Prospective Validation of the CLIP Score: A New Prognostic System for Patients With Cirrhosis and Hepatocellular Carcinoma

THE CANCER OF THE LIVER ITALIAN PROGRAM (CLIP) INVESTIGATORS*

Prognosis of patients with cirrhosis and hepatocellular carcinoma (HCC) depends on both residual liver function and tumor extension. The CLIP score includes Child-Pugh stage, tumor morphology and extension, serum alfa-fetoprotein (AFP) levels, and portal vein thrombosis. We externally validated the CLIP score and compared its discriminatory ability and predictive power with that of the Okuda staging system in 196 patients with cirrhosis and HCC prospectively enrolled in a randomized trial. No significant associations were found between the CLIP score and the age, sex, and pattern of viral infection. There was a strong correlation between the CLIP score and the Okuda stage. As of June 1999, 150 patients (76.5%) had died. Median survival time was 11 months, overall, and it was 36, 22, 9, 7, and 3 months for CLIP categories 0, 1, 2, 3, and 4 to 6, respectively. In multivariate analysis, the CLIP score had additional explanatory power above that of the Okuda stage. This was true for both patients treated with locoregional therapy or not. A quantitative estimation of 2-year survival predictive power showed that the CLIP score explained 37% of survival variability, compared with 21% explained by Okuda stage. In conclusion, the CLIP score, compared with the Okuda staging system, gives more accurate prognostic information, is statistically more efficient, and has a greater survival predictive power. It could be useful in treatment planning by improving baseline prognostic evaluation of patients with HCC, and could be used in prospective therapeutic trials as a stratification variable, reducing the variability of results owing to patient selection. (HEPATOLOGY 2000;31:840-845.)

The prognostic assessment of patients with cirrhosis and hepatocellular carcinoma (HCC) usually takes into account liver function alone, tumor extension alone, or both.[1-3] The Child-Pugh staging classification[1] is the most widely used to estimate the degree of liver damage in patients with cirrhosis; it can also be applied when patients develop HCC, but it does not account for tumor characteristics. The tumor node metastasis (TNM) staging[2] is not widely used in clinical practice because the diagnostic work-up required to reliably ascertain the nodal and, particularly, the metastasis categories is usually performed only in patients who are candidates for surgical procedures (resection or transplantation) or in symptomatic patients (*e.g.*, with bone pain) because of the low incidence of distant metastases. The Okuda staging system[3] is the most diffuse system for staging and predicting the prognosis of patients with cirrhosis and HCC, accounting for both liver function and tumor extension. Until new prognostic systems are correctly validated, it should be regarded as the most standardized way of assessing the prognosis of patients with HCC. Recently, a new prognostic score was proposed by the Cancer of the Liver Italian Program (CLIP) group.[4] The CLIP score was derived from a retrospective evaluation of 435 Italian patients with HCC diagnosed from 1990 to 1992. It is easily computed and includes Child-Pugh stage, tumor morphology and extension, presence of portal vein thrombosis, and serum level of alfa-fetoprotein (AFP) (Table 1). The CLIP score was successful in discriminating patients with HCC: the higher the score, indeed, the poorer the prognosis. The CLIP score, calculated at the time of HCC diagnosis, can be used to inform the patient properly and to decide the treatment strategy. However, as in most prognostic studies, we could not exclude two potential biases: first, an overoptimistic discriminatory ability because of over-fitting, although an internal cross-validation was applied, and, second, a selection bias inherent to the retrospective data used for devising the score. The aim of this article is to validate the CLIP score in an independent group of patients prospectively enrolled between 1995 and 1997 in the CLIP-01 multicenter randomized clinical trial of tamoxifen therapy for HCC,[5] and to compare it with the Okuda staging system.

