

Predictive Factors for Early Mortality after Hepatic Resection for Hepatitis C Virus Related Hepatocellular Carcinoma: A Single Center Experience

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Abstract

Background: Hepatocellular Carcinoma (HCC) is the most common malignancy affecting the liver. It accounts for almost ninety percentage of primary malignancies affecting the liver. HCC develops on a carcinogenic background of liver cirrhosis.

Aim of Study: To evaluate our center experience of liver resection for Hepatitis C Virus (HCV) related Hepatocellular Carcinoma (HCC) to determine the predictive factors of early post-operative mortality.

Patients and Methods: We reviewed the data for all consecutive patients who underwent liver resection for HCV related HCC during the period between January 2010 and June 2018.

Results: Two hundred fourteen consecutive patients were included in the study. The median age was 59 years (18-78), and median MELD score was 7 (6-16). The median operation time was 170 minutes (70-380) and median blood loss was 680ml (100-5000).

The median hospital stay was 5 days (2-60). Post-operative morbidities occurred in 120 patients (56%). Early post-operative mortality occurred in 19 patients (8.9%), all of them developed variable degrees of post-hepatectomy liver dysfunction.

The median follow-up duration was 22 months (5-110). Recurrence occurred in 130 patients (60.7%). The 1-, 3-, and 5-years disease-free survival rates were 69.2%, 35.4%, and 17.6%, respectively. Late mortality occurred in 59 patients (27.6%). The 1-, 3-, and 5-years overall survival rates were 78.2%, 59.1%, and 50%, respectively.

Predictive factors for early mortality included pre-operative albumin, Child-Pugh score, MELD score, blood loss, severe post-operative morbidities, renal complications, and post-hepatectomy liver dysfunction.

Conclusion: Proper selection of liver resection candidates based on pre-operative laboratory findings, together with

meticulous surgical techniques to minimize blood loss can help to avoid early post-operative mortality.

Key Words: Hepatocellular carcinoma – Liver resection – Early mortality – Post-hepatectomy liver dysfunction.

Introduction

HEPATOCELLULAR Carcinoma (HCC) is the most common malignancy affecting the liver. It accounts for almost ninety percentage of primary malignancies affecting the liver. HCC develops on a carcinogenic background of liver cirrhosis [1]. In Egypt, hepatitis C virus remains the most common underlying cause of liver cirrhosis and subsequently HCC [2].

Liver resection and liver transplantation remain the main curative treatment modalities for patients with HCC [1,2]. Due to the several limitations of liver transplantation especially in a country like Egypt where deceased donors are not allowed yet, liver resection remains a corner stone in HCC curative treatment. In the recent years, great improvements had been accomplished in the surgical techniques and perioperative patient care. However, unexpected early mortality after liver resection can occur which is greatly depressive to the surgeon and the patient's family [4]. Previous studies from tertiary centers had reported a varying incidence of early post-operative mortality after liver resection for HCC ranging between 2.6% and 8.4% [5,6]. This is mainly dependent on the identification of the time frame for early post-operative mortality. Identification of different risk factors that can predict the occurrence of early post-operative mortality is essential to avoid the occurrence of this catastrophic event.

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The current study was done to review our center experience of liver resection for Hepatitis C Virus (HCV) related HCC and determine the incidence, causes, and predictive factors affecting early post-operative mortality in a tertiary high-volume center.

Patients and Methods

Study design:

We retrospectively reviewed the data of consecutive patients who underwent liver resection for HCV-related HCC at Gastrointestinal Surgery Center, Mansoura University, Egypt during the period between January 2010 and June 2018.

An informed consent was obtained from each patient prior to surgical procedure. The study was approved by Institutional Review Board and Local Ethical Committee at College of Medicine, Mansoura University, Egypt.

Pre-operative evaluation:

Pre-operative evaluation included detailed patient complaint evaluation, general and abdominal examination, laboratory investigations including serum alpha-fetoprotein, and radiological evaluation including abdominal ultrasonography and triphasic computed tomography or magnetic resonance imaging. Upper gastrointestinal endoscopy was done to rule out esophageal varices and metastatic work up was performed to rule out distant metastasis.

Patients were discussed in multidisciplinary meetings to select the appropriate treatment strategy. Liver resection was applied for patients with adequate liver functions (Child A or early B) with sufficient future liver remnant.

