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Predictors of Recurrence in Hepatitis C Virus Related Hepatocellular Carcinoma after Hepatic Resection: A Retrospective Cohort Study

Karaciğer Rezeksiyonu Sonrası Oluşan Hepatit C Virüsü ile Bağlantılı Hepatosellüler Karsinom Rekürrensi Prediktörleri: Retrospektif Bir Çalışma

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Abstract

Objective: Egypt is one of the hot spots in the international map of Hepatocellular carcinoma (HCC), which is where hepatitis C virus (HCV) infection is the major risk factor in development of HCC (80%). Due to low organ donation rates and lack of deceased liver transplantation, hepatic resection is the main line of treatment for HCC patients with sufficient liver reserve. We introduce our experience with patients who had HCV related HCC who underwent hepatic resection to determine various predictors of tumour recurrence in this group. This is the first study to come from a country where chronic HCV hepatitis is endemic.

Materials and Methods: This is a retrospective cohort study of 208 cases of HCC in hepatitis C virus positive patients with cirrhotic livers who underwent first-time liver resection, in Gastroenterology Surgical Centre, Mansoura University, Egypt during the period from January 2002 to December 2011. Shapiro-Wilk test was used to assess normality of data. Predictors of HCC recurrence were assessed by bivariate correlation tests, univariate analysis using the chi-square and t-test and binary logistic regression analysis. A P value <0.05 was considered statistically significant.

Results: Tumour recurrence occurred in 88 patients (42.3%). Most of the recurrences occurred within the first year 55 patients (62.5%). The most common site for recurrence was the liver (n=68, 77.3%). Based on the univariate analysis; significant variables predicting tumor recurrence were alpha feto-protein (AFP), blood transfusion, multifocality, cut margin, microvascular invasion, lack of capsule, tumour grade and stage. Based on multivariate analysis, the main variables predicting tumor recurrence were blood transfusion, cut margin, tumour capsule and microvascular invasion.

Conclusion: Although the predictors of recurrence are the same for both HBV and HCV related HCC, the rate and aggressiveness of recurrence are higher in HCV related HCC.

Key Words: HCV related HCCs, liver resection, recurrent HCC

Özet

Amaç: Mısır; hepatit C virüsü (HCV) enfeksiyonunun Hepatocellular karsinomun (HCC) görülmesinde önemli (% 80) bir risk faktörü olduğu, uluslararası HCC haritasındaki sıcak noktalardan biridir. Organ bağışı oranlarının düşük olması ve kadavradan karaciğer nakli eksikliği sebebiyle, karaciğer rezeksiyonu, yeterli karaciğer rezervi olan HCC hastalarının tedavisinde ana yöntemdir. Bu grupta HCV'ye bağlı HCC'si olan hastalarda tümör nüksünün çeşitli faktörlerini araştırmak için karaciğer rezeksiyonu deneyimimizi aktarmak amacındayız. Bu, kronik HCV hepatitinin endemik olduğu bir ülkeden gelen ilk çalışmadır.

Gereç ve Yöntem: Bu, Ocak 2002-Aralık 2011 süresince Mısır'ın Mansoura Üniversitesi, Gastroenterolojik Cerrahi Merkezinde ilk kez karaciğer rezeksiyonu yapılan sirotik karaciğerli HCC, hepatit C virüsü pozitif hastalarda 208 vakanın retrospektif kohort çalışmasıdır. Verilerin normalliğini değerlendirmek için Shapiro-Wilk testi kullanılmıştır. HCC nüks prediktörleri ikili korelasyon testleri, tek değişkenli ki- kare ve t - testi analizi ve lojistik regresyon analizi kullanılarak değerlendirilmiştir. p<0,05 istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular: Tümör nüksü 88 hastada (%42,3) görülmüştür. Nükslerin çoğu ilk yıl içinde 55 hasta (%62,5) olmuştur. Nüks için en fazla (n=6, %77,3) karaciğerde görülmüştür. Tek değişkenli analize dayanarak, tümör nüksünü tahmin etmekte anlamlı değişkenler; AFP, kan transfüzyonu, multifokalite, kesi sınırı, mikrovasküler invazyon, kapsül eksikliği, tümör derecesi ve evresi idi . Çok değişkenli analize dayanarak, tümör nüksü tahmininde ana değişkenler; kesi sınırı, tümör kapsülü ve mikrovasküler invazyon, kan transfüzyonu idi.

Sonuç: Nüks prediktörleri HBV ve HCV'ye bağlı HCC'nin her ikisi için de aynı olmasına rağmen, nüks oranı ve agresiflik HCV'ye bağlı HCC'de daha yüksektir.