PATIENTS AND METHODS

Patient Selection. Details of the CLIP-01 randomized trial are outlined elsewhere.[5] Patients with HCC were randomly assigned to the tamoxifen arm (40 mg/d) or no therapy. Broad inclusion criteria were used so that all patients with HCC diagnosed less than 2 years before randomization and with a life expectancy longer than 3 months were eligible. In both arms of the study, local treatment and supportive care could be decided according to the guidelines of participating institutions. Tamoxifen was found to be ineffective in prolonging overall survival rates.

Among those randomized in the CLIP-01 trial, 196 patients whose HCC had been diagnosed less than 1 month before randomization and who had an underlying liver cirrhosis were eligible for the present analysis.

Statistical Analysis. Because one of the eligibility criteria of the CLIP-01 trial was a life expectancy longer than 3 months, the CLIP score categories 4 to 6 were grouped for statistical analysis. A χ^2 test

Abbreviations: HCC, hepatocellular carcinoma; CLIP, Cancer of the Liver Italian Program; AFP, alfa-fetoprotein; LR, likelihood ratio; AIC, Akaike information criterion.

*See appendix for list of contributors.

Received March 1, 1999; accepted January 10, 2000.

Presented in part at the 49th annual meeting of the American Association for the Study of Liver Diseases, Chicago, Illinois, November 6-10, 1998, and published in abstract form in HEPATOLOGY 1998;28:337A.

Address reprint requests to: Francesco Perrone, M.D., Ph.D., CLIP Secretariat, Ufficio Sperimentazioni Cliniche Controllate, Istituto Nazionale Tumori, via M. Semmola, 80131 Napoli, Italy. E-mail: fr.perrone@agora.stm.it; fax: (39) 0817702938.

0270-9139/00/3104-0005$3.00/0

doi:10.1053/he.2000.5628

TABLE 1. CLIP Scoring System

Variable	Score
Child-Pugh stage	
A	0
B	1
C	2
Tumor morphology	
Uninodular and extension ≤50%	0
Multinodular and extension ≤50%	1
Massive or extension >50%	2
AFP	
<400	0
≥400	1
Portal vein thrombosis	
No	0
Yes	1

was applied to test the association between the CLIP score and other variables. Survival was defined as the time elapsed from the date of diagnosis and either the date of death or the date of last follow-up information, as available by the end of June 1999. Patients lost before the last collection of follow-up information were censored at the time of their last visit. Univariate survival curves were estimated using the Kaplan-Meier method[6] and compared by using the Mantel-Haenszel test.[7]

A formal statistical comparison of CLIP score and Okuda stage was performed by using a Cox proportional hazard regression model[8] stratified by locoregional therapy, as we did before.[4] Independent contribution of the two prognostic indices was tested by a likelihood ratio (LR) test comparing the full model (with both indices) with the two models with each index alone as a covariate. Akaike information criterion (AIC) was also calculated to find the best model.[9] AIC penalizes for the number of parameters of the model; as a consequence, the best model (*i.e.*, the most statistically efficient) is the one with the minimum AIC. We also performed separate analyses for subgroups of locally-treated or untreated patients.

Predictive power of the CLIP score and the Okuda stage on survival was assessed by means of squared error loss function with censoring at 24 months as a measure of explained variation.[10] This value measures the proportional reduction of variance owing to the spread of survival curves predicted for subgroups defined by the score categories over the unconditional predicted survival (*i.e.*, the expected survival of the whole group). It is affected both by the discriminatory power of the score and the heterogeneity of survival within each subgroup; the higher the value of the explained variation the greater the predictive power of the score. Kaplan-Meier curves were used to model the predicted survivals of the different score categories. As a reference, the percentage of explained variation was also calculated for Child-Pugh stage, which takes into account liver function alone.

