Role of Hepatic Resection for HCC in the era of Transplantation; an Experience of Two Tertiary Egyptian Centers

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Abstract The surgical treatments of hepatocellular carcinoma (HCC) in a cirrhotic liver include both hepatic resection and liver transplant. While the liver transplant is considered as a golden therapy, it has some obstacles including shortage of organs especially living donors, economic circumstances, and the progression of a tumor while waiting for the transplant so the second choice which is resection should have a role. In this study, 84 patients with HCC (who were legible for transplant according to Milan and extended selection criteria) were enrolled for hepatic resection. The outcome including complication and the oncologic outcome was evaluated. We followed our patients for 15 months as a median follow-up (range from 3 to 50 months); we noticed 10 tumor relapse (11.7%) and seven lost (8.3%). We also noticed no recurrence. Patients' overall survival showed a median of 15 and 50 months, respectively. We can conclude that there is reasonability for HR as an effective optional treatment for patients with HCC who are legible for transplant particularly for patients with a Child-A scoring.

Keywords Hepatocellular carcinoma · Resection · Transplantation · Donors

Introduction

Hepatocellular carcinoma (HCC) constitutes about 90% of the primary liver malignancy and has an increasing incidence [1]. According to the international agency for research on cancer in 2012, the incidence of hepatocellular carcinoma is the first in men and second in women in Egypt (Figs. 1 and 2). Surgical resection is considered the only chance for cure; it provides the only effective treatment for HCC. It includes either partial liver resection or total liver resection with orthotopic liver transplantation (OLT) [2]. Theoretically, LT is the best choice as it cures the tumor and the underlying risk factor for recurrence which is cirrhosis at the same time. [3] The criteria developed by Mazzaferro and associates, known as the Milan criteria, have been well accepted and used universally for selection of HCC patients who are candidate for LT [4]. Unfortunately, despite strict selection criteria, LT has a limited role in HCC treatment due to the real shortage of donors [5] with long waiting lists and ultimate disease death in up to 30% of patients [6]. Hepatic resection is the cornerstone management of hepatocellular carcinoma worldwide. The continuous technologic upgrading and changes in the instruments used for operations and increased awareness about post-operative complications, causes of tumor relapse, and survival greatly allowed better, safe, and more effective resection techniques. Various teams have provided an experience that made resection to be done in specialized hospitals with death rates lower than 3% and 5-year survival approaching 70% [7]. From the oncologic point of view, adequate hepatic resection is the treatment of choice for non-cirrhotic patients with a tumor of less than 5 cm in size [8]. The “dropout” of patients due to tumor progression while waiting for OLT is reported to be at least 20% [9]. This problem has led to the use of local-regional control therapy while awaiting transplantation such as trans-arterial chemo-embolization (TACE),

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Fig. 1 Incidence of HCC in Egyptian men in 2012 (International Agency for Research on Cancer) (WHO)

radiofrequency ablation (RFA), and percutaneous ethanol injection (PEI) [10]. Hepatic resection can also be used as a bridge before transplantation [11]. Many results discuss that resection is risky in patients with serum bilirubin greater than 1 mg as it includes a high risk for irreversible post-operative liver decompensation and reduced survival (less than 50% at 5 years) [12].

Patients and Methods

This non-randomized prospective and retrospective study was conducted at two tertiary centers during the period between December 2010 and February 2015 (total 50 months). Eighty-four patients who were diagnosed with hepatocellular carcinoma by radiological studies and tumor markers were treated with hepatic resection. All Patients were classified as Child-A according to the Child-Pugh classification. The Criteria of patients' inclusion was to have a single lesion less than 5 cm or two tumors in the same surgical lobe with no gross vascular invasion, nodal infiltration, or extra hepatic spread. Patients with multifocal HCC or with bilobar tumor, patients with extra hepatic malignancy including nodal or peritoneal involvement, those with malignant portal vein thrombosis, and those

with significant cardio pulmonary dysfunction were excluded from this study.

Pre-operative Evaluation

Pre-operative evaluation included the following: pre-operative history taking, clinical examination including general, abdominal, chest, and cardiac examination, laboratory assessment with investigations for patients' fitness, assessment of liver function, tumor, and hepatitis markers, investigation of hepatic focal lesion by CT or even MRI, investigation for metastatic workup, and CT volumetry for assessment of the residual liver volume. A percentage of 45% FLV was satisfactory to carry out resection surgery in a well-compensated Child-A patient. In cases with less FLV Child-A patients, selective arterial embolization or selective portal embolization to the planned segment for resection was used to augment the residual volume after resection.