Anahtar Kelimeler: HCV'ye bağlı HCC'ler, karaciğer rezeksiyonu, tekrarlayan HCC

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, and the third most common aetiology of cancer-associated mortality [1]. The incidence of HCC in the Europe is 8.29/100 000, while in Asia and Africa it is 120/100 000 owing to high rates of viral hepatitis (B and C) [2]. Nowadays, Egypt is considered as one of the hot spots in the international map of HCC, that is where hepatitis C virus (HCV) infection (genotype 4) is the major risk factor in development of HCC (approximately 80% of the cases) [3].

Hepatic resection and liver transplantation are the main lines of curative treatment for HCC [1]. In countries (such as Egypt) with a high incidence of HCC owing to endemic viral hepatitis, low organ donation rates and lack of deceased liver transplantation, primary hepatic resection is the first line of treatment for HCC patients with sufficient liver reserve [4].

In this study, we introduce our experience after long term follow-up of patients who underwent hepatic resection for HCV related HCC in cirrhotic liver.

Materials and Methods

This is a retrospective cohort study of 208 cases of HCC in hepatitis C virus positive patients with cirrhotic livers who underwent first-time liver resection, in the Gastroenterology Surgical Centre, Mansoura University, Egypt during the period from January 2002 to December 2011. Patient data was retrieved from internal web-based registry system supplemented by paper records included in the medical archive.

Patient selection criteria were Child-Pugh class A or B, performance status 0-2, and positive markers for HCV. Other patients with positive serum markers for hepatitis B virus (HBV) or negative for both HCV and HBV were excluded.

The extent of the hepatic resection was based on the International Hepato-Pancreato-Biliary Association classification. Major hepatectomy was defined by resection of three or more hepatic segments according to Couinaud's classification, and segmentectomy was defined by resection of less than three hepatic segments [5].

All patients were followed up every month in the first 3 months and every 3-6 months thereafter. The visit consisted of physical examination, liver function tests, serum alpha fetoprotein (AFP) level, abdominal ultrasound (US), and triphasic computed tomography (CT) when recurrence is suspected.

Shapiro-Wilk test was used to assess normality of data. Numerical data is presented as means and standard deviations or as medians with ranges. A P value <0.05 was considered statistically significant. Bivariate correlation tests were done to estimate the correlation between different variables and recurrence. Univariate analysis then was done for all the correlated factors (independent variables) using the chi-square and t-test. The variables that were significant by univariate analysis were subsequently analysed using the binary logistic regression analysis. Statistical analysis was done with the help of IBM SPSS v. 20.

Results

The clinical characteristics of the patients and operative data is shown in (Table 1). Postoperative pathological data is shown in (Table 2). The mean hospital stay was 9.04 days

Table 1. Clinical and operative data

Clinical Data	Number (208)	Per cent (%)
Age in years		
• Range	26-75	
• Mean	55.4	
• S.D.	9.3	
Sex		
• Males	157	75.5%
• Females	51	24.5%
Clinical presentation		
• Pain	152	73.1%
• Accidentally discovered	31	14.9%
• Mass	17	8.2%
• Jaundice	4	1.9%
• Others	4	1.9%
Child Pugh classification		
• Class A	183	88%
• Class B	25	12%
Resection type		
• Major resection	73	35.1%
• Segmentectomy	74	35.6%
• Localized resection	61	29.3%
Operative time in hours		
• Range	1-6	
• Mean	3.08	
• S.D.	0.94	
Pringle's manoeuvre		
• Absent	117	56.2%
• Present	91	43.8%
Perioperative blood transfusion		
• Absent	77	37%
• Present	131	63%

(range: 4-32 days). Hospital morbidity occurred in 76 patients (36.6%). Hospital mortality occurred in 19 patients (9.1%) from acute liver insult; 10 of them were Child B. The median survival after resection was 14 months. One year survival was 62.9%, 3 years survival was 25.9% and 5 years survival was 19.1%. Tumour recurrence occurred in 88 patients (42.3%). Most of the recurrences occurred within the first year 55 patients (62.5%). The most common site for recurrence was the liver (n=68, 77.3%) (Table 3).

Various clinical, laboratory, operative and pathological variables were analysed to determine its relation to tumour recurrence. Clinical variables include age, sex, symptoms and Child-Pugh classification. Laboratory variables include pre-operative serum albumin, bilirubin, aspartate transaminase (AST), alanine transaminase (ALT) and AFP. Operative variables include type of resection, perioperative blood transfusion, use of Pringle's manoeuvre and operative time. Pathological variables include site of tumour, size of tumour, multifocality, portal vein invasion, cut margin infiltration, positive lymph nodes, lack of capsule, tumour grade and stage.