TABLE 2. Characteristics of Patients

Median age, yr (range)	67 (44-84)
Men, no. (%)	141 (71.9)
Cause of liver cirrhosis (missing = 13), no. (%)	
Viral	179 (97.8)
Hepatitis B virus	18 (10.0)
Hepatitis C virus	153 (85.5)
Hepatitis B + C virus	8 (4.5)
Alcoholic	3 (1.6)
Other	1 (0.5)
Mean (SD) serum bilirubin, mg/dL	2.3 (3.5)
Mean (SD) serum albumin, g/dL	3.5 (0.6)
Mean (SD) prothrombin activity	72% (17)
Child-Pugh stage, no. (%)	
A	90 (45.9)
B	73 (37.2)
C	33 (16.8)

RESULTS

Patients had a median age of 67 years (range 44 to 84) and were predominantly men (Table 2). Cirrhosis was of viral origin in almost all the patients (97.8%). Antibodies against hepatitis C virus were present in 90% of patients with viral cause. Most patients (45.9%) were in the Child-Pugh A category, whereas Child-Pugh stage C was least represented. HCC diagnosis was confirmed with a cytological or histological examination in 80.1% of the patients (Table 3). Nearly one half of the tumors were uninodular. Okuda stage II category was the most frequent (47.4%). One fifth of the patients had tumors not secreting AFP. Portal vein thrombosis, either partial or complete, was detected in 21.4% of patients. More

TABLE 3. Characteristics of the Tumor

	No. (%)
Type of diagnosis	
Cyto/histological	157 (80.1)
Imaging + AFP >400	35 (17.9)
Imaging only	4 (2.0)
Tumor morphology	
Uninodular	89 (45.6)
Multinodular	80 (41.0)
Massive	26 (13.3)
Okuda stage	
I	84 (42.9)
II	93 (47.4)
III	19 (9.7)
AFP category	
≤10 ng/dL	41 (20.9)
11 to 400 ng/dL	76 (38.8)
>400 ng/dL	79 (41.3)
Portal vein thrombosis	
Absent	154 (78.6)
Partial	27 (13.8)
Complete	15 (7.6)
Involved liver volume	
≤50%	154 (78.6)
>50%	42 (21.4)
Locoregional treatment	
None	110 (56.1)
Orthotopic liver transplantation	5 (2.6)
Surgical resection	10 (5.1)
PEI	50 (25.5)
TACE	16 (8.2)
Surgery + PEI	2 (1.0)
PEI + TACE	3 (1.5)
Systemic treatment	
Tamoxifen	95 (48.5)
No therapy	101 (51.5)
CLIP score	
0	38 (19.4)
1	46 (23.5)
2	40 (20.4)
3	26 (13.3)
4	25 (12.8)
5	18 (9.2)
6	3 (1.5)

Abbreviations: PEI, percutaneous ethanol injection; TACE, transartherial chemoembolization.

TABLE 4. Patient Characteristics According to CLIP Score

	CLIP Score					
	0 (%)	1 (%)	2 (%)	3 (%)	4 to 6 (%)	*P* Value
Age						.27
≤67	21 (55.3)	24 (52.2)	14 (35.0)	10 (40.0)	25 (54.3)	
>67	17 (44.7)	22 (47.8)	26 (65.0)	15 (60.0)	21 (45.7)	
Sex						.43
Men	27 (71.1)	29 (63.0)	28 (70.0)	20 (76.9)	37 (80.4)	
Women	11 (28.9)	17 (37.0)	12 (30.0)	6 (23.1)	9 (19.6)	
Viral cause						.36
B	3 (8.6)	5 (12.5)	2 (5.3)	5 (19.2)	3 (7.5)	
C	30 (85.7)	32 (80.0)	36 (94.7)	21 (80.8)	34 (85.0)	
B + C	2 (5.7)	3 (7.5)	—	—	3 (7.5)	
Okuda stage						<.0001
I	28 (73.7)	32 (69.6)	15 (37.5)	3 (11.5)	6 (13.0)	
II	10 (26.3)	13 (28.3)	24 (60.0)	22 (84.6)	24 (52.2)	
III	—	1 (2.2)	1 (2.5)	1 (3.8)	16 (34.8)	
Locoregional treatment						<.0001
None	7 (18.4)	15 (32.6)	23 (57.5)	23 (88.5)	42 (91.3)	
OLT	1 (2.6)	4 (8.7)	—	—	—	
Surgery	5 (13.2)	2 (4.3)	3 (7.5)	—	—	
PEI	20 (52.6)	19 (41.3)	9 (22.5)	2 (7.7)	—	
TACE	2 (5.3)	6 (13.0)	3 (7.5)	1 (3.8)	4 (8.7)	
Surgery + PEI	1 (2.6)	—	1 (2.5)	—	—	
PEI + TACE	2 (5.3)	—	1 (2.5)	—	—	

