Treatment options for HCC: a combined hospital experience

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Received 16 August 2014
Accepted 27 September 2014

The Egyptian Journal of Surgery
2014, 33:245–251

Background
In past years, the diagnosis of hepatocellular carcinoma (HCC) was always made when the disease was advanced, when patients were symptomatic. However, due to the revolution in the diagnostic tools many patients now are diagnosed at an early stage while liver function is still preserved. In addition, there are different treatment modalities available that will have a positive impact on survival.

Patients and methods
This prospective study was conducted upon 50 patients with HCC, treated and followed up from March 2008 to May 2012 at Zagazig University hospitals, AL-Azhar University hospitals, and International Medical Center.

Results
Regarding liver resection, nine patients underwent right hepatectomy, two patients had left hepatectomy, and atypical (localized) resection had been performed in four patients. With respect to living donor liver transplantation, 15 patients had right lobe graft. Regarding radiofrequency ablation, 10 patients underwent this procedure under general anesthesia. With respect to transarterial chemoembolization, 17 sessions were performed for 10 patients.

Conclusion
Radiofrequency ablation and liver resection are comparable in small HCC lesions. Transarterial chemoembolization is sometimes the only available way for unfit patients and when surgical resection is contraindicated. Liver transplantation is the remaining treatment left for many patients with end-stage liver disease who fulfill Milan criteria.

Keywords:
hepatocellular carcinoma, liver resection, living donor liver transplantation, radiofrequency ablation, transarterial chemoembolization

Egyptian J Surgery 33:245–251

1110-1121

Introduction

The accurate knowledge of parenchymal structure, blood supply, lymphatic drainage, and variant anatomy is very important in hepatobiliary surgery [1–3]. In the past few decades, the development of hepatic surgery, with appreciation for the complex anatomy, has overcome the misleading minimal external knowledge of hepatic secrets [4]. The risk of developing hepatocellular carcinoma (HCC) correlates with:

(a) Etiology,
(b) Duration, and
(c) Inflammatory activity of the liver disease.

However, about 15% of HCC patients had no risk factors [5].

Unfortunately, Egypt has the largest epidemic hepatitis C virus (HCV) in the world, and this is documented in the international medical scientific literature. The recently released Egyptian Demographic Health Survey tested a representative sample of the entire country for HCV antibody. The overall prevalence (percentage of people) positive for antibody to HCV was 14.7% [6].

Investigations

Usually, the combination of imaging studies is superior to any one test alone in diagnosis of liver pathology. Triphasic computed tomography (CT) is the gold standard imaging modality in diagnosis of HCC. MRI identifies certain intrahepatic tumors better than CT scan but does not outline anatomic borders similar to CT. PET scans are sensitive in detecting up metastatic disease. Ultrasonography (US) is an excellent screening test for many patients; however, operator experience, underlying hepatic disease, and overlying bowel gas can limit its use [7].

Surgical resection is the treatment of choice for HCC in noncirrhotic patients, who only account for 5% of the cases in Western countries and 40% in Asia, as they could tolerate major resections with low morbidity, but in cirrhotic patients it could lead to liver failure [8]. After resection, tumor recurrence rate reaches up to 70% at 5 years, due to dissemination and de-novo tumors. The most powerful predictor of recurrence is the presence of microvascular invasion. Recurrence due to dissemination usually appears during the first 3 years of follow-up [9].

 DOI: 10.4103/1110-1121.147616

Complications of hepatic resection include hemorrhage (intraoperative or postoperative), hepatic insufficiency (ascites, encephalopathy, jaundice, gastrointestinal bleeding), bile leak, acute hepatic failure, sepsis, abscess, or biliary stricture [10].

Child–Pugh scoring system is used to assess the degree of liver dysfunction due to cirrhosis, which consists of clinical and biochemical measurements. More recently, model for end-stage liver disease has been used as a predictor of death within 3 months due to chronic liver disease. Model for end-stage liver disease is calculated from serum creatinine, bilirubin, and international normalized ratio [11].

Multidisciplinary team consisting of hepatologists and surgeons, dieticians, psychologists, social workers, transplant coordinators, and radiologists is needed for evaluating patients undergoing liver transplantation. A comprehensive medical assessment is essential to determine significant comorbid conditions that may have an impact on the patient's perioperative and/or postoperative course. In addition, evaluation of the extent of liver disease, the presence of complications of cirrhosis, and the need of urgency for transplantation are important [12].

