SIGNIFICANCE OF TNM CLASSIFICATION IN PROGNOSTIC EVALUATION OF HEPATOCELLULAR CARCINOMA FOLLOWING HEPATECTOMY

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ABSTRACT

Objective: To analyze correlation between TNM classification of hepatocellular carcinoma (HCC) and disease-free survival in order to evaluate its significance in predicting the long-term result after hepatctomy. Methods: A retrospective survey was carried out in 1,725 cases with HCC patients performed hepatectomy from January 1990 to December 1995. The follow-up rate was 84.5%. The prognostic factors were analyzed by Cox proportional hazards survival model and disease-free survival was calculated by Kaplan-Meier estimation. Results: Univariate analysis showed thirteen clinicopathological prognostic factors including TNM staging. Multivariate analysis revealed four significant predictors such as preoperative lesion number, tumor size, daughter nodules and vascular invasion, which were encompassed in TNM classification. The 5-year disease-free survival rate were 24.6% of stage I, 38.4% of stage II, 15.9% of stage III, and 5.3% of stage IVa respectively. There was no significant difference in disease-free survival between stages I and II. Conclusion: TNM staging is one of the most significant prognostic factors in predicting disease-free survival of HCC patient after hepatectomy, but some items need modifying.

Key words: Hepatocellular carcinoma, Hepatectomy, TNM classification, Disease-free survival, Prognosis

To date, the optimal treatment for hepatocellular carcinoma (HCC) is still surgical resection with curative intent.[1] However the long-term results of these patients are not satisfied because of the poor disease-free survival. The present clinical staging is impossible to exactly reflect the prognosis of the patients after hepatectomy. By a retrospective survey in HCC patients having hepatectomy, , the correlative analysis was carried out between TNM staging and some clinicopathological factors which might influence the disease-free survival in order to explore the significance of TNM classification in evaluating the prognosis of HCC patients after hepatectomy through Cox model[2] and Kaplan-Meier estimation.

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METHERIALS AND METHODS

Patients

A total of 1,725 patients had radical or relatively radical hepatectomy for HCC confirmed pathologically in the Hepatobiliary Surgery Department of Changhai Hospital (excluding inhospital deaths) between January 1990 and December 1995. The retrospective survey was carried out from January to October 1997. The criteria of radical resection were found the whole tumor removed, no tumor thrombus found by naked eye, no tumor remaining in other part or margin. Those of relatively were the main tumor removed, daughter nodules resected or solidified with intratumor ethanol injection or with microwave, and tumor thrombus sucked out completely.

Statistical Methods

Eighteen variables about recurrence were studied according to correlative clinicopathological and prognostic materials. They were sex, age, clinical stage,[3] hepatitis record, HbsAg, anti-HbcAg, preoperative portal thrombus, preoperative lesion number, intraoperative lesion number, extent of resection, tumor size, Es's classification, growing style, capsular containment, daughter nodule, vascular invasion, TNM stage[4,5] and postoperative AFP value.

The end of local-regional disease-free survival time was defined as finding recurrent lesion confirmed by diagnostic imaging such as B-ultrasonography, computed tomography(CT), magnetic resonance imaging (MRI) and hepatic artery angiography; no recurrence at survey time; and death not for recurrence or losing connection at survey time. Merely AFP positive and finding extrahepatic metastasis or other unrecurrent diseases can not be described as the end incident.

Univariate and multivariate analyses were carried out by Cox proportional hazards survival analysis model. Disease-free survival was calculated with Kaplan-Meier estimation. Statistics software was the SAS 6.12 system and epidemiological graphics, estimation, and testing package (EGRET package).

RESULTS

Summary of Patients

1,457 cases had the follow-up results, and the rate was 84.5%. The male to female ratio was 7.0 to 1. The ages of the patients ranged from 9 to 75 years (mean, 49.0 years). The patients with hepatitis B record accounted for 49.4%, the HBsAg positive 73.0%, and the anti-HBcAg 82.5%. TNM stage I patients accounted for 3.0%, stage II 38.6%, stage III 36.7%, stage IVa 20.5%, and stage IVb 1.2%.

Univariate Analysis

The prognostic factors were as follows: age, clinical stage, preoperative lesion number, preoperative portal thrombus, intraoperative lesion number, extent of resection, tumor size, growing style, capsular containment, daughter nodule, vascular invasion, TNM stage and postoperative AFP value ($P<0.05$).

Multivariate Analysis

The most significant clinicopathological predictors were preoperative lesion number, tumor size, daughter nodule and vascular invasion (Table 1).