Abbreviations: OLT, orthotopic liver transplantation; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization.

than half of the liver volume was involved by the tumor in 21.4% of patients. More than half of the patients did not receive any locoregional treatment. Patients were distributed among CLIP score categories with fewer patients falling in the categories with worse prognosis (higher scores), as a consequence of the eligibility criterion of a life expectancy longer than 3 months in the CLIP-01 trial.

There was no significant association between the CLIP score and age or sex of patients or pattern of viral infection. As expected, there was a strong correlation between the CLIP score and Okuda stage. However, all the Okuda categories were represented within each CLIP score category, with the exception of Okuda stage III in the CLIP score 0 category. Most patients within the worse CLIP categories did not receive any treatment, whereas those with lower CLIP scores usually received some kind of locoregional treatment (Table 4).

As of June 1999, 150 patients (76.5%) had died. Overall median survival time was 11 months (95% confidence interval, 8 to 15 months); 1-, 2-, and 3-year survival rates were 48%, 28%, and 20%, respectively. Both the CLIP score and the Okuda stage clearly differentiated ($P < .0001$ for both) patients with different survival experiences (Fig. 1). However, the CLIP score did better in discriminating pa-

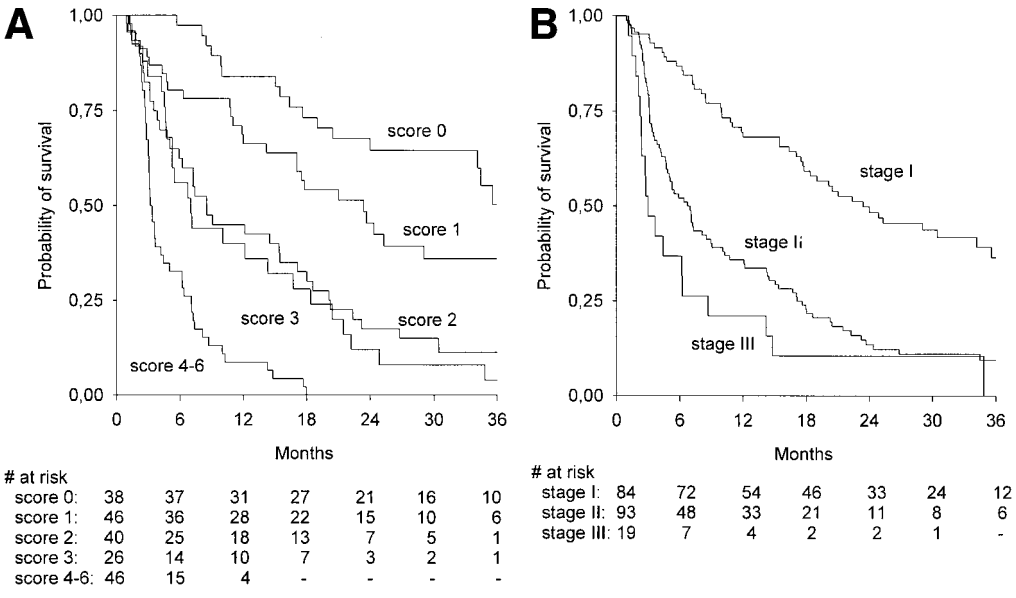

FIG. 1. Kaplan-Meier estimated survival curves by (A) CLIP score ($P < .0001$) and (B) Okuda stage ($P < .0001$).

tients, mainly by identifying a subgroup of patients with a life expectancy clearly longer than that estimated by Okuda stage I (Table 5).