Surgical Technique of Resection

Laparoscopic exploration was done with laparoscopic intra-operative ultrasound for assessment of resectability of the tumor, degree of liver cirrhosis, and for exclusion of other focal

Fig. 2 Incidence of HCC in Egyptian women in 2012 (International Agency for Research on Cancer) (WHO)

lesions that were not detected during pre-operative phase. Bilateral subcostal incision was used (chevron or bucket handle) with or without an upper midline extension; mobilization of the liver was done. Then hilar dissection with inflow control was carried out and was followed by ligation of branches of hepatic artery, portal vein, and bile ducts (Fig. 3). Outflow control was achieved by ligation of the corresponding hepatic vein and retro hepatic short veins.

Parenchymal Transection

With progress of the technology, the parenchymal dissection is conducted with a Harmonic scalpel together with the use of intraoperative Doppler for identification of vascular and biliary structures that were clipped by vascular clips and the raw surface was efficiently coagulated with argon beam coagulation.

Hemostasis and Closure

This was done using spray diathermy with ligation of sizable vessels and bile ducts with liga-clips, closure of wound with continuous monofilament nylon loop with abdominal drain.

Statistical Analysis

The statistical analysis of data was done by SPSS (SPSS, Inc., Chicago, IL) program statistical package for social science version 16. Patient data were analyzed using frequency and descriptive analysis. The median time to death was defined as the time where 50% of patients have died. Follow up was calculated from the date of HR to the date of last follow up at February 2014. $P \leq 0.05$ was considered statistically significant.

Results

Forty-four patients were within the UCSF standard and 40 within the Milan one. Eighty-four patients with HCC were enrolled. There were 63 male (75%) and 21 female (25%)

Fig. 3 Hilar dissection with ligation of branches of the hepatic artery, portal vein, and bile ducts

patients. The median age was 57 (ranging between 50 and 62 years). Twenty one of them (25%) suffered from chronic hepatitis B disease; 63 patients (75%) suffered from chronic hepatitis C disease, and all patients were classified as Child-Pugh A (100%). Fifty-six patients (66.7%) had a tumor in the right lobe while 28 (32.3%) had tumors in the left lobe. Majority of patients ($n = 67$ patients = 79.7%) had a single tumor and 17 patients (20.3%) had two lesions but in a single lobe. Seventeen patients (20.3%) had a tumor size of less than 3 cm while the other 67 patients (79.7%) has a tumor size more than 3 cm. Regarding the medical illness other than hepatitis, 31 patients (36.9%) were diabetics, 4 patients had portal hypertension (4.8%), and 1 patient (1.2%) had pulmonary hypertension. Patients' data including tumor stage, marker, tumor features, and operation type are described in Tables 1 and 2. Major HR was performed in 10 patients (25%). Nonanatomical resection including the resection of the lesion with a safety margin about 2 cm guided with a frozen section was performed in 25 patients = (62.5%). Five patients (12.5%) have been treated with segmental resection.

Complications (Table 3)

Three patients (3.57%) were complicated by pulmonary embolism that was diagnosed by chest CT and they were treated by anti-coagulant (two died and one passed). Three patients (3.57%) were complicated by biliary leakage; two of them progressed to peritonitis with eventual death and the remaining one passed with exploration and drainage. Six patients (7.14%) suffered from cholangitis. Two patients (2.3%) were complicated by spontaneous bacterial peritonitis that was treated with antibiotics. Nine patients (10.7%) were complicated by chest infection; four patients (4.71%) were complicated by sub-phrenic collection. Nine patients (10.7%) were complicated by acute liver decompensation (three died and the

Table 1 Patient characteristics

	L R = 40	P value
Median age of patients	57.20 (± 9.32)	0.246
Men/women	63/21	
Hepatitis virus positivity		
B	21 (25%)	
C	63 (75%)	
B + C	0	
Child-Pugh classification		
A	84	0.010
B	0	
C	0	
Medical diseases other than cirrhosis		
D. M	31 (36.9%)	0.690
Portal hypertension	4 (4.8%)	1.000
Pulmonary hypertension	1 (1.2%)	0.309

Table 2 Tumor characteristics

	Total = 84	<i>P</i> value
Lobe affection		
RT	56 (66.7%)	0.069
LT	21 (32.5%)	
Both lobes	0	
Lesion no		
Solitary	67 (79.7%)	0.121
Multiple	17 (20.3%)	
C.T evaluation		
		0.364
≤3 cm	17 (20.3%)	
>3 cm	67 (79.7%)	
Vascular invasion after histo-pathological examination		
+ve	2 (2.3%)	0.682
−ve	82 (97.6%)	
A.F.P (ng/ml)	(189.87 ± 502.6)	

rest passed with medical support); and finally, one patient (1.2%) was complicated by biloma after leakage that was treated by guided aspiration.

