Prognostic Factors of Liver Resection for Large Hepatocellular Carcinoma in Cirrhotic Patients

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Abstract

Background: Prognostic modeling in hepatocellular carcinoma patients has a high complexity and should consider 4 tightly related aspects; tumor stage, degree of liver function impairment, patient's general condition and treatment efficacy Objectives: The aim of this study was to determine the different prognostic factors of liver resection for large hepatocellular carcinoma in cirrhotic patients. Patients and Methods: In this retrospective cohort study, 65 cirrhotic patients had liver resection for large hepatocellular carcinoma in the period from January 2015 until December 2019, at National liver institute, Menoufia University and Benha Faculty of Medicine, Benha University. The recurrence and survival data along with patients' data were recorded to identify potential prognostic factors in those patients. Results: Recurrence had occurred in 33 patients (52.38%) while mortality occurred in 15 patients (23.1%). Findings on upper endoscope, the site and size of the tumors, the preoperative AJCC stages and pathological grade of tumors affected the recurrence significantly (p 0.015, 0.001, <0.001, 0.035 and <0.001, respectively) while the preoperative serum albumin, the presence of vascular invasion and Barcelona class affected mortality significantly (p 0.002, 0.002 and 0.024, respectively). By multivariate analysis, the mean size of HCC and the pathological grade of tumor were the most significant factors that affected the recurrence while the presence of portal vein invasion by the tumor was the most significant factor that affected the survival. Conclusion: Findings on upper endoscope, the site and size of the tumors, the preoperative AJCC stages and pathological grade of tumors were independently associated with recurrence while preoperative serum albumin, the presence of vascular invasion and Barcelona class were associated with survival. On multivariate analysis, the mean size of HCC and the pathological grade were the most significant factors affected the recurrence while the presence of vascular invasion was the most significant factors that affect the survival.

Keywords: Prognostic factors, liver resection, HCC in liver cirrhosis.

1. Introduction

Hepatocellular carcinoma (HCC) represents the fifth most common cancer and the third most common cause of cancer death, behind only lung and stomach cancer. HCC accounts for the majority of these primary cancers of the liver. Despite even aggressive surgical approaches, most patients who have HCC or liver disease are advanced to permit treatment with "curative" intent [1].

The prognosis of cancer patients is solely related to tumor stage. However, this is not the case in HCC patients. Cirrhosis underlies the neoplasm in most individuals and thus, their outcome is related to these two entities that simultaneously determine the applicability and efficacy of treatments. Accordingly, prognostic modeling in HCC patients has a high complexity and should consider 4 tightly related aspects: tumor stage, degree of liver function impairment, patient's general condition, and treatment efficacy [2].

Prognostic systems assessing just one of these aspects (Child-Pugh classification, TNM stage, performance status) have a marginal usefulness. The Okuda staging based on bilirubin, albumin, ascites, and tumor burden has been used for years, but it is unable to distinguish between early and advanced HCC and mostly serves to identify end-stage individuals [3].

The aim of this study was to determine the different prognostic factors of liver resection for large hepatocellular carcinoma in cirrhotic patients.

2. Patients and Methods

This was a retrospective cohort study to analyze the different prognostic values after liver resection of large hepatocellular carcinoma in cirrhotic patients in the period from January 2015 until December 2019, at National liver institute, Menoufia University and Benha Faculty of Medicine, Benha University.

After a primary review of all patients' records from clinic files, operative notes, pathology records, laboratory evaluations and other imaging studies in the allocated period, the data of 65 patients were found to be eligible to be included in the study. The collected data were demographic data including age, sex and previous history of medical disease, preoperative data including laboratory results, radiology results, results of upper endoscopy and preoperative AJCC staging and Child and MELD score, operative data including type of operation and type and method of resection, postoperative data and results of follow-up.

Data were collected and entered to the computer using SPSS (Statistical Package for Social Science) program version 26.0, SPSS Inc., Chicago, Illinois, USA for statistical analysis. Descriptive statistics was expressed as mean, SD and range in quantitative data and as frequency and percentage in qualitative analysis. Analytical statistics was done by using Chi-

square test for qualitative data, Student t-test for quantitative data, Kaplan-Meier survival analysis and multiple logistic regression analysis for multivariate analysis. P (probability) value was considered statistically significant if it was less than 0.05.