Independent contributions of CLIP score and Okuda stage were investigated by means of an LR test within a Cox proportional hazard regression model. As shown in Table 6, removal of the CLIP score from a model containing both Okuda stage and CLIP score did significantly reduce the goodness of fit of the model, whereas removal of the Okuda stage was not significant. This was true both for the whole group of patients and for subgroups of locally-treated or untreated patients. As it could be expected that the CLIP score worked better than Okuda staging just because of the higher number of categories, we calculated the AIC values that penalize for the number of parameters of the model. AIC values were always higher (worse) when removing the CLIP score, though being only marginally affected by removal of the Okuda stage, indicating the higher statistical efficiency of the CLIP score system.

Finally, we evaluated the predictive power of the CLIP score and Okuda stage on survival by measuring the percentage of explained variation at a censoring time of 24 months. Values of explained variation were 37% for the CLIP score and 20.5% for the Okuda stage. As a reference, the Child-Pugh stage accounted for 21.2% of explained variation.

TABLE 5. Patient Survival by CLIP Score and Okuda Stage

	No. (%) of Deaths	Median Survival (mo)	Interquartile Range	1-Year Survival	2-Year Survival
CLIP score					
0	18 (47.4)	35.7	16.8*	84%	65%
1	27 (58.7)	22.1	10.8*	66%	45%
2	35 (87.5)	8.5	3.5-20.1	45%	17%
3	24 (92.3)	6.9	4.6-18.0	36%	12%
4 to 6	46 (100)	3.2	2.7-6.7	9%	0%
Okuda stage					
I	48 (57.1)	23.4	9.9*	68%	48%
II	84 (90.3)	6.7	3.1-17.1	36%	13%
III	18 (94.7)	2.9	2.2-6.9	21%	10%

*Upper quartile not measurable.

TABLE 6. Evaluation of the Independent Contribution of CLIP Score and Okuda Stage to Cox Proportional Hazard Model

Model	Log-Likelihood	LR Test	*P* Value*	AIC
All patients (n = 196)				
CLIP + Okuda	−559.8224	—	—	1,131.6448
Removing Okuda	−562.1455	4.6	.10	1,132.2910
Removing CLIP	−578.3497	37.0	<.0001	1,160.6994
Patients receiving a locoregional treatment (n = 86)				
CLIP + Okuda	−196.4275	—	—	404.8550
Removing Okuda	−197.7546	2.6	.26	403.5092
Removing CLIP	−202.6612	12.5	.01	409.3224
Patients not receiving a locoregional treatment (n = 110)				
CLIP + Okuda	−362.3688	—	—	736.7376
Removing Okuda	−364.0023	3.3	.19	736.0046
Removing CLIP	−375.1325	25.5	<.0001	754.2650

**P* values indicate the statistical significance of the decrease of the goodness of fit of the model.

DISCUSSION

In a previous article, we proposed the CLIP score as a new prognostic system for patients with HCC.[4] In this article, we externally validated the CLIP score in 196 patients with HCC enrolled in an independent, randomized clinical trial of the same collaborative group.[5] We confirmed the greater predictive efficacy of the CLIP score compared with the Okuda staging system, which is the most diffuse system accounting for both liver function and tumor extension. In addition, we showed that only the CLIP score gave a statistically significant contribution to the goodness of fit of a multivariate prognostic model including both the CLIP and the Okuda stage. The CLIP score had additional explanatory power above that of the Okuda staging system. Finally, the amount of survival variability explained by the distribution of the patients across the CLIP score categories is 1.8 times higher than that explained by the Okuda stage, which, incidentally, does not work better than the Child-Pugh stage classification system.