Milan criteria for liver transplantation for HCC include single tumor less than 5 cm diameter or up to three tumors less than 3 cm diameter, no vascular invasion, and no extrahepatic disease. However, University of California, San Francisco criteria include single tumor less than 6.5 cm diameter or no more than three tumors largest less than 4.5 cm and total diameter less than 8 cm [13]. The right lobe allograft, accounting for greater than 60% of the donor's total liver mass, is the most commonly used allograft for living donor liver transplantation (LDLT) worldwide. Utilization of a right lobe allograft was initially described by Habib (Hammersmith hospital London) and Tanaka of Kyoto, who were attempting to obtain left lobe for LDLT when anatomical considerations favored a right lobe hepatectomy [14].

Postoperative complications are a major issue both in the donor and in the recipient. Bile leak, bleeding, thrombosis, or infection may occur in either the recipient or the donor or both. Rejection is an additional complication in the recipient [15].

Radiofrequency ablation (RFA) has a specific role in dealing with small single lesions. However, it also has a role in multiple lesions. In patients who were considered unsuitable for surgery at initial presentation due to the presence of multiple or bilateral lesions, surgical resection could be achieved in one segment or lobe, whereas the multiple lesions in the remaining lobe or segments could be successfully ablated. Hence, the resectability of those patients was increased [16]. Common complications following RFA are bile leaks, liver abscesses, hemorrhage, and heat damage to surrounding organs. Local recurrence is variable and often unacceptably high. Once these tumors recur, they are often more difficult to treat and are associated with a worse prognosis [17].

In transarterial chemoembolization (TACE), three-step mechanism can explain the way of TACE function. First, delivering high concentrations of chemotherapeutic agents directly to the tumor cells. Second, the oily medium (lipiodol) enhances the antitumor effect of chemotherapy because it remains within HCC nodules for long periods of time. Third, particle embolization of the tumor-feeding arteries renders the tumor ischemic, which may also potentiate the effects of the chemotherapy by allowing the drugs to penetrate inside the cancer cells with greater ease [18,19]. Procedural errors and complications after chemoembolization make it hazardous. Liver failure, abscess or infarction, biloma, cholecystitis, and the effects of extrahepatic embolization are the usual complications [20].

Patients and methods

Group A (surgical intervention) (30 patients 60%): subgroup 1: liver resection

In all, 15 patients were managed by liver resection (30%); nine of them underwent right hepatectomy (18%), two left hepatectomy (4%), and four nonanatomical resection (8%) (Fig. 1).

Follow-up: early postoperative (2–4 weeks)

Complete laboratory investigations were performed including complete blood count (CBC), liver function test (LFT), kidney function test (KFT), and coagulation profile. Clinical and radiological evaluation were performed by abdominal US for detection of early postoperative complication. CT was performed if US is not conclusive.

Long-term follow-up

Patients' data were collected at 3, 6, 12, and 18 months, including clinical follow-up, laboratory results (CBC, LFT, KFT, bleeding profile, and level of α-fetoprotein), and radiological changes (CT).

Subgroup 2: living donor liver transplantation

In all, 15 patients were managed by LDLT (30%) with right lobe graft.

Inclusion criteria for LDLT

Patients with Child class B and C and Milan criteria fulfillment were the inclusion criteria. After fulfillment of these investigations, there was informed special consent for each of these patients; they had to sign it.

Follow-up: short term: for donor

Patients were admitted to ICU for 1–2 days, then for about another 5 days in ward with daily laboratory tests (CBC, LFT, KFT, bleeding profile) and abdominal US. After discharge, the patients were followed up for 1 month with weekly investigations as before (Fig. 2).

For recipient

Patients were admitted to ICU for about 1 week with daily tests such as CBC, LFT, KFT, random blood sugar (RBS), blood gases, lactate dehydrogenase, ammonia, bleeding profile, chest radiography, liver duplex, and abdominal US.

Thereafter, patients were admitted to isolation room for about another 2 weeks with daily laboratory tests (CBC, LFT, KFT, and RBS). CT, abdominal US, chest radiography, and liver duplex were performed as needed. The level of immunosuppressive was determined every 3 days to adjust the dose and to change the regimen when needed (Fig. 3).

Long-term follow-up

Data of the patients were collected at 3, 6, 12, and 18 months, including clinical follow-up, laboratory results (CBC, LFT, KFT, and bleeding profile), radiological changes (US), level of α-fetoprotein, and immunesuppressive level.