Surgical technique:

The surgical procedure had been described elsewhere [2,7]. Brisbane 2000 terminology was used to identify the different types of curative liver resection [8]. Categories of liver resection were subdivided into minor liver resection (≤ 2 contiguous segments) and major liver resection (> 2 contiguous segments) depending on Couinaud classification. Parenchymatous dissection was done using harmonic scalpel (Ethicon, Cincinnati, OH, USA) and clamp crush technique with the aim of at least 2cm safety margin. Pringle maneuver was used in some cases either elective or emergent to minimize the blood loss during parenchymal transection.

Post-operative care and follow-up:

After surgery, patients were transferred to the intensive care unit or to the ward for monitoring of vital signs and abdominal drains. All patients

underwent daily laboratory evaluation including liver functions. Abdominal ultrasonography and chest radiographs were performed routinely in all patients. Oral fluids were started once intestinal sounds are restored. Abdominal drains were removed when daily output is less than 100cc with absence of any abdominal collections.

After discharge, patients were followed-up in the outpatient clinic every 2 weeks in the first month, every month during the first 3 months, then every three months for the first year. Biannual visits were arranged later. Follow-up visit included physical examination, laboratory evaluation including alpha fetoprotein, abdominal ultrasonography, and triphasic computed tomography when recurrence is suspected.

Clinical outcomes:

Post-operative morbidity was demarcated as any deviation from the regular post-operative path. Post-operative morbidities were recorded and categorized depending on the Clavien-Dindo classification [9]. Severe post-operative morbidities included patients with complication grade (III) or more.

Early post-operative mortality was defined as death during the first 90 days following the operation. Post-operative biliary fistula and posthepatectomy liver failure were defined according to the International Study Group of Liver Surgery [10,11].

Overall survival (OS) was estimated from the surgery day to death or censored at the day of last follow-up visit. Disease Free Survival (DFS) was estimated from the surgery day to confirmed tumor recurrence day.

Statistical analysis:

Data management and statistical analyses were done using SPSS for Windows (IBM-SPSS version 22). Shapiro-Wilk test was used to assess the normality of the data.

Parametric data were presented as number and percentage while non-parametric data were presented as medians and range. Survival analysis was performed by the Kaplan-Meier method and compared by Log-Rank test. Univariate and multivariate analysis for predictive factors for early mortality was performed by Cox regression analysis.

Significant factors determined in the univariate analysis are included in the subsequent multivariate analysis. A *p*-value < 0.05 was considered statistically significant.

Results

During the study period, 214 patients underwent liver resection for HCV-related HCC and were included in the current study.

Baseline characteristics: The demographic data of the study patients are summarized in (Table 1). The median age was 59 years (18-78), and median MELD score was 7 (6-16).

Table (1): Baseline characteristics and operative data of the study patients.

Variables	Data
Baseline characteristics	
Age (years)	59 (18-78)
<i>Sex:</i>	
Male	170 (79.4%)
Female	44 (20.6%)
Albumin (g/dl)	3.8 (2.7-5)
Bilirubin (mg/dl)	0.7 (0.4-11.2)
International normalized ratio	1 (1.0-1.8)
Platelet (X 10 ³ /mm)	145 (34-433)
Creatinine (mg/dl)	0.8 (0.5-1.7)
Alpha feto-protein (ng/ml)	30 (1-2000)
Model for end stage liver disease	7 (6-16)
<i>Child Pugh classification:</i>	
A	211 (98.6%)
B	3 (1.4%)
Esophageal varices	38 (17.6%)
Operative data:	
<i>Lesion number:</i>	
Single	196 (91.6%)
Multiple	18 (8.4%)
<i>Lesion site:</i>	
Right hemi-liver	114 (53.3%)
Left-hemi-liver	90 (42.1%)
Caudate lobe	5 (2.3%)
Bilobar	5 (2.3%)
<i>Resection category:</i>	
Minor	162 (75.7%)
Major	52 (24.3%)
<i>Resection type:</i>	
Localized resection	102 (47.7%)
Segmentectomy	5 (2.3%)
Left lateral sectionectomy	44 (20.5%)
Right anterior sectionectomy	1 (0.5%)
Right posterior sectionectomy	1 (0.5%)
Caudate lobectomy	5 (2.3%)
Right hemi-hepatectomy	38 (17.8%)
Left hemi-hepatectomy	7 (3.3%)
Extended right hemi-hepatectomy	5 (2.3%)
Extended left hemi-hepatectomy	1 (0.5%)
Central hepatectomy	1 (0.5%)
Multiple resections	4 (1.9%)
Pringle maneuver	34 (15.9%)
Operation time (minutes)	170 (70-380)
Blood loss (ml)	680 (100-5000)
<i>Blood transfusion:</i>	
Yes	109 (50.9%)
No	105 (49.1%)

Operative data:

The operative data of the study patients are summarized in (Table 1). Solitary lesion was found in 196 patients (91.6%) while multiple lesions was found in 18 patients (8.4%). The median operation time was 170 minutes (70-380) and median blood loss was 680ml (100-5000).