Although the usefulness of the CLIP score has been confirmed by the present analysis, some discrepancies in survival data compared with those reported in our previous retrospective study[4] were found in the whole series of patients as well as in each category of both CLIP score and Okuda stage. These discrepancies may be explained by three concurrent mechanisms. In the whole group of patients, overall survival is shorter than in the previous study,[4] possibly because of selection of patients with more favorable prognosis and model over-fitting in the retrospective data set. In the CLIP score 0 and, though to a lesser extent, in the Okuda stage I categories, survival may be slightly underestimated because of a still short follow-up time. The distribution of censoring and event times in the CLIP score 0 subgroup (data not shown), indeed, suggests that the median survival time actually estimated at 35.7 months, could still be prolonged with further follow-up time. Finally, in the worse prognostic categories (CLIP score 3 and 4 to 6 and Okuda stage III), survival is longer than that reported in the previous study. This is explained by the selection of patients with a life expectancy of at least 3 months to be eligible for the CLIP-01 trial. Another discrepancy is represented by the very similar behavior of survival curves for CLIP score 2 and 3 categories. Although this could be partially explained by the earlier-discussed mechanisms of patient selection for the randomized trial, we cannot rule out that groups 2 and 3 should actually be considered together.

In clinical practice, the CLIP score is an easy and useful prognostic tool to assist physicians during the therapeutic decision-making process when a new diagnosis of HCC is made. It may help physicians decide the more appropriate management, both by reducing over-treatment of patients with very short life expectancy and by selecting those patients that could benefit from more intensive and hopefully effective treatment strategies. In addition, the CLIP score may be largely effective in stratifying patients in therapeutic trials, reducing the overly optimistic results owing to patient selection, on one side, and the large heterogeneity among studies, on the other side. Only a few randomized studies,

indeed, have been performed in the field of HCC therapies and the choice of the locoregional treatment often depends on subjective opinions or resource availability. Therefore, the prognostic studies on subgroups of patients treated with different therapeutic strategies frequently produce inconsistent or even contrasting results, which increase confusion and do not help the medical practice.

Recently, two articles dealing with the prognosis of patients with HCC have been published. In the first,[11] a 3-category classification system is provided, starting with 5 variables correlated with survival: performance status (subjectively stated by physicians), serum bilirubin, alkaline phosphatase, AFP, and portal vein thrombosis. The investigators used a correct cross-validation approach for internal validity and adjusted for local treatments in the model. When compared with the Okuda score, the new score identifies a subgroup of patients with a lower risk of death than those in the Okuda stage I, similar to the CLIP score. However, no quantitative assessment of the relative predictive ability is performed; thus, a further quantitative assessment of reliability is needed. The second article[12] combines the results of a number of previously published articles of the Barcelona Clinic Liver Cancer group. From these data, the investigators derive a staging classification that, contrary to the CLIP score, is based on the possibility of radical interventions. Therefore, rather than a prognostic model, their system is the explication of the treatment-decision algorithm they use in their clinic.

The CLIP score does not include any biological features. Recently, the number of biological variables (*e.g.*, p73, p53, interleukin-2 receptor, intercellular adhesion molecule 1) for which a prognostic importance in HCC has been claimed or proposed is rapidly increasing.[13-18] It will be of interest to investigate whether such variables add anything to the predictive value of the CLIP score.

In conclusion, the CLIP score seems the best available prognostic system for patients with HCC. Compared with the Okuda staging system, it gives more precise prognostic information, is statistically more efficient, and has a greater predictive power on survival. Thus, it seems reasonable to claim it can improve the baseline prognostic evaluation of patients with HCC, which is important for treatment planning in clinical practice. In addition, it should be incorporated into the design and the analysis of future therapeutic trials to improve the reliability of their results.

APPENDIX

Prepared the draft and the final paper: Francesco Perrone,[1,29] Bruno Daniele,[1] Giovanni Battista Gaeta,[11] Sandro Pignata,[1] and Ciro Gallo[28,29] (biostatistician).