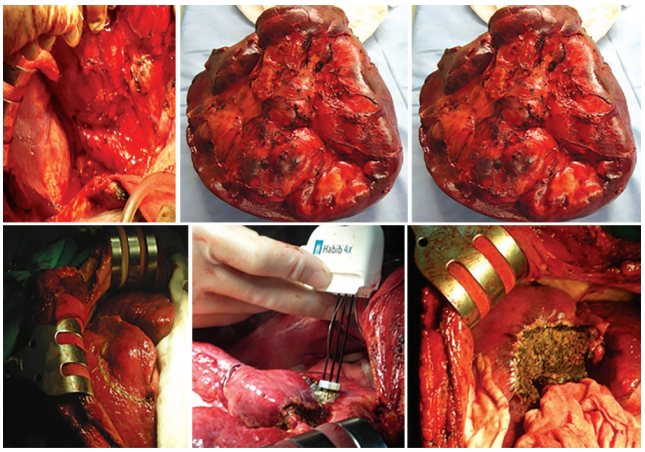
Group B (nonsurgical management) (20 patients 40%): subgroup 3: radiofrequency ablation

Ten patients were managed by RFA (20%). We assessed the efficacy of the RFA using spiral CT and α-fetoprotein assays within 1 month after the procedure. The presence of well-defined, nonenhancing tissue on images obtained during both phases of contrast-enhanced CT was indicative of tissue necrosis. Long-term follow-up studies included serum α-fetoprotein assay and triphasic CT every 3 months in the first year and every 6 months thereafter up to 2 years.

Subgroup 4: transarterial chemoembolization

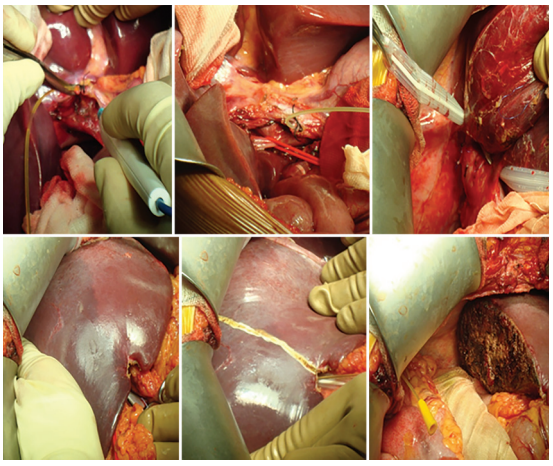
Ten patients were managed by TACE (20%). Noncontrast CT scan was performed on the second day after the procedure to assess postembolization lipiodol distribution. Follow-up US and liver function assessment were performed after 3 weeks. Precontrast and postcontrast CT scan was performed after 6 weeks to determine the residual lipiodol distribution, residual enhancement within the lesion to detect development of recent tumor nodule and to plan the next chemoembolization session.

Figure 1



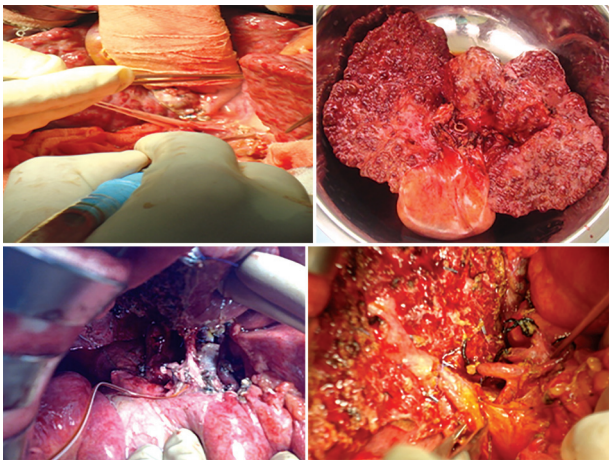
Liver resection operation.

Figure 2



Donor operation.

Figure 3



Recepient operation.

Results

Laboratory investigations

According to Child–Pugh classification, our patients were classified into 20 patients with class A, another 20 patients with class B, and 10 patients with class C (Tables 1).

Radiological investigations

Preoperative abdominal US and triphasic CT revealed site and size of the tumor (Tables 2).

Group A (surgical management): subgroup 1: liver resection (15 patients): morbidity and mortality

Mortality

Six- and 18-month mortality was 13.3 and 26.6%, respectively. The causes of death in this group were intraoperative bleeding in one patient, liver cell failure in three patients, and progression of the tumor with local and distant metastasis in two patients (Tables 3-4).

Subgroup 2: living donor liver transplantation (15 patients): morbidity and mortality

Recipient

Mortality: Six-month and 2-year mortality was 13.3 and 26.6%, respectively. The causes of death in this group were intraoperative bleeding in one patient, septicemia in another patient, liver cell failure in one patient, and progression of the tumor with local and distant metastasis in one patient (Tables 5).

Donors

Wound infection was present in two patients. Only one patient was complicated with bile leak, which was managed conservatively. Another one patient was complicated with biloma.

Mortality: No mortality was present in our donors.

Group B (nonsurgical management): subgroup 3: radiofrequency ablation (10 patients): morbidity and mortality

Generally, the patients tolerated the procedure well. No fatal or major complications were related to this way of management.