Table (2): Post-operative and pathological data of the study patients.

Variables	Data
Post-operative data	
Hospital stay (days)	5 (2-60)
Post-operative morbidities	120 (56%)
Severe morbidities	40 (18.7%)
<i>Clavien-Dindo grades:</i>	
I	46 (21.5%)
II	34 (15.9%)
IIIA	10 (4.7%)
IIIB	9 (4.2%)
IVA	2 (0.9%)
V	19 (8.9%)
Internal hemorrhage	6 (2.8%)
Biliary complications	11 (5.1%)
Liver dysfunction	111 (51.9%)
<i>Vascular complications:</i>	
Portal vein thrombosis	5 (2.3%)
Abdominal collection	14 (6.5%)
Respiratory complications	17 (7.9%)
Renal complications	4 (1.9%)
Reoperation	7 (3.3%)
Early mortality	19 (8.9%)
Pathological data:	
<i>Background liver status:</i>	
Cirrhosis	212 (99.1%)
Fibrosis	2 (0.9%)
<i>Lesion number:</i>	
Single	196 (91.6%)
Multiple	18 (8.4%)
Size (cm)	6.5 (2-17)
<i>Safety margin:</i>	
R0	188 (87.9%)
R1	26 (12.1%)
<i>Microvascular invasion:</i>	
Yes	104 (48.6%)
No	110 (51.4%)
<i>Grading:</i>	
I	42 (19.6%)
II	120 (56.1%)
III	48 (22.4%)
IV	4 (1.9%)
<i>Staging:</i>	
T1	41 (19.2%)
T2	120 (56.1%)
T3	20 (9.3%)
T4	33 (15.4%)

Post-operative data:

The post-operative data of the study patients are summarized in (Table 2). The median hospital stay was 5 days (2-60). Post-operative morbidities

occurred in 120 patients (56%). Early post operative mortality occurred in 19 patients (8.9%), all of them developed variable degrees of post-hepatectomy liver dysfunction. Two patients (0.9%) developed severe portal vein thrombosis which failed to respond to anticoagulant therapy. Four patients (1.9%) developed hepato-renal syndrome. Four patients (1.9%) developed complicated pleural effusion that required radiology guided CVP insertion. One patient (0.5%) developed attack of hematemesis (variceal bleeding) one month post-operatively, for whom endoscopic banding was performed but the patient died with multi-organ failure.

Pathological data:

The pathological data of the study patients are summarized in (Table 2). Liver cirrhosis was found in 212 patients (99.1%) while liver fibrosis was found in 2 patients (0.9%). The median tumor size was 6.5cm (2-17). R0 resection was achieved in 188 patients (87.9%).

Survival outcomes:

The median follow-up duration was 22 months (5-110). Recurrence occurred in 130 patients (60.7%). Most of recurrences occurred in the remnant liver (100 patients-46.7%). Most of recurrences were multifocal and were treated by palliative supportive care (74 patients-34.6%). The 1-, 3-, and 5-years DFS rates were 69.2%, 35.4%, and 17.6%, respectively (Table 5) and Fig. (1).

Late mortality occurred in 59 patients (27.6%). The 1-, 3-, and 5-years OS rates were 78.2%, 59.1%, and 50%, respectively (Table 5) and Fig. (2).

Predictive factors for early mortality:

Several factors were analyzed to determine the predictive factors for early mortality among the study patients (Table 4). On univariate analysis, pre-operative albumin, pre-operative INR, pre-operative alpha feto-protein, Child-Pugh score, MELD score, presence of macrovascular invasion, resection extent, blood loss, blood transfusion, severe post-operative morbidities, respiratory complications, renal complications, vascular complications, and posthepatectomy liver dysfunction were associated with early post-operative mortality.

On multivariate analysis, pre-operative albumin, Child-Pugh score, MELD score, blood loss, severe post-operative morbidities, renal complications, and post-hepatectomy liver dysfunction were significant predictors for early post-operative mortality.

Table (3): Long-term survival outcomes of the study patients.