Survival, Mortality Rate, and Recurrence (Table 4)

We followed our patients for a median of 15 months (range 3–50 months); 10 tumor relapses occurred (11.9%), and 7 patients died (8.3%). The causes of death were pulmonary embolism (two cases), liver decompensation (three cases), and sepsis (two cases). The median tumor relapse-free and overall survival were 15 and 50 months, respectively. The median

Table 3 Post-operative complication

	Total = 84
Intraoperative	
Bleeding	5 (5.9%)
I.V.C. tear	2 (2.3%)
Diaphragmatic tear	1 (0.84%)
C.B.D. injury	2 (2.3%)
Intestinal tear	1 (0.84%)
Intestinal edema	0
Post-operative	
Pulmonary embolism	3 (3.57%)
Biliary leakage	3 (3.57%)
Cholangitis	6 (7.14%)
Peritonitis	2 (2.3%)
Chest infection	9 (10.71%)
Sub-phrenic collection	4 (4.71%)
Liver decompensation	9 (10.71%)
Fungal infection	0
Biloma	1 (0.84%)
Biliary stricture	0

Table 4 Recurrence

	Local recurrence	<i>P</i> value
3 months	67	0.020
6 months	63	0.025
12 months	55	0.058
24–36 months	55	0.068
48 months	55	0.142

tumor relapse-free and total survival in patients fulfilling UCSF standard was 25 and 50 months, respectively. Three-year survival was 60%. In patients fulfilling Milan criteria with HCC who were legible for transplant and treated with resection, there were five tumor relapses (5.9%) and 2 patients died (2.3%). The median tumor relapse-free and total survival were 30 and 50 months, respectively. As regard, 3-year survival was 70%.

Discussion

This study tried to evaluate safety, efficacy, and the oncologic outcome of hepatic resection in patients with HCC associated with liver cirrhosis in the era of the liver transplantation. Our department does not practice LT. But although the other contributing center in this study has a program for liver transplant yet due to the long waiting list, resection is still an option for transplantable cases of HCC. This is an important issue for many reasons; first, the statistical data that have proven a rising incidence of HCC in our country. In our locality in Egypt, the incidence of HCC constitutes the first incidence in men and second in women according to the International Agency for Research on Cancer in 2012. Another factor is the shortage of donors as there is a chronic problem in Egypt called “endemic chronic hepatitis C infection” that leads to increased demand for the liver transplant for the end-stage liver disease. This has led to a long waiting period so the disease becomes more advanced with an eminent exclusion from the transplantation program. The increased cost of liver transplant also forces the government toward the direction of hepatic resection as a feasible treatment of resectable HCC. In this study, the result of the HR as a primary treatment for HCC in cirrhotic patients (with a legible tumor criteria for transplant), the data displayed that the median tumor relapse-free and the total patients’ survival periods of 40 patients who fulfilled the Milan criteria were 30 and 50 months, respectively. The median tumor relapse-free and the total patients’ survival periods of 44 patients who fulfilled the less limiting UCSF standard were 25 and 50 months, respectively. Cherqui and his coworkers [13] analyzed 67 patients with liver resection. Although patients were within the Milan spectrum, the 5-year relapse-free and overall survival were 44 and

72%, respectively. In our study, the 3-year survival was better while the 5-year survival was still not assessed. Excellent oncologic results have also been displayed by other teams presenting that liver resection may be a valid option in selected patients even though they are liable for transplant [14, 15]. However, these data must be applied with prudence. It must be noticed that the transplant is still the only curative treatment for patients suffering from moderate or marked cirrhosis with significant affection of liver function. In this work, all patients had well-compensated liver of Child-A score. In the work of Cherqui et al., he selected patients for resection so cautiously (97% were Child-A score). Most of the centers have proven that liver resection is less effective in patients with more advanced Child score and a transplant is the best option in this situation. In our study, only 10% had experienced acute liver decompensation (treated conservatively). In comparison to Bigourdan's work in 2003, the perioperative morbidity in the HR group was 6 patients (30%), including 5 showing ascites (patients with more than twice normal serum alanine aminotransferase (ALAT) levels had a significantly higher risk of developing ascites and liver insufficiency after HR), which means that 25% of his patients developed decompensation [16]. In our study, the incidence of decompensation was 10.71% as we strictly selected our patients; also, we used limited resection techniques. Saving liver transplants may be more optimum by offering resection firstly to patients with a well-functioning liver within transplantation criteria. Liver transplantation is better to be saved for people with a more severe illness. On view of the relatively small sample size of this study, further investigation is mandatory to confirm the result of resection in patients who are legible for transplant with well-compensated cirrhotic disease.

Conclusion

Hepatic resection is an effective therapeutic tool in Child-A score patients suffering from HCC who are candidates for transplantation according to Milan or UCSF criteria. It is an effective therapy that can compensate for donors' shortage. Further studies with a larger number of patients are required to prove this value in such group of patients.

Compliance with Ethical Standards This study was performed with self-funding.

Conflict of Interest The authors declare that they have no conflict of interest.

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