Based on the univariate analysis; significant variables predicting tumour recurrence were AFP, blood transfusion, multifocality, cut margin, microvascular invasion, lack of capsule, tumour grade and stage (Table 4). Based on multivariate analysis, the main variables predicting tumour recurrence were blood transfusion, cut margin, tumour capsule and microvascular invasion (Table 5).

Table 2. Postoperative pathological data

Pathological Data	Number (208)	Per cent (%)
Tumour size		
• <5 cm	39	18.8%
• 5-10 cm	111	53.4%
• >10 cm	58	27.9%
Capsule		
• Absent	154	74%
• Present	54	26%
Cut margin		
• Free	168	81.2%
• Infiltrated	40	18.8%
Microvascular invasion		
• Absent	151	72.6%
• Present	57	27.4%
Lymph nodes		
• Negative	194	93.3%
• Positive	14	6.7%
Tumour grade		
• I	48	23.1%
• II	91	43.7%
• III	69	33.2%
Tumour stage		
• I	133	63.9%
• II	31	14.9%
• IIIa	27	13%
• IIIb	4	1.9%
• IIIc	13	6.2%

Discussion

With advancement of surgical techniques and postoperative care, hepatic resection in cirrhotic patients with HCC became a safe procedure and the gold standard treatment for HCC patients. The long term outcome of hepatic resection remains unsatisfactory due to tumour recurrence [6]. The incidence is extremely high, with 40-100% 5-year cumulative recurrence rates and 80-95% of recurrences occur in the remnant liver [7, 8]. In our study tumour recurrence occurred in 88 patients (42.3%) and most recurrences occurred in the liver (77.3%). The cumulative recurrence rates of HCV related HCCs are higher than HBV related HCCs [9-11]. This could be explained by the high viral replication and hepatic inflammation in HCV related HCCs. Also, HCV related HCCs have a higher incidence of tumour multicentricity [9, 10]. Recently, it is found that HCV related HCCs are associated with expression of Twist (a regulator of mesenchymal cells transition), which plays an important role in invasiveness and metastasis [11].

Table 3. Recurrence: RFA, TACE

	Number (208)	Percent (%)
Recurrence		
• Absent	120	57.7%
• Present	88	42.3%
Site of recurrence		
• Liver	68	77.3%
• Distant	8	9.1%
• Both	12	13.6%
Treatment of recurrence		
• RFA	5	5.7%
• TACE	15	17%
• Medical	68	77.3%

RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization

Table 4. Univariate analysis for predictors of tumour recurrence: AFP

Variable	No recurrence		Recurrence		
	Number (101)	Percent (%)	Number (88)	Percent (%)	*p* value
Preoperative AFP					
<400 ng/mL (n=107)	64	59.8%	43	40.1%	0.012
≥400 ng/mL (n=82)	37	45.1%	45	54.9%	
Blood transfusion					
No (n=76)	46	60.5%	30	39.4%	
Yes (n=113)	55	48.7%	58	51.3%	0.000
Multifocality					
Single (n=157)	90	57.3%	67	42.7%	
Multiple (n=32)	11	34.4%	21	65.6%	0.015
Cut margin					
Free (n=153)	93	60.8%	60	39.2%	
Infiltrated (n=36)	8	22.2%	28	77.8%	0.000
Microvascular invasion					
No (n=137)	76	55.5%	61	44.5%	
Yes (n=52)	25	48.1%	27	51.9%	0.005
Tumour capsule					
Absent (n=136)	60	44.1%	76	55.9%	
Present (n=53)	41	77.4%	12	22.6%	0.000
Tumour grade					
I (n=41)	29	70.7%	12	29.3%	
II (n=83)	43	51.8%	40	48.2%	
III (n=65)	29	44.6%	36	55.4%	0.029
Tumour stage					
Stage I (n=121)	76	62.8%	45	37.2%	
> Stage I (n=68)	25	36.8%	43	63.2%	0.000

AFP: Alpha feto-protein

The prognosis of patients with a single tumour nodule is better than those with multiple nodules [12]. Tumour multifocality is due to either intrahepatic metastasis or multicentric occurrence. Both of them could cause recurrence in the remaining liver [7, 8]. In our study, tumour multifocality was a significant predictor for tumour recurrence. This is corroborated by other studies for both HCV related HCCs [3, 9] and HBV related HCCs [6, 10, 13].

A wide resection margin to ensure R0 resection is a general rule in oncological surgery. Despite multiple studies evaluating the importance of wide resection margin for HCC, its importance remained a matter of debate. In Egyptians, the associated liver cirrhosis in HCC patients, due to chronic HCV, limits the extent of hepatic resection. In those patients, if a major hepatic resection is performed, they may die from liver cell failure, as occurred in 10 of our cases. In our study, infiltrated safety margin was a significant variable predicting tumour recurrence. In comparison to other studies evaluating the recurrence in HBV related HCCs; the role of the resection margin is also controversial. Some studies supported a wide safety margin (more than 1 cm) and found it a significant predictor of tumour recurrence [13, 14]. Other studies found no significant association between safety margin and tumour recurrence [15-17].