Three (30%) of the 10 patients experienced mild to moderate abdominal pain during the RF procedure; this was treated medically. Other three patients (30%) complained from persistent fever for 24 h. Ascitis was found in two patients (20%) diagnosed by follow-up US. One patient (10%) was with hematoma, which was managed conservatively. No late complications were observed. One patient (10%) died of unrelated cause (cardiac cause; heart failure).

Subgroup 4: transarterial chemoembolization (10 patients): morbidity

Post-TACE syndrome in the form of persistent unrelieved pain, fever, and vomiting for more than 1 week occurred in one patient. Other complications were mild anaphylaxis, puncture site hematoma, fever, and ascitis in four patients with complete rapid relieve on the same or next day.

Mortality

Six-month, 1-year, and 18-month mortality was 80, 50, and 20%, respectively. The causes of death in this group were liver cell failure in two patients, progression

Table 1 Age and sex distribution of our patients

Variables	Surgical [*n* (%)]		Nonsurgical [*n* (%)]	
	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4
Age				
<50	2 (4)	2 (4)	1 (2)	0
50–60	11 (22)	13 (26)	8 (16)	5 (10)
>60	2 (4)	0	1 (2)	5 (10)
Sex				
Male	11 (22)	13 (26)	9 (18)	9 (18)
Female	4 (8)	2 (4)	1 (2)	1 (2)

Table 2 Tumor size and number of masses in our patients

Variables	Surgical		Nonsurgical	
	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4
Tumor size (cm)				
≤3 cm	5	7	10	0
>3 cm	10	8	0	10
Number of masses				
Single	15	11	8	1
Multiple	0	4	2	9
Site (lobe)				
Right	11	11	6	4
Left	4	4	2	2
Both	0	0	2	4

Table 3 Complications of surgery in the liver resection group

Variables	*N* (%)
Surgical resection	15 (100)
Early	
Intraoperative bleeding	2 (13.3)
Acute LCF	2 (13.3)
Bile leak	2 (13.3)
Intraperitoneal collection	2 (13.3)
Wound infection	1 (6.7)
Pleural effusion	2 (13.3)
Late	
Recurrence	3 (20)
6 month	1 (6.7)
Within 2 years	2 (13.3)
Liver cell failure	2 (13.3)

LCF, liver cell failure.

Table 4 Factors affecting recurrence rate in the liver resection group

Pathological variables	Number	χ^2	*P*
Vascular invasion			
With (2)	2	4.36	0.03*
Without (13)	1		
Grade of differentiation			
Well differentiated (3)	0	3.28	0.19 NS
Moderately differentiated (8)	1		
Undifferentiated (4)	2		
Active cirrhosis			
With (3)	2	5.1	0.02*
Without (12)	1		
Satellites			
With (1)	1	4.29	0.03*
Without (14)	2		
Tumor size			
≤3 cm (5)	0	0.47	S
>3 cm (10)	3		
Hepatitis virus			
Positive B&C (2)	1	0.04	0.81 NS
Positive C (15)	2		
Type of surgery			
Right (9)	3	2.5	0.28 NS
Left (2)	0		
Nonanatomical (4)	0		
Blood transfusion			
Without (4)	0	0.19	0.66 NS
With (11)	3		

NS, nonsignificant; S, significant.

Table 5 Complications of surgery (LDLT group) (recipient)

Variables	*N* (%)
Liver transplantation (recipient)	
Early complications	
Bleeding	1 (6.7)
Wound infection	2 (13.3)
Bile leak	2 (13.3)
Septicemia	1 (6.7)
Pleural effusion	2 (13.3)
Late complications	
Bile stricture	2 (13.3)
Recurrence	1 (6.7)
Liver cell failure	1 (6.7)

LDLT, living donor liver transplantation.

of the tumor with incomplete response to therapy in three patients, and local and distant metastasis in three patients.

Discussion

HCC typically arises in the setting of underlying liver disease or cirrhosis, which makes it difficult in management. Hence, if damage to the underlying functioning liver is obvious, actual destruction of HCC is not enough to cure the patient. This may explain the relative failure of the traditional weapons against liver cancer. Surgical resection and liver transplantation are the only two treatment options that may lead to cure. However, only 10–15% of patients with HCC are suitable for such treatments, either because of the advanced stage of the disease at the time of diagnosis or because of the presence of comorbid disease [21].

There are limitations of the ordinary weapons against liver cancer (surgery, systemic chemotherapy, and radiation therapy), besides the fact that liver cancer has a tendency to stay confined to the liver. These factors have led to locoregional therapy [22].

Our study included 15 patients who underwent liver resection; regarding age, two patients were