3. Results

In this study, 2 patients died in the early postoperative period while recurrence had occurred in 33 patients (52.38%). According to recurrence data in the remaining 63 patients, Table 1 shows the difference among the patients (Table 1). Findings on upper endoscope, the site and size of the tumors, the preoperative AJCC stages and pathological grade of tumors differed significantly between both groups

(p0.015, 0.001, <0.001, 0.035 and <0.001, respectively). By multivariate analysis, the mean size of HCC and the pathological grade were the most significant factors that affect the recurrence among the patients included in the study. Table (1)

In this study, mortality occurred in 15 patients (23.1%). According to survival data, Table 2 shows the difference among the patients (Table 2). The preoperative serum albumin, the presence of vascular invasion and Barcelona class differ significantly between both groups (p 0.002, 0.002 and 0.024, respectively). By multivariate analysis, the presence of portal vein invasion by the tumor was the most significant factor that affects the survival among the patients included in the study. Table (2)

Table (1) Data of the patients according to recurrence (N=65)

Data	No Recurrence group (N=30)	Recurrence group (N=33)	p value
Age (Years)	56.9 ± 6.62 (45 - 70)	58.27 ± 6.21 (42 - 70)	0.401 ^
Male Gender	28 (93.33%)	28 (84.85%)	0.285 #
Positive Medical History	27 (90%)	33 (100%)	0.063 #
Hepatitis B virus	2 (6.67%)	1 (3.03%)	0.498 #
Hepatitis C virus	27 (90%)	33 (100%)	0.063 #
Diabetes Mellitus	6 (20%)	6 (18.18%)	0.859 #
Hypertension	3 (10%)	6 (18.18%)	0.354 #
Serum Bilirubin (mg/dl)	0.95 ± 0.33 (0.2 - 1.5)	0.99 ± 0.45 (0.39 - 2.3)	0.660 ^
Serum Albumin (g/dl)	3.37 ± 0.58 (2.4 - 4.3)	3.34 ± 0.55 (2 - 4.4)	0.848 ^
Prothrombin Concentration (%)	90.93 ± 10.60 (70 - 100)	85.03 ± 14.29 (40 - 100)	0.066 ^
Serum Creatinine (mg/dl)	0.82 ± 0.2 (0.4 - 1.2)	0.84 ± 0.18 (0.46 - 1.3)	0.641 ^
Alpha Feto-protein (ng/ml)	1127.42 ± 2362.78 (2.7 - 9071)	48.04 ± 786.95 (4.7 - 4276)	0.166 ^
Carcinoembryonic Antigen (ng/ml)	6.31 ± 7.74 (0 - 23)	9.14 ± 8.16 (0 - 27)	0.164 ^
Normal upper endoscope	19 (63.33%)	27 (81.82%)	**0.015 #***
MELD Score	7.3 ± 1.39 (6 - 10)	7.94 ± 2.22 (6 - 13)	0.173 ^
Left Hepatic Mass	6 (20%)	21 (63.64%)	**0.001 #***
Tumor Size	6.2 ± 2.59 (5 - 9)	10.7 ± 3.33 (8 - 11)	**<0.001 ^***
Single tumor	29 (96.67%)	28 (84.85%)	0.110 #
Preoperative AJCC Stage I	26 (86.67%)	19 (57.58%)	**0.035 #***
Barcelona Class A	18 (60%)	12 (36.36%)	0.131 #
Open Resection	30 (100%)	32 (96.97%)	0.336 #
Anatomical resection	2 (6.67%)	7 (21.21%)	0.099 #
Use of Habib Sealer	14 (46.67%)	25 (75.76%)	0.160 #
Use of RFA	0 (0%)	3 (9.09%)	0.182 #
Grade III Tumor	6 (20%)	24 (72.73%)	**<0.001 ^***
Portal vein Invasion	3 (10%)	2 (6.06%)	0.563 #
Involved Surgical Margins	13 (43.33%)	11 (33.33%)	0.414 #

Data in mean±SD (Range), N(%)   ^ Student t test # Chi-Square test   * Statistically Significant

Table (2) Data of the patients according to Survival (N=65).