Variables	Data
Mortality	59 (27.6%)
Recurrence	130 (60.7%)
Recurrence time (months)	15 (4-110)
<i>Recurrence site:</i>	
Intra-hepatic	100 (46.7%)
Extra-hepatic	2 (0.9%)
Both	28 (13.1%)
<i>Intrahepatic management:</i>	
Redo surgery	4 (1.9%)
Transarterial chemoembolization	31 (14.5%)
Radiofrequency ablation	9 (4.2%)
Microwave ablation	3 (1.4%)
Combined	7 (3.3%)
Palliative	74 (34.6%)
<i>Extrahepatic location:</i>	
Lung	17 (7.9%)
Bone	3 (1.4%)
Adrenal	1 (0.5%)
Abdominal wall	1 (0.5%)
Peritoneum	4 (1.9%)
Multi-site	4 (1.9%)

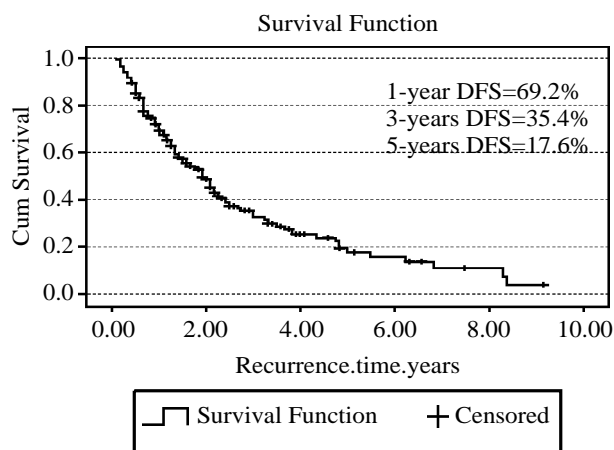


Fig. (1): Kaplan Meier disease free survival curve of the study patients.

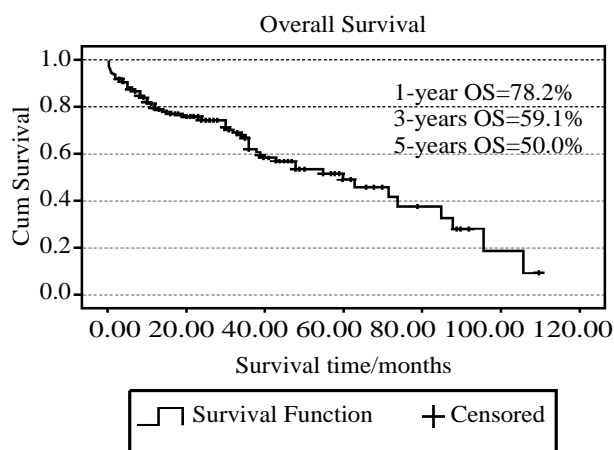


Fig. (2): Kaplan Meier overall survival curve of the study patients.

Table (4): Predictive factors of early mortality.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age		0.645		
Sex		0.07		
Albumin	0.241 (0.106-0.55)	0.001	0.003 (0-7.253)	0.009
Bilirubin		0.286		
INR	62.8 (8.076-489.19)	0.001	0.61 (0-75.798)	0.12
Platelets		0.546		
Creatinine		0.838		
Alpha feto-protein	1.001 (1-1.001)	0.035	1 (0.998-1.002)	0.85
CTP score	4.961 (1.12-21.84)	0.034	0.03 (0.001-0.248)	0.009
MELD score	1.31 (1.11-1.54)	0.002	5.635 (1.36-23.25)	0.017
Lesion number (tumor multifocality)		0.539		
Macrovascular invasion	3.883 (1.34-11.17)	0.012	2.417 (0.006-1021.3)	0.775
Resection extent (minor vs major)	2.676 (0.997-7.187)	0.051	3.665 (0.003-416.22)	0.717
Portal thrombectomy		0.296		
Pringle use		0.090		
Operation time		0.067		
Blood loss	1.001 (1-1.001)	0.009	1.61 (1.09-2.64)	0.042
Blood transfusion	0.140 (0.032-0.615)	0.009	0.026 (0-1896.59)	0.522
Sever morbidity	18.15 (6.88-47.84)	0.001	16.82 (4.66-60.64)	0.015
Respiratory complication	0.222 (0.072-0.688)	0.009	0.065 (0-11.428)	0.3
Renal complication	0.012 (0.003-0.046)	0.001	0.001 (0-0.076)	0.002
Biliary complications		0.530		
Vascular complications	0.158 (0.036-0.683)	0.014	0.055 (0.001-5.498)	0.217
Liver dysfunction	22.53 (5.72-88.77)	0.001	237.61 (3.09-182.74)	0.013
Reoperation		0.406		
Tumor size		0.101		
Resection margin		0.136		
Microvascular invasion		0.279		
Tumor grade		0.852		
Tumor stage		0.156		

Discussion

HCC is one of the most common malignancies worldwide. Surgery is the mainstay of HCC treatment. Liver resection and liver transplantation are considered the only curative treatment modalities, and achieve the best outcomes in properly-selected candidates, with 5-year survival rate of 60-80% [3,12].