Alpha feto-protein (AFP) has been suggested as a strong predictor of survival and tumour recurrence after hepatic

Table 5. Uni- and multivariate analysis for predictors of tumour recurrence: AFP

Variable	Univariate analysis	Multivariate analysis
	p value	*p* value
Preoperative AFP	0.012	0.213
Blood transfusion	0.000	0.012
Multifocality	0.015	0.394
Cut margin	0.000	0.003
Microvascular invasion	0.005	0.001
Tumour capsule	0.000	0.005
Tumour grade	0.029	0.549
Tumour stage	0.000	0.161

AFP: Alpha feto-protein

resection [18]. This arises from the association between high AFP levels and tumour size, multifocality and microvascular invasion, which are all recognized predictors of HCC recurrence [19]. HCCs associated with high AFP level had a higher cell proliferative activity and more aggressive behaviour [20]. In our study, AFP was a significant predictor of HCC recurrence; similar to other studies evaluating HCV related HCCs [3, 21] and hepatitis B virus (HBV) related HCCs [13, 22].

Hepatocellular carcinoma (HCC) is characterized by its high affinity for vascular invasion (microvascular or microvascular invasion), which indicates aggressive biological manner of the tumour and is currently one of the most grave predictors of HCC recurrence [23]. The presence of vascular invasion is a reported risk factor for HCC recurrence after hepatic resection for both HCV related HCCs [3, 24] and HBV related HCCs [10, 13, 19]. This was similar to findings in our study.

Hepatic resection for cirrhotics is associated with a high incidence of blood transfusions. Numerous studies reported that blood transfusion causes nonspecific immunosuppression, and affects postoperative complications and prognosis of HCC [25, 26]. It is reported that blood transfusion is associated with increased incidence of HCC recurrence especially in early stages (I or II) and absence of vascular invasion [27]. In our study, perioperative blood transfusion was a significant predictor of tumour recurrence. Several studies reported that perioperative blood transfusions are significantly associated with increased the incidence of tumour recurrence irrespective to its viral aetiology [13, 27-29].

The modified tumor-lymph node-metastasis system (pTNM) includes tumour size, number, and vascular invasion in its tumour (T) classification. Therefore, it should be a significant predictor to HCC recurrence. However it has been widely evaluated and showed low prognostic significance regarding HCC recurrence after hepatic resection for both HCV and HBV related HCCs [10, 13, 16, 30]. Few studies had shown that pTNM staging provides a significant predictor for recurrence in HCV related HCCs [3] and HBV related HCCs [9, 11, 31]. This significant correlation was similar to the findings in our study.

The effects of tumour encapsulation and histologic differentiation of HCC on recurrence risk are less convincing. The prognostic significance of tumour encapsulation on recurrence risk had been debated for both HCV and HBV related HCCs. Absence of tumour capsule has been associated with a higher incidence of recurrence in some studies [3, 32], although not in other studies [9, 10]. Both viewpoints have a theoretical foundation. Encapsulated tumours displace, rather than invade, the surrounding normal parenchyma and vasculature which comprise a better prognosis [3]. Conversely, the presence of tumour capsule is a predictor of portal venous invasion attributed to tumour invasion of blood vessels in the capsule [33]. In our study, lack of tumour capsule was a significant predictor of tumour recurrence.

Also, the prognostic significance of tumour differentiation on recurrence risk has also been debated for both HCV and HBV related HCCs. Some studies found that the tumour grade was a significant predictor for tumour recurrence [19, 34]. This was similar to findings in our study. However, tumour grade was not a significant predictor on the recurrence risk in other studies [9, 10, 13].

In our experience from a tertiary high volume centre for hepatic surgery, significant variables predicting tumour recurrence were AFP, blood transfusion, multifocality, cut margin, microvascular invasion, lack of capsule, tumour grade and stage. In Egypt with high incidence of HCV related HCCs, although the predictors of recurrence are the same for both HBV and HCV related HCC, the rate and aggressiveness of recurrence are higher in HCV related HCC.

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Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions

Concept - A.W.M.; Design - A.S.; Supervision - A.W.M.; Funding - A.W.M.; Materials - H.H.; Data Collection and/or Processing - T.S.; Analysis and/or Interpretation - A.E.; Literature Review - T.S.; Writer - A.W.M., A.S.; Critical Review - A.W.M.

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