Table 1. Results of multivariate analysis by Cox model

Variables	Regression coefficient	Standard error	*P* value	Hazard ratio
Preopertive lesion number	1.467	0.506	0.004	4.336
Daughter nodules	2.226	0.479	<0.001	9.259
Vascular invasion	0.9789	0.362	0.007	2.662
Tumor size	0.3181	0.123	0.010	1.374

Disease-free Survival Analysis

The average disease-free survival time of the whole group was 20.2 months, and the mean time was 13.7 months. The survival rates of pTNM stage were shown in Table 2.

Table 2. Disease-free survival of pTNM stage

PTNM stage	Disease-free survival rate(%) after hepatectomy				Mean disease-free survival time
	0.5 year	1 year	3-year	5-year	
I	90.7	79.7	45.8	24.6	34.4
II	86.6	75.5	51.8	38.4	38.3
III	62.6	41.5	20.6	15.9	10.0
IVa	33.0	18.6	8.0	5.3	4.1
IVb	42.3	35.3	--	--	4.3

DISCUSSION

Univariate analysis showed that the patients of older, in subclinical stage, without portal thrombus, with solitary lesion, with small tumor, with capsule positive, having no daughter nodules, having no vascular invasion, or in early TNM stage had a better disease-free survival. Multivariate analysis further indicated that preoperative solitary or multiple lesions, tumor size, daughter nodules and vascular invasion were the significant prognostic factors of disease-free survival. Although TNM staging was excluded out of prognostic factors in multivariate analysis, some index of T classification in TNM were included such as solitary or multiple tumors, size, daughter nodules, and vascular invasion. It means that TNM staging is

an important criterion for forecasting the prognosis after hepatectomy. Izumi, et al.[6] reported that disease-free surival was analyzed in 104 HCC patients undergoing hepatectomy, and showed portal vein invasiion was the most influential factor. The difference between each stage in the modified TNM classification was significant with respect to disease-free survival. Wittekind[7] indicated that TNM stage was the most important prognostic factors for HCC after hepatectomy or liver transplantation.

Yamasaki[8] reported cumulative survival at 5-year was 93% in TNM stage I. Yang[9] reported that cumulative survival at 3-year after radical hepatectomy for HCC was 88.3% of stage I, 60.0% of stage II, 28.0% of stage III and 12.1% of stage IVa. But there were fewer articles about disease-free survival in each TNM stage of HCC after hepatectomy. The current study showed that the 3-year disease-free survival rates were 45.8% of stage I, 51.8% of stage II, 20.6% of stage III and 8.0% of stage IVa respectively. It also showed the survival of stage I and stage II was much better than that of stage III and stage IV. TNM classification basically reflects the prognosis of HCC patients after hepatectomy. Therefore, cooperating with clinical staging, TNM classification can presage the long-term result and is helpful for clinical doctors to choose more suitable treatment to individual patients.

The 0.5, 1 and 2-year disease-free survival rates of stage IVb were higher than that of stage IVa. It did not mean stage Ivb's prognosis was better than stage IVa's, and it was due to that three patients with solitary hepatic lesion and solitary matastatic pulmonary lesion who were performed radical hepatectomy and pneumonactomy, and had a long-term disease-free survival. While it also indicates that surgical resection should not be abandoned completely for those patients with extrahepatic metastasis especially of lesions limited unilateral lobe of lung because of advanced stage.

The current TNM classification of the liver was published in 1987 by International Union Against Cancer (UICC), which is the same as the staging system in the general rules for the Clinical and Pathological Study of Primary Liver Cancer by the Liver Cancer Study Group of Japan, and was proposed by Japanese TNM Committee. Some researchers[6-8,10] indicated that the current TNM can not meet the latest knowledge of advancing hepatic oncology. From the data of the current study, there was no evident difference of disease-free survival between TNM stage I and stage II, and that of stage IVb was even better than that of stage IVa. It indicated that the current TNM classification needs having some modification. We believe that the item of TNM classification should include some other clinicopathological factors, which are significant predictors of disease-free survival, such as capsular containment, growing style and range of vascular invasion (including tumor nest vessel, peripheral vessesl of tumor, 2 or 3 grade of portal branch). It should also be considered that the classification of multicentric lesions confirmed by histopathology, which are distributed different lobe, might not be classified as T_4. If this kind of HCC was classified as stage IV, it was not exact to predict the prognosis of disease-free survival.

Although the current TNM classification is not very satisfactory and needs to be modified and replenished, but it can basically predict the prognosis of disease-free survival of HCC patients after surgical resection and it is valuable for doctors to choose the most suitable treatment for HCC patients.

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