Liver resection is accepted as the first line treatment in non-cirrhotic patients with HCC, as well as in cirrhotic patients with well-preserved liver function, and no signs of clinically significant portal hypertension. Unfortunately, the majority of patients presenting with HCC cannot undergo curative resection due to either impaired liver function, presence of portal hypertension, or tumor stage, and only 10-20% are considered surgical candidates [12].

In spite of the recent improvements in the surgical techniques and perioperative patient care, liver resection for HCC still a major procedure that conveys considerable risks for postoperative morbidity and mortality [4]. The occurrence of

early post-operative mortality is one of the most depressive morbidities not only for the patient's family but also to the surgical team. Previous studies from tertiary centers had reported a varying incidence of early post-operative mortality after liver resection for HCC ranging between 2.6% and 8.4% [4-6]. In the current study, early post-operative mortality occurred in 19 patients (8.9%) after liver resection for HCV-related HCC. The main underlying cause for the development of early post-operative mortality was post-hepatectomy liver dysfunction. Two patients (0.9%) developed severe portal vein thrombosis which failed to respond to anticoagulant therapy. Four patients (1.9%) developed hepato-renal syndrome. Four patients (1.9%) developed complicated pleural effusion that required radiology guided CVP insertion. One patient (0.5%) developed attack of hematemesis (variceal bleeding) one month post-operatively, for whom endoscopic banding was performed but the patient died with multi-organ failure. We previously reported that Egyptian patients experienced higher incidence of post-hepatectomy liver failure compared to other HCC series with other underlying pathologies [2]. In the current series, post hepatec-

tomy liver failure occurred in 111 patients (51.9%). Most of the patients experienced grade A liver dysfunction only, however other patients experienced more severe dysfunction and even failure which was the main underlying cause of early post-operative mortality.

We analyzed possible underlying risk factors for the development of early post-operative mortality. On multivariate analysis, pre-operative albumin, Child-Pugh score, MELD score, blood loss, severe post-operative morbidities, renal complications, and post-hepatectomy liver dysfunction were significant predictors for early post-operative mortality.

Multiple clinical parameters can be used to assess a patient's liver reserve status before liver resection and predict development of severe post-hepatectomy liver dysfunction and hence early mortality such as serum albumin, bilirubin level, INR, platelet count, the presence esophageal varices and other signs of portal hypertension, MELD score, Child-Pugh score and Indocyanine Green (ICG) clearance test. Greco et al., identified ICG-15min >15%, INR >1.2 and MELD score as independent predictors of severe post-hepatectomy liver dysfunction and early mortality [13]. This in agreement with our current study, which identified that pre-operative albumin, Child-Pugh score, and MELD score were independent predictors for the development of early post-operative mortalities.

Intraoperative blood loss and subsequently the need for blood transfusion had been reported to be associated with the development of severe immunological reactions and increased risk for post-operative morbidities especially infectious complications [14,15]. In the current study, both intraoperative blood loss and transfusion requirement were significant predictors for early post-operative mortality in univariate analysis but only intraoperative blood loss was significant in multivariate analysis.

Morbidity rate after liver resection remains high as reported in recent studies, with an incidence of 32-55.5% [16,17]. This variability of morbidity rate in the literature is because of a lack of proper definition of surgical complications especially those which are liver related complications. Harimoto and his colleagues mentioned in the study over 966 patients that severe post-operative complications were identified in 17.1% of patients. Severe complications included; early mortality 0.9%, bile leakage 3.4%, liver failure and ascites 2.6%, pleural effusion 2.1% and intra-abdominal collection 2.9% [18]. Okamura and his colleagues mentioned in

their study over 376 patients that post-operative complications were identified in 47.1% of patients while severe post-operative complications were identified in 28.5%. Overall complication included; early mortality 4.5%, bile leakage 9.3%, liver failure and ascites 9%, pleural effusion 15.7%, intra-abdominal collection 5.3%. They concluded also that whether complications were major or minor, the overall survival of patients with post-operative complications is significantly poorer than that of those without post-operative complications [19]. In the current study, post-operative morbidities occurred in 120 patients (56%) and severe morbidities occurred in 40 patients (18.7%). The development of severe post-operative morbidities especially liver dysfunction and renal troubles were significant predictors of early post-operative mortality.