Revised the draft and gave significant contribution: Francesco Izzo,[1] Oreste Cuomo,[2] Gaetano Capuano,[3] Giuseppe Ruggiero,[4] Roberto Mazzanti,[5] Fabio Farinati,[6] Silvana Elba.[7]

Participating Investigators: Bruno Daniele,[1] Sandro Pignata,[1] Francesco Cremona,[1] Francesco Izzo,[1] Valerio Parisi,[1] Francesco Fiore,[1] Paolo Vallone,[1] Francesco Perrone[1,29]; Oreste Cuomo,[2] Massimo Di Palma,[2] Emilio Manno,[2] Giuseppe Militerno[2]; Gabriele Budillon,[3] Gaetano Capuano,[3] Lucia Cimino,[3] Domenico Pomponi[3]; Luigi Elio Adinolfi,[4] Enrico Ragone,[4] Giuseppe Ruggiero,[4] Riccardo Utili[4]; Umberto Arena,[5] Giuseppe Di Fiore,[5] Paolo Gentilini,[5] Roberto Mazzanti[5]; Fabio Farinati,[6] Michela Rinaldi[6]; Silvana Elba,[7] Angelo Coviello,[7] Onofrio Giuseppe Manghisi[7]; Bernardino Crispino,[8] Raffaele Laviscio,[8] Guido Piai[8]; Nicola Caporaso,[9] Ilario De Sio[9]; Giulio Belli,[10] Antonio Iannelli,[10] Mario Luigi Santangelo[10]; Giovanni Battista Gaeta,[11] Tiziana Ascione,[11] Giuseppe Giusti[11]; Valentina D'Angelo,[12] Giampiero Francica,[12] Giampiero Marone[12]; Giuseppe Pasquale,[13] Felice Piccinino,[13] Maria Stanzione[13]; Angelo Raffaele Bianco,[14] Sabino De Placido,[14] Giovannella Palmieri[14]; Luciano D'Agostino,[15] Daniele Mattera,[15] Alessandro Puzziello[15]; Antonino Aiello,[16] Oscar Ferraù,[16] Maria Antonietta Freni[16]; Vincenza Aloisio,[17] Antonio Giorgio,[17] Anna Perrotta[17]; Maria Calandra,[18] Luigi Castellano,[18] Camillo Del Vecchio Blanco[18]; Fabiana Castiglione,[19] Gabriele Mazzacca,[19] Antonio Rispo[19]; Raffaele Colurcio,[20] Bruno Galanti,[20] Michele Russo[20]; Bruno Palmentieri,[21] Marcello Persico[21]; Martina Felder,[22] Laura Zancanella[22]; Mario Belli,[23] Giuseppe Colantuoni,[23] Guido De Sena[23]; Francesco Guardascione,[24] Gino Petrelli[24]; Bruno Lamorgese,[25] Luigi Manzione[25]; Tonino Pedicini[26]; Modesto D'Aprile[27]; Ciro Gallo.[28,29]

Participating Institutions [1]Istituto Nazionale Tumori, Napoli; [2]Ospedale A.Cardarelli, Napoli; [3]Gastroenterologia II, Università Federico II, Napoli (FED); [4]Terapia Medica II Seconda Università di Napoli (SUN); [5]Medicina Interna Università di Firenze; [6]Malattie dell'apparato digerente Università di Padova; [7]IRCCS De Bellis, Castellana Grotte; [8]Ospedale di Marcianise; [9]Dipartimento di Internistica Clinica F. Magrassi, SUN; [10]Chirurgia Generale e dei Trapianti, FED; [11]Istituto di Malattie Infettive I, SUN; [12]Ospedale Ascalesi, Napoli; [13]Malattie Tropicali e Subtropicali SUN; [14]Oncologia Medica FED; [15]Dipartimento Patologia Digestiva e Chirurgia Generale FED; [16]Gastroenterologia, Università di Messina; [17]Ospedale Cotugno, Napoli; [18]Gastroenterologia SUN; [19]Gastroenterologia I, FED; [20]Servizio AIDS, SUN; [21]VII Medicina Generale ed Epatologia, SUN; [22]Ospedale Civile, Bolzano; [23]Ospedale Civile, Avellino; [24]Ospedale di Giugliano, Napoli; [25]Ospedale S.Carlo, Potenza; [26]Ospedale Fatebenefratelli, Benevento; [27]Ospedale S. Maria Goretti, Latina; [28]Metodologia Epidemiologica Clinica, SUN; [29]Centro Elaborazione Dati Clinici del Mezzogiorno, CNR PF ACRO.