Data	Survival Group (N=50)	Mortality Group (N=15)	p value
Age (Years)	57.52 ± 6.39 (45 - 70)	57.8 ± 6.21 (42 - 65)	0.88 ^
Male Gender	45 (90%)	13 (86.67%)	0.715 #
Positive Medical History	47 (94%)	15 (100%)	0.331 #
Hepatitis B virus	2 (4%)	1 (6.67%)	0.666 #
Hepatitis C virus	47 (94%)	15 (100%)	0.331 #
Diabetes Mellitus	6 (20%)	6 (18.18%)	0.205 #
Hypertension	3 (10%)	6 (18.18%)	0.572 #
Serum Bilirubin (mg/dl)	0.94 ± 0.39 (0.2 - 2.3)	1.12 ± 0.39 (0.4 - 1.8)	0.111 ^
Serum Albumin (g/dl)	3.48 ± 0.48 (2.4 - 4.3)	2.9 ± 0.57 (2 - 4.4)	**0.002 ^***
Prothrombin Concentration (%)	89.44 ± 10.95 (70 - 100)	79.8 ± 17.54 (40 - 100)	0.06 ^
Serum Creatinine (mg/dl)	0.84 ± 0.18 (0.46 - 1.3)	0.8 ± 0.19 (0.4 - 1.09)	0.514 ^
Alpha Feto-protein (ng/ml)	863.78 ± 1936.8 (2.7 - 9071)	508.3 ± 504.09 (1.5 - 1420)	0.246 ^
Carcinoembryonic Antigen (ng/ml)	7.39 ± 8.48 (0 - 27)	9.72 ± 7.01 (1 - 23)	0.291 ^
Normal upper endoscope	35 (70%)	11 (73.33%)	0.071 #
MELD Score	7.52 ± 1.67 (6 - 13)	8.27 ± 2.46 (6 - 13)	0.286 ^
Left Hepatic Mass	25 (50%)	3 (20%)	0.110 #
Tumor Size	8.28 ± 4.02 (5 - 11)	9.07 ± 2,52 (5 - 11)	0.368 ^*
Single tumor	46 (92%)	13 (86.67%)	0.531 #
Preoperative AJCC Stage I	38 (76%)	9 (60%)	0.115 #
Barcelona Class A	27 (54%)	5 (33.33%)	**0.024 #***
Open Resection	49 (98%)	15 (100%)	0.581 #
Anatomical resection	7 (14%)	2 (13.33%)	0.984 #
Use of Habib Sealer	29 (58%)	11 (73.33%)	0.636 #
Use of RFA	3 (6%)	0 (0%)	0.654 #
Grade III Tumor	22 (44%)	10 (66.67%)	0.270 ^
Portal vein Invasion	1 (2%)	4 (26.67%)	**0.002 #***
Involved Surgical Margins	17 (34%)	7 (46.67%)	0.373 #

Data in mean±SD (Range), N(%)   ^ Student t test # Chi-Square test   * Statistically Significant

4. Discussion

Hepatocellular carcinoma recurrence is divided into early recurrence (less than 2 years) and late recurrence (more than 2 years) according to the time to recurrence after surgery. Early recurrence within 2 years after surgery is most likely the consequence of occult metastasis from the initial tumor, whereas late recurrence after 2 years post surgery is often of clonal origin, which is different from the original tumor, suggesting a de novo second primary HCC [4].

In this study, recurrence had occurred in 33 patients (52.38%). at resection site in 5 patients (7.94%), at other segments in 28 patients (44.44%) and at distant areas in 6 patients (9.52%). In Xu and colleagues study (2019), recurrence occurred in 41.3% of the 734 patients. In 303 patients with late recurrence, 273 (90.1%) had intrahepatic recurrence only, 30 (9.9%) had both intrahepatic and extrahepatic

recurrence, and none had extrahepatic recurrence only [4].

In this study, findings on upper endoscope, the site and size of the tumors, the preoperative AJCC stages and pathological grade of tumors affected the recurrence (p 0.015, 0.001, <0.001, 0.035 and <0.001, respectively). By logistic regression multivariate analysis, the mean size of HCC and the pathological grade were the most significant factors. In Xu and colleagues study (2019), Male sex, cirrhosis, multiple tumors, satellite nodules, tumor size greater than 5 cm, and macroscopic and microscopic vascular invasion were independent risk factors of recurrence [4].

The definition of perioperative mortality in most published studies was death in hospital or death within 30 days after the operation. Recent studies reported perioperative mortality rates of 2.6% to 8.4% for HCC patients undergoing major liver resection. In this

study, postoperative mortality occurred in 2 patients (3.08%); one at the first postoperative day and the other after 12 days. In Lee and colleagues study (2016), the 30-day mortality rate was 1.8% [5].

In this study, the preoperative serum albumin, the presence of vascular invasion and Barcelona class affected the survival (p 0.002, 0.005, 0.002 and 0.024, respectively). By logistic regression multivariate analysis, the presence of portal vein invasion by the tumor was the most significant factor. In Lee and colleagues study (2016), they found that diabetes mellitus, hypoalbuminemia, high AFP, massive blood loss, and major surgical procedure are independently associated with early mortality for patients undergoing liver resection [5].

5. Conclusion

Findings on upper endoscope, the site and size of the tumors, the preoperative AJCC stages and pathological grade of tumors were independently associated with recurrence while preoperative serum albumin, the presence of vascular invasion and Barcelona class were associated with survival. On multivariate analysis, the mean size of HCC and the pathological grade were the most significant factors affected the recurrence while the presence of vascular invasion was the most significant factors that affect the survival.

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