arrows reflect the absence of a set upper limit.

maximum HCC diameter was consistently between 5 and 6 cm (except Hangzhou with 8 cm), a wide range of tumors number was allowed (from 3 to no restriction as to the upward number).

Discussion

This registry-based study estimates that the number of HCC transplant candidates would increase by 12–20% with the application of conservative (Seoul, Valencia, TTV/AFP and UCSF) and by up to 63% with less conservative (Hangzhou) selection criteria.

Until now, the expected number of newly recruited HCC transplant candidates could not be accurately predicted as most previous studies were retrospective or based on highly preselected patient populations. Conversely, this work provides an estimate of the potential HCC transplant candidate pool, utilizing all patients diagnosed with HCC within a defined region. Of note, the presently reported incidence of HCC (4.2/100 000) matches previous reports from similar populations, including all of Canada, the United Kingdom and the United States of America, with incidences <5/100 000 [26], which should be viewed as a validation of the quality of the ACR database.

While several factors could be accurately quantified (patient age, presence or absence of macro-vascular tumor invasion or of metastases), others like alcohol abstinence or the presence of medical co-morbidities were not taken into account. This is related to the fact that most patients included in this study, did not undergo a formal transplant assessment, and that these potential contra-indications could not be accurately identified. Both the alcohol abstinence and medical co-morbidities however are independent from the number and the size of HCCs. We can therefore be confident that patients with such contra-indications were distributed homogeneously within the studied population and that the reported rates of increase in the number of HCC transplant candidates were accurate.

The 12 expanded selection criteria that were studied lead to an extremely wide variety of increase in the number of transplant candidates with HCC. The most conservative ones, Seoul, Valencia, TTV/AFP and UCSF, induced an increase of 12–20% as compared with Milan [2,4,6,14,17]. Conversely, Dallas, TTV and Hangzhou criteria lead to 41–63% increase [5,12,15]. We believe that the selection of new expanded selection criteria should be based solely on the observation that the newly recruited patients (beyond Milan, but within the new score) have stable and acceptable post-transplant outcomes as compared with those within Milan criteria. As such, the data included in this study should not be viewed as arguments

to favor one score or the other. They will however help Centers and policy agencies in predicting potential increase in the number of transplants and the associated work load. Both will require appropriate planning, including potentially looking for alternative sources of organs such as live donors or donors after cardiac death.

Authorship

Designed research/study: C. Toso, D. Bigam, Collected data: C. Toso, Analyzed data: C. Toso, N. Kneteman, D. Bigam, Wrote the paper: C. Toso, N. Kneteman, J. Shapiro, D. Bigam.

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