REFERENCES

1. Pugh RNH, Murray-Lyon IM, Dawson J-L, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646-649.
2. Sobin LH, Wittekind C, eds. TNM Classification of Malignant Tumours. 5th ed. New York: John Wiley & Sons, 1997.
3. Okuda K, Ohtsuki T, Obata H, Tominatsu M, Okazaki N, Hasegawa H, Nakajima Y, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Cancer 1985;56:918-928.
4. The Cancer of the Liver Italian Program (CLIP) Investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. HEPATOLOGY 1998;28:751-755.
5. CLIP Group (Cancer of the Liver Italian Program). Tamoxifen in the treatment of hepatocellular carcinoma: a randomised controlled trial. Lancet 1998;352:17-20.
6. Kaplan EL, Meier P. Non parametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457-481.
7. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50:163-170.
8. Cox DR. Regression models and life tables. J R Stat Soc Series B 1972;34:187-220.
9. Stone M: Akaike's criteria. In: Armitage P, Colton T, eds. Encyclopedia of Biostatistics. Chichester: Wiley, 1998;123-124.
10. Korn EL, Simon R. Measures of explained variation for survival data. Stat Med 1990;9:487-503.
11. Chevret S, Trinchet JC, Mathieu D, Rached AA, Beaugrand M, Chastang C, for the Groupe d'Etude et de Traitment du Carcinome Hepatocellulaire. A new prognostic classification for predicting survival in patients with hepatocellular carcinoma. J Hepatol 1999;31:133-141.

12. Llovet JM, Brù C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329-337.
13. Ng IO. Prognostic significance of pathological and biological factors in hepatocellular carcinoma. J Gastroenterol Hepatol 1998;13:666-670.
14. Shimizu Y, Minemura M, Tsukishiro T, Kashii Y, Miyamoto M, Nishimori H, Higuchi K, et al. Serum concentration of intercellular adhesion molecule-1 in patients with hepatocellular carcinoma is a marker of the disease progression and prognosis. HEPATOLOGY 1995;22:525-531.
15. Izzo F, Cremona F, Delrio P, Leonardi E, Castello G, Pignata S, Daniele B, et al. Soluble interleukin-2 receptor levels in hepatocellular cancer: a more sensitive marker than alfa fetoprotein. Ann Surg Oncol 1999;6:178-185.
16. Tannapfel A, Wasner M, Krause K, Geissler F, Katalinic A, Hauss J, Mossner J, et al. Expression of p73 and its relation to histopathology and prognosis in hepatocellular carcinoma. J Natl Cancer Inst 1999;91:1154-1158.
17. Shiota G, Kishimoto Y, Suyama A, Okubo M, Katayama S, Harada K, Ishida M, et al. Prognostic significance of serum anti-p53 antibody in patients with hepatocellular carcinoma. J Hepatol 1997;27:661-668.
18. Saffroy R, Lelong JC, Azoulay D, Salvucci M, Reynes M, Bismuth H, Debuire B, et al. Clinical significance of circulating anti-p53 antibodies in European patients with hepatocellular carcinoma. Br J Cancer 1999;79:604-610.