The current study had some limitation including it is single-center retrospective study which is liable to some selection bias. A future multicenter study among Egyptian centers including larger number of HCC patients is needed to confirm our findings.

In conclusion, early post-operative mortality after liver resection for HCC is a catastrophic event not only for the patient's family but also to the surgical team. We found that pre-operative albumin, Child-Pugh score, MELD score, blood loss, severe post-operative morbidities, renal complications, and post-hepatectomy liver dysfunction were significant predictors for early post-operative mortality. Proper selection of candidates for liver resection based on preoperative laboratory findings, together with meticulous surgical techniques to minimize blood loss can help to avoid this catastrophic event.

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العوامل التنبؤية للوفيات المبكرة بعد الإستئصال الكبدى لسرطان الخلايا الكبدية المرتبطة بفيروس التهاب الكبد الوبائى سى؛ دراسة خبرة مركز واحد

الهدف من الدراسة: تقييم خبرة مركز جراحة الجهاز الهضمى - جامعة المنصورة للإستئصال الكبدى لسرطان الخلايا الكبدية المرتبطة بفيروس التهاب الكبد الوبائى سى لتحديد العوامل التنبؤية للوفيات المبكرة بعد الإستئصال الكبدى.

طريقة الدراسة: قمنا بمراجعة بيانات المرضى الخاضعين للإستئصال الكبدى لسرطان الخلايا الكبدية المرتبطة بفيروس التهاب الكبد الوبائى سى مركز جراحة الجهاز الهضمى - جامعة المنصورة خلال الفترة من يناير ٢٠١٠ ويناير ٢٠١٨.

نتائج الدراسة: ضمت الدراسة مائتين وأربعة عشر مريضاً على التوالى. وقد وجدنا أن متوسط العمر ٥٩ عاماً (١٨-٧٨)، ومتوسط درجة إعتلال الكبد ٧ (٦-١٦). كان متوسط وقت الجراحة ١٧٠ دقيقة (٧٠-٣٨٠) ومتوسط فقد الدم أثناء الجراحة ٦٨٠ مل (١٠٠-٥٠٠).

وكذلك وجدنا أن متوسط الإقامة فى المستشفى ٥ أيام (٢-٦٠). حدثت مضاعفات ما بعد الجراحة فى ١٢٠ مريضاً (٥٦٪). حدثت الوفيات المبكرة بعد العملية الجراحية فى ١٩ مريضاً (٨.٩٪)، وقد وجدنا أن جميعهم طوروا درجات متفاوتة من الفشل الكبدى بعد الإستئصال الكبدى.

كان متوسط مدة المتابعة ما بعد الجراحة ٢٢ شهراً (٥-١١٠). حدث إرتداد الورم فى ١٣٠ مريضاً (٦٠.٧٪). كانت معدلات البقاء على قيد الحياة الخالية من إرتداد الورم لمدة ١ و ٣ و ٥ سنوات ٦٩.٢٪ و ٣٥.٤٪ و ١٧.٦٪ على التوالى. حدثت الوفيات المتأخرة فى ٥٩ مريضاً (٢٧.٦٪). كانت معدلات البقاء على قيد الحياة لمدة ١ و ٣ و ٥ سنوات ٧٨.٢٪ و ٥٩.١٪ و ٥٠٪ على التوالى.

تضمنت العوامل التنبؤية للوفيات المبكرة نسبة الألبومين قبل الجراحة، ودرجات إعتلال وظائف الكبد، ونسبة فقدان الدم أثناء الجراحة، والمضاعفات الشديدة بعد الجراحة، والمضاعفات الكلوية، ودرجات الفشل الكبدى بعد إستئصال الكبد.

الإستنتاجات: من خلال الدراسة يمكننا أن نستنتج أن الإختيار المناسب لمرضى الإستئصال الكبدى بناءً على النتائج المعملية ما قبل الجراحة، بالإضافة إلى التقنيات الجراحية الدقيقة لتقليل فقد الدم يساعد على تقليل حدوث الوفيات المبكرة بعد الإستئصال الكبدى لسرطان الخلايا الكبدية المرتبطة بفيروس التهاب الكبد الوبائى سى.