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Liver Resection for Early Stage Hepatocellular Carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is a major global health problem. HCC is difficult to manage compared to other malignancies due to the underlying liver cirrhosis caused by viral hepatitis. Hepatic resection and transplantation remain the standard curative therapies for HCC. However, the best treatment strategy for patients with well-preserved liver function, absence of portal hypertension, and early-stage HCC is debated

Objectives: To assess the outcomes for patients with early stage HCC treated with liver resection, short and long term results, as well as the effect of different risk factors on the survival of HCC patients treated by liver resection.

Methods: This prospective and retrospective study was carried out between January 2008 and June 2012. 24 early HCC patients (Child's A and B) had liver resection in the Liver unit at Queen Elizabeth Hospital, University of Birmingham NHS Trust, Birmingham, UK. 21 (87.5%) had right hepatectomy and 3 (12.5%) had left hepatectomy. 7 (29.1%) had extended resection in which more than 4 segments were removed while 17 (70.83%) had non-extended resection in which the maximum number of resected segments did not exceed 4 segments. Vascular occlusion (Pringle's maneuver) was done in 5 (20.83 %) cases during the operation. 2 (8.33%) patients had vascular injury during the operation.

Results: 24 patients (17 males and 7 females) had liver resection for HCC. Their age ranged from 34.4 years to 86.6 years with a mean of 71.37 ± 14.13 years. Fibrosis (5 patients, 20. 83 %) was the most common underlying liver disease. .Cirrhosis was found in 8 (33.33%) patients. Following liver resection, 2 (8.3 %) patients died during the first month after surgery, one of them was the result of hepatic insufficiency and the other had portal vein thrombosis followed by multi-organ failure. 7 (29.16 %) patients had post-operative complications in the form of either pleural effusion, pulmonary infection, bile leak from the cut surface of the liver or confusion and they were dealt with accordingly the recurrence free survival was 12.26 ± 9.18 months and the overall survival was 13.76 ± 9.89 months. The one year overall survival was 68.42 % and the 2 year overall survival was 46.15 %. During follow up time recurrence was detected in two patients one was within the first year and the other was after one year, one was still alive at the end of the study and the other died within two months from the detection of recurrence. Patients who had vascular injury to any of the major hepatic vessels intra-operatively showed significantly lower overall and recurrence free survival (P =0.02 and *P*=0.004, respectively) than patients who had no vascular injury.

Conclusion Surgical resection should remain the first line of therapy for patients with early stage HCC and compensated liver function.

Background

Hepatocellular carcinoma (HCC) is a major global health problem. It is the fifth most common type of cancer and the third most common cause of cancer-related mortality in the world. Over 80% of HCC develops in cirrhotic liver, and is mainly attributable to chronic viral infection with hepatitis B or C. The great majority of HCC cases occur in developing countries with a very high incidence in Asia and Sub-Sahara Africa, however its incidence is increasing in Japan, United States, and other western countries with the rise of infection with hepatitis C (1, 2, 3).

HCC is difficult to manage compared to other malignancies due to the underlying liver cirrhosis caused by viral hepatitis (4). Current options for the treatment of the early-stage HCC-conforming to the Milan criteria-consist of liver transplantation, hepatic resection (HR), transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) (4,5,6,7).

Hepatic resection and transplantation remain the standard curative therapies for HCC. These treatments are limited to either patients with early-stage tumors in the case of transplantation or patients with preserved liver function in the case of resection. Currently, patients with early-stage tumors and advanced liver disease are best served by transplant evaluation; however, the best treatment strategy for patients with well-preserved liver function, absence of portal hypertension, and early-stage HCC is debated (8).

Although only 30–40% of patients with HCC are eligible for surgery, it remains the most feasible and efficient treatment. The three most important factors that have led to reduce mortality, with a 70% expectation of 5-year survival, are: i) better liver function assessment, ii) understanding of the segmental liver anatomy through more accurate imaging studies and iii) technical advances in surgical procedures (9).

In patients with preserved liver function and early HCC, liver resection (LR) achieves an overall 5-year survival comparable with that of transplantation, with minimal morbidity and mortality. Recurrence of HCC after LR is expected, and salvage liver transplantation (LT) can be offered for intrahepatic recurrences (10,11,12).

LR has generally been accepted as the first treatment of choice for HCC in many centers. Nevertheless, the associated cirrhosis limits the extent of surgery and thus increases the risk of postoperative liver failure (13).

So, the aim of this work is to study the outcomes for patients with early stage HCC treated with liver resection, short and long term results, as well as the effect of different risk factors on the survival of HCC patients treated by liver resection.

Patients and Methods

Between January 2008 and June 2012, 24 hepatocellular carcinoma (HCC) patients who underwent liver Resection in the Liver unit at Queen Elizabeth Hospital, University of Birmingham NHS Trust, Birmingham, UK, were prospectively and retrospectively evaluated by chart review.

Exclusion criteria:

In the study we excluded patients that were diagnosed with any benign or malignant tumor other than HCC.

- Patients who were medically unfit to have resection.
- Patients with metastatic disease that is not amenable for resection or cure by any other method. The exception for this was extra-hepatic tumor spread that can be resected completely in the same session with the liver (ex. tumor extension to the diaphragm)

Inclusion criteria for liver resection:

- Child's A or B patients
- The remaining liver tissue after resection can perform the normal hepatic function.

Preoperative procedures:

The goal was to confirm the diagnosis of HCC, decide whether resection is appropriate for the patient, evaluate the liver's function and evaluate patient's fitness for surgery. Evaluation included:

1. History taking from the patient.
2. Complete clinical examination with special emphasis if there are any evidence suggesting hepatic decompensation or disseminated malignancy.
3. ECG and echocardiogram
4. Laboratory tests:
   - Liver function assessment: ALT, AST, serum albumin, alkaline phosphatase, GGT, bilirubin, prothrombin time and concentration.
   - Preoperative fitness: CBC, Urea, creatinine, random glucose.
   - Virology: HBV antigens, HCV antibodies: some of the positive cases were further subjected for liver biopsy to assess the liver parenchymatous condition.
   - Tumor markers: AFP, other markers may be required according to the case
5. Imaging procedures:
   - Chest X-ray: for patient's fitness
   - Abdominal US: for liver cirrhosis, tumor characteristics, portal hypertension, extra-hepatic disease spread
   - Multi-detector or spiral triphasic contrast-enhanced CT abdomen (Fig. 1,2,3): tumor characteristics, relation to major blood vessels and bile ducts (it was not done for the aim of any volumetric study for the remnant hepatic volume)
   - Dynamic gadolinium-enhanced MRI : in case further confirmation of tumor characteristics was required
   - PET-CT : when extra-hepatic spread is suspected
6. Biopsy: if the nature of the tumor was not yet surely confirmed.
7. Upper endoscopy: in cases of HCC on top of cirrhotic liver to rule out varices.
8. Anesthetic consultation.

The tailored treatment strategy for each case was agreed upon by consultants from each of; the liver unit (surgeons and hepatologists), radiology, interventional radiology, pathology and oncology departments as well as and nutritionists during the Multi-Disciplinary Team (MDT) meeting held on weekly basis.

Surgical procedures:

- *Anesthesia*. General anesthesia combined with epidural analgesia was the rule for most patients. Central venous pressure was lowered during the operation (< 5 cm. water) and until either the resection is completed with the aim to decrease the blood loss. Prophylactic antibiotic was given at time of induction of anesthesia.
- *Patient's position.* Patient was placed in supine position. In most cases the table was tilted 15

degree down in order to keep the intestine away from the operating field.

- *Incision.*
  a. Right subcostal incision was made followed of exploration of the abdominal cavity to assure the absence of metastasis.
  b. Then a left subcostal incision is added but nearly only half the length of the right one.
  c. Self-retaining retractors were used to allow opening of the costal angle.
- Liver mobilization
  The round ligament was divided as well as the falciform ligament which was divided up to the level of the hepatic veins.

In right sided liver resection: The right lobe was detached from the diaphragmatic attachments. The peritoneum was divided from lateral to medial in relation to the inferior border of the liver. Veins draining the posterior liver to the IVC were either clipped or ligated by (3-0) silk till the hepatic venous confluence with the IVC. The IVC ligament (containing vessels and hepatic parenchyma) is divided with endovascular stapler in order to expose the right hepatic vein (Fig. 4).

In left sided liver resection: The left lobe was detached by dividing the left triangular and the left coronary ligaments. The lesser omentum was incised and the ligamentum venosum was ligated and cut.

- Vascular control Dissection at the porta hepatis of the liver pedicle to the lobe to be resected was done by lowering the hilar plate, occluding the pedicle to demarcate the liver segments required to be removed. Then cutting the components of the pedicle (hepatic artery, portal vein and bile duct) separately. Sometimes the pedicle was left intact till the end of the parenchymal dissection to assure no damage to the improper bile duct has occurred.
  This is followed by dissection of the hepatic vein draining the segment required to be removed and cutting it using endo-vascular stapler.Prigle's maneuver was applied in some cases with the aim of controlling the blood flow to the liver and ensure haemostasis (occlusion time ranged from 6 to 80 min divided into several 10 min. intervals).
- Parenchymal transaction Parenchymal division starts by marking the line of transection (demarcation line appearing after the inflow pedicle is controlled) by cutting the liver capsule with monopolar diathermy. Most of the dissection was done using either ultrasonic dissector,Cavitron Ultrasonic Aspirator (CUSA) and water jet dissector

Statistical analysis

Statistical analysis was performed with SPSS version 18.0 (PASW), released July 30, 2009 (IBM Corporation, Somers, NY). Chi-square test was used for categorical variables. Survival curves were performed by Kaplan-Meier method and the Log-Rank (Mantel Cox) test was used for survival comparisons. Statistical significance was defined as $P < 0.05$.

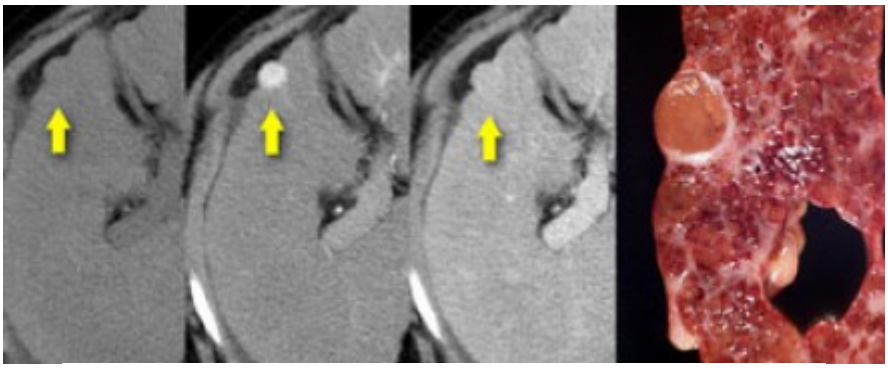

Fig. 1: Small HCC seen only in arterial phase in a patient with cirrhosis

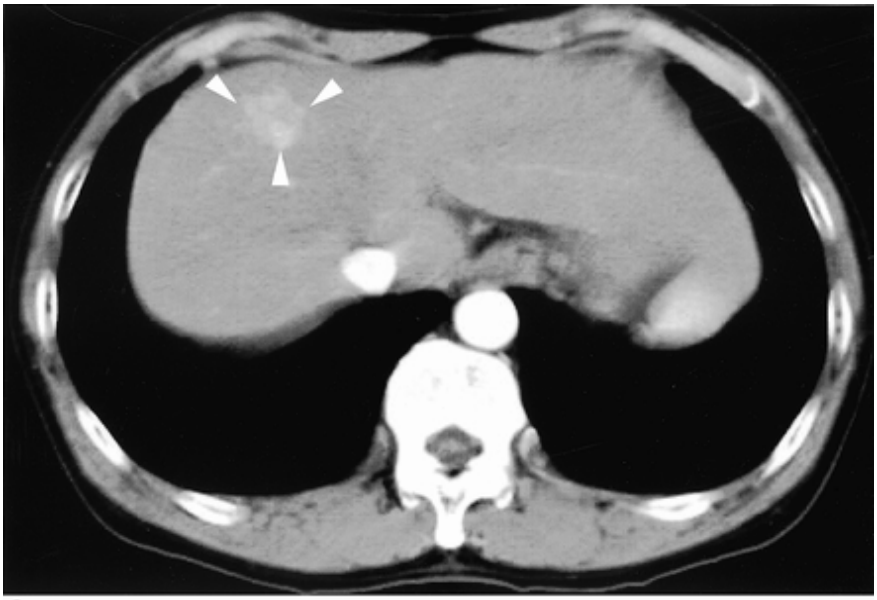

Fig. 2: Images from a 59-year-old man with a 2-cm HCC in the liver segment VIII, Contrast-enhanced CT scan showing a hyperdense HCC (arrowheads) at the arterial phase.

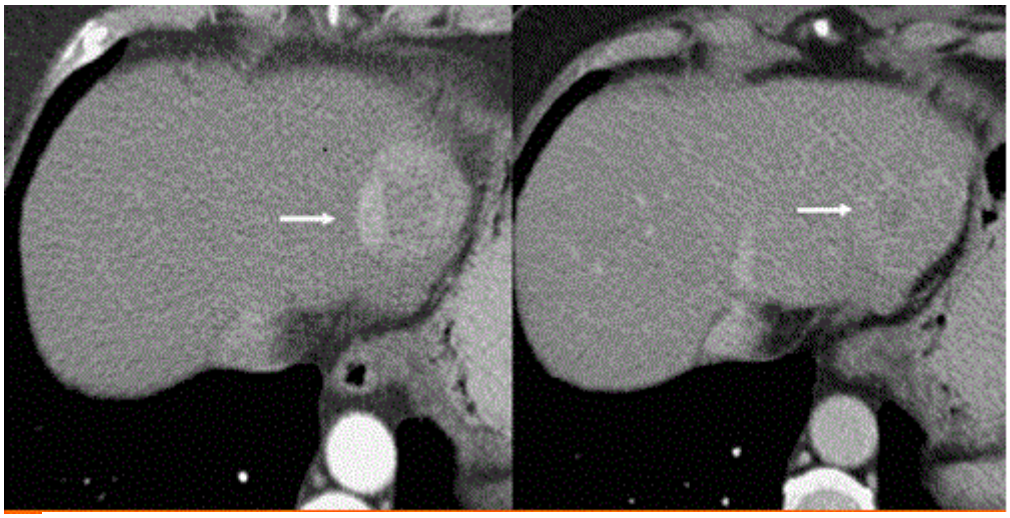

Fig. 3: Small HCC in segment 4 demonstrating bright arterial enhancement and rapid washout

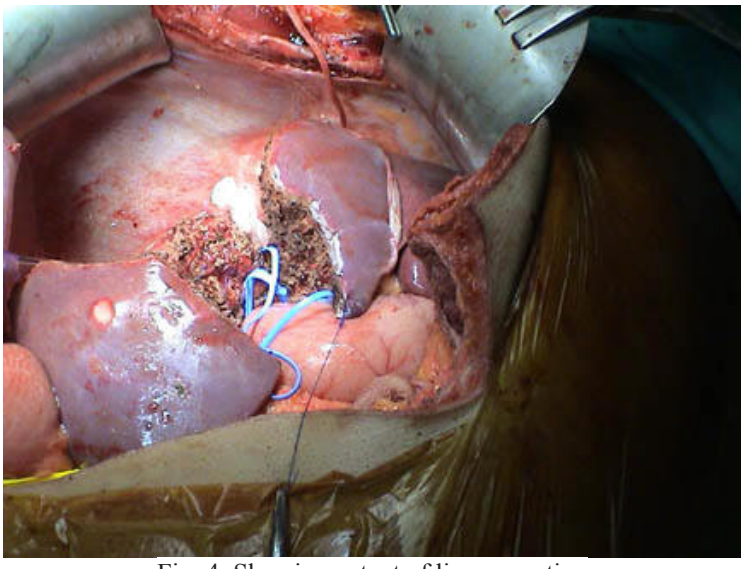

Fig. 4: Showing extent of liver resection

Results

24 patients (17 males and 7 females) had liver resection for HCC. Their age ranged from 34.4 years to 86.6 years with a mean of 71.37 ± 14.13 years. Their body mass index (BMI) was 28.00 ± 5.43. Cirrhosis (8 patients, 33.33 %) was the most common underlying liver disease. .Cirrhosis was found in 8 (33.33%) patients. Their pre-operative AFP level was 63.1 ± 119.85 ng/ml. ranging from 1- 405 ng/ml. (Table 1).

Concerning their tumor characteristics; the number of tumor(s) was 1.25 ± 0.61 ranging from 1 to 3 tumors and the total tumor(s) size(s) was 9.08 ± 5.40 cm. ranging from 1.5 to 22 cm. Milan criteria was met in 6 cases representing 25% of the resection cases. None of the patients received pre-operative treatment (Table 1).

Table (1): Clinical profile of HCC patients who had liver resection (LR) (n=24)

Patients' characteristics	
Age (year) Mean (range)	71.37±14.13 (34.4 - 86.6)
Gender Male: Female	17 (70.8%): 7 (29.2%)
BMI Mean (range)	28.00 ± 5.43 (19.1 - 39.7)
Underlying liver diseases no. (%)	
• Fibrosis	5 (20.83 %)
• Steatohepatitis	4 (16.7%)
• Hemochromatosis	2 (8.3 %)
• HBV	1 (4.1 %)
Cirrhosis, no. (%)	8 (33.33 %)
AFP level (pre-operative) (ng/ml) Mean (range)	63.1 ± 119.85 (1-405)
Tumor characteristics	
Number of tumors Mean (range)	1.25 ± 0.61 (1.0 - 3.0)
Tumor(s) total size(s) (cm) Mean (range)	9.08 ± 5.40 (1.5 - 22.0)
Within Milan no. (%)	6 (25 %)
Preoperative treatment, no (%)	0 (0%)

BMI = body mass index, HBV =hepatitis B virus, AFP = alpha fetoprotein

Of the 24 patients 21 (87.5%) had right hepatectomy and 3 (12.5%) had left hepatectomy. 7 (29.1%) had extended resection in which more than 4 segments were removed while 17 (70.83%) had non-extended resection in which the maximum number of resected segments did not exceed 4 segments. Vascular occlusion (Pringle's maneuver) was done in 5 (20.83 %) cases during the operation. 2 (8.33%) patients had vascular injury during the operation (Table 2).

Following liver resection, the patients' hospital stay was 8.88 ± 4.23 days ranging from 5 days to 20 days including their ITU stay that ranged from 1 to 16 days with a mean duration of 1.92 ± 3.08 days. 2 (8.3 %) patients died during the first month after surgery, one of them was the result of hepatic insufficiency and the other had portal vein thrombosis followed by multi-organ failure. 7 (29.16 %) patients had post-operative complications in the form of either pleural effusion, pulmonary infection, bile leak from the cut surface of the liver or confusion and they were dealt with accordingly (Table 3).

Table (2): Operative details of the resection group

Variable	No.	%
Type of resection		
• Right hepatectomy	21	87.5%
• Left hepatectomy	3	12.5%
Resection group		
• Extended	7	29.1%
• Not-extended	17	70.9%
Vascular injury	17	70.9%
Vascular occlusion	5	20.83%

Table (3): Short term results

Hospital stay (days) Mean (range)	8.88 ± 4.23 (5.0 - 20.0)
ITU stay (days) Mean (range)	1.92 ± 3.08 (1.0 - 16.0)
Complications, no. (%)	7 (29.16 %)
Operative mortality, no. (%)	2 (8.3%)

Operative mortality=death within 1month

The recurrence free survival (defined as the time passed since the initial treatment is finished while the patient did not show any sign of disease recurrence) was 12.26 ± 9.18 months ranging from 0.2 to 30.9 months. And the overall survival (defined as the time passed from the date in which the initial treatment is finished while the patient is still alive) was 13.76 ± 9.89 months ranging from 0.5 to 34 months. The one year overall survival (the percentage of patients who are still alive at the end of the first year after the initial treatment modality is applied) was 68.42 % and the 2 year overall survival (the percentage of the patients who are still alive at the end of the second year after the initial treatment modality is applied) was 46.15 % (Table 4). During follow up time recurrence was detected in two patients one was within the first year and the other was after one year, one was still alive at the end of the study and the other died within two months from the detection of recurrence.

Table (4): Post-operative survival results

Follow up time (months) Mean (range)	13.58 ± 9.99 (0.53 - 34.0)
Recurrence free survival (months)	
Mean (range)	12.26 ± 9.18 (0.2 - 30.9)
Median	12.5 (0.2 - 30.9)
Overall survival (months)	
Mean (range)	13.76 ± 9.89 (0.5 - 34.0)
Median	12.8 (0.5 - 34.0)

We selected some variables that may predict the overall and recurrence free survival. The two statistically significant variables were the BMI (< 25 vs. ≥ 25) and vascular injury: The overall and recurrence free survival of patients with BMI ≥ 25 were significantly higher than those with BMI < 25 (*P* =0.029, *P*=0.048, respectively). Also, patients who had vascular injury to any of the major hepatic vessels intra-operatively showed significantly lower overall and recurrence free survival (P =0.02 and *P*=0.004, respectively) than patients who had no vascular injury. Recurrence free survival was higher in patients who had a maximum mass size of 5 cm than those who had more than 5 cm (14.73 months versus 10.17 months). The overall and recurrence free survival were higher in patients who had a maximum of 4 segments resected than it was in those who had less than 4 segments resected (13.23 months versus 8.13 months and 12.83 months versus 4.33 months respectively) and in patients who had only one nodule in the resected specimen than those who had more than one (12.83 months versus 0.63 months and 12.83 months versus 0.53 months respectively) (Table 5), (Figs. 1,2).

Table (5): Univariate analysis of variables related to liver resection

	Overall survival		P-value	Recurrence free survival		P-value
	Mean ± SE	**Median**		**Mean ± SE**	**Median**	
Age:≤ 55 years	13.13 ± 8.47	4.67	0.661	12.93 ± 8.27	4.67	0.970
> 55 years	14.73 ± 2.22	12.83		12.20 ± 1.98	12.17	
Sex: Male	15.85 ± 2.45	14.73	0.880	13.87 ± 2.39	13.23	0.149
Female	12.82 ± 4.29	8.13		8.94 ± 2.70	4.20	
BMI: ≤ 25	8.07 ± 3.23	4.33	0.029*	7.04 ± 2.86	4.33	0.048*
> 25	16.78 ± 2.58	14.73		13.84 ± 2.10	14.73	
No. of segments: ≤ 4	14.70 ± 2.39	13.23	0.973	12.92 ± 2.31	12.83	0.334
> 4	14.03 ± 4.38	8.13		10.28 ± 3.06	4.33	
Total size:≤ 5 cm	13.47 ± 2.60	10.17	0.457	16.55 ± 5.11	14.73	0.234
> 5 cm	20.56 ± 4.10	14.73		11.05 ± 2.17	10.17	
Mass number: 1	14.90 ± 2.16	12.83	0.656	13.42 ± 1.92	12.83	0.210
> 1	12.02 ± 11.38	0.63		6.46 ± 5.66	0.53	
Cirrhosis Yes	13.15 ± 10.37	12.17	0.842	13.46 ± 9.95	1.73	0.630
No	13.16± 9.68	12.83		11.65± 8.4	12.83	
Within Milan: Yes	13.00 ± 4.69	13.23	0.574	8.97 ± 3.92	1.73	0.276
No	15.00 ± 2.40	12.17		13.35 ± 2.13	12.17	
VAS injury: Yes	4.77 ± 3.37	1.40	0.020*	2.48 ± 1.08	1.40	0.004*
No	15.57 ± 2.17	13.23		13.15 ± 1.93	12.83	

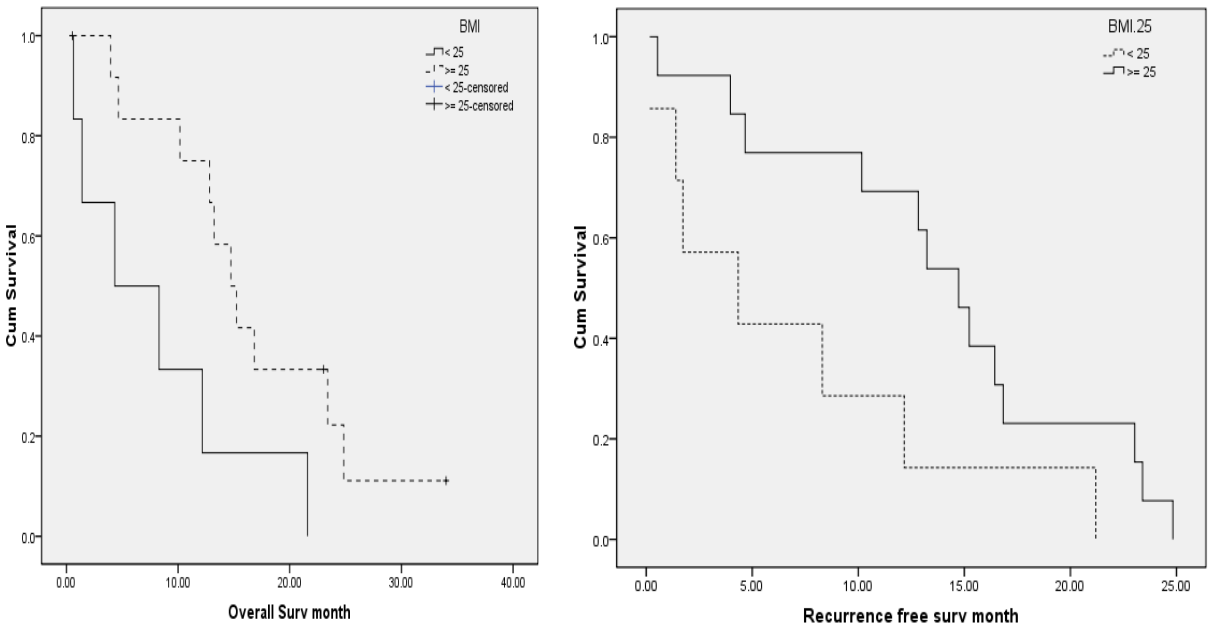

Fig. (1): Overall survival and Recurrence free survival in relation to the BMI (resection group)

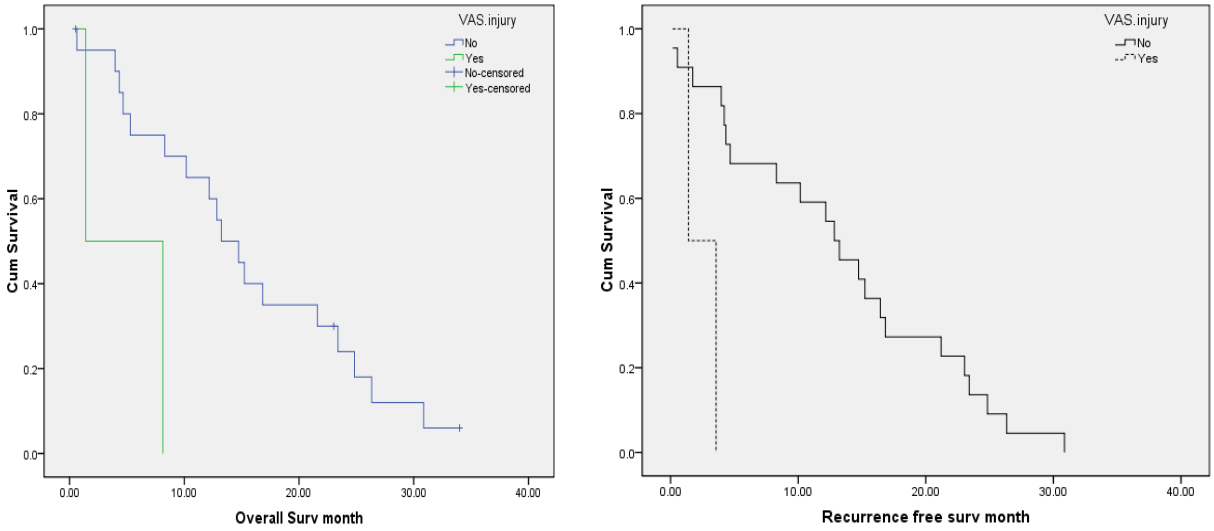

Fig. (2): Overall survival and Recurrence free survival in relation to vascular injury (resection group)

Discussion

Both the American (AASLD) (14) and European (EASL) Associations for the Study of the Liver (15) have recently published updated guidelines for the management of hepatocellular carcinoma (HCC). These are based on a stratification of patients according to the Barcelona Clinic Live Cancer (BCLC) classification, which classifies patients according to tumor burden, liver function as assessed by Child-Pugh score, and performance status, into five distinct prognostic categories with different first line treatment recommendations (16).

Among the many treatment modalities offered for HCC, only surgical approaches, including liver resection (LR) and liver transplantation (LT), are considered to be curative. It is currently accepted that LR is the best option for treatment of HCC with reserved liver function, and LT is preferred with severe impaired liver function. Some controversy remains, however, over treatment of patients with well-reserved liver function who could tolerate LR or LT (8).

In this study, we retrospectively evaluated the outcome of 24 patients with HCC selected for LR. We evaluated patients' characteristics, short-term results such as hospital stay, postoperative complication, mortality, and long-term results such as overall and recurrence-free survival.

24 HCC patients (17 males and 7 females) treated with liver resection .Their mean age was 71.4 ± 14.1

years with a body mass index (BMI) of 28.0±5.4. Cirrhosis was detected in 33.3% of patients. The maximum number of tumors was 3 for each liver while the mean total tumor sizes was 9.08 ± 5.4 cm. None of the patients received preoperative treatment prior to resection. AFP mean value was 63.1 ±119.85 ng / ml. 7 (29.1 %) patients underwent extended LR and vascular injury of one or more of the intra-hepatic artery was reported in 2 (8.3 %) patients.

As regard to short-term results , the present study showed short hospital stay as well as short ITU stay for HCC patients treated by LR (7 and 1 day ,respectively). Early post-operative death (death within 1 month after surgery) was reported in 8.3 % of patients. The most common post-operative complications (pleural effusion, pulmonary infection, bile leak from the cut surface of the liver or confusion) were reported in 29.16% of patients treated by liver resection. The lower morbidity for the LR patients was that the resection avoided the risks associated with immunosuppression in HCC patients underwent liver transplantation (LT). These risks include toxicities (especially nephrotoxicity), infectious complications, and post-transplantation de novo neoplasms (4).

Poon et al. (17) reported a significantly longer hospital stay following LT group than following LR; 9 versus 18 days, respectively, (P<0.001). Similarly, Lee et al (8) study showed the Length of hospital stay after LT to be significantly longer than after LR. However, incidence of postoperative complications and early mortality, that is death within 1 month after surgery, were not different between the two groups. In Margarit et al (12), the mortality for LR patients (5.6%) was higher than for LT patients (3.4%).

Of the 204 LR patients, no patient died in the hospital after LR, whereas the mortality rate was 3.4% for the LT group in Poon's report in 2002 (18). A similar conclusion was reached in Bigourdan et al (19) .A review of almost 60 cases of either LR or LT found that the mortality following transplantation was higher than that following resection (20). In Lei et al study (21) the complication rate after LT was much higher than after LR, the in-hospital mortality was not significantly different between the two groups. Recipients who received an allogenic liver graft, either full or partial size, all needed to take an immunosuppressant, such as tacrolimus, mycophenolate mofetil or steroids, and nephrotoxicity and immunosuppression may affect graft and patient survival (22, 23).

In the present study, both recurrence free and overall free survival were calculated from the time of LR till death or the last follow up. An overall 2 years survival was reported in 46.15 %. Vascular injury of one of the intra-hepatic arteries ,during liver resection ,was associated with significantly lower recurrence and overall free survival compared to those with no vascular injury ($p < 0.004$ and 0.020 , respectively) while patients with BMI ≥ 25 were associated with significantly better recurrence and overall free survival among LR patients($p < 0.048$ and $p < 0.029$,respectively).

Most of the results have shown that the rates of long-term survival and recurrence after transplantation are superior to those observed following resection (22,24,25,26). Bigourdan et al (27) showed significantly higher overall and recurrence free survival in the LT group than in the LR group .Others have shown similar overall survival rates for the two groups and a higher recurrence-free survival rate for the LT group (12 ,28, 8).

Post operatively, recurrences were reported in 8.3 % patients (2 of 24 patients) treated with LR .In the present study all recurrences occurred in less than 2 years post operatively. The most common site of recurrence was in the liver and the lung. Death was reported in 60 % of patients who had recurrence and death occurred in less than 12 months after diagnosis of recurrence. The majority of recurrences are due dissemination from the primary tumor and not metachronus tumors developed in a liver with cirrhosis (14).

Lee et al (8) mentioned that patients who underwent LR experienced significantly higher recurrence of HCC than those who underwent LT; 11 patients (47.8%) of 23 after LT developed tumor recurrence in the liver graft, while 59 patients (88.1%) of 67 after LR experienced recurrence in the remnant liver

In Lei et al (21) study most of the patients in the LT and LR groups had their HCC recurrence within three years. Only two patients had tumor recurrence four years after LT or LR. However, the tumor recurrence rate after LR increased over time, and the long-term survival rates between the LR and LT groups differed significantly. Meanwhile, the post-operative antiviral therapies may also contribute to the good outcome after resection and LT in our study, it is because controlling viral replication halts disease progression and decreases the risk of tumor recurrence or developing new lesions (29).

Many studies have reported predictors of prognosis based on univariate analyses .In the present study we choose 3 predictors; tumors number, tumor sizes and vascular invasion Patients with single tumors showed higher overall and recurrence free survival in comparison to multiple tumor (12.83 m vs. 0.63 m and 12.83 m vs. 0.53m, respectively). Recurrence free survival was higher in patients with tumor mass size > 5 cm (a median of 14.73 months vs. 10.17 months) .Also patients who had vascular injury to any of the major intrahepatic vessels intraoperatively showed significantly lower overall and recurrence free survival ($p< 0.020$ and $p< 0.004$, respectively).

In Faccuiti et al. study (13) the strongest independent predictor for poor outcome was tumor size >3 cm, which represented a risk shared by patients undergoing LR or OLT, and those within or outside the Milan criteria.

Conclusion

In conclusion, these results suggest that surgical resection should remain the first line of therapy for patients with HCC and compensated liver function who are candidates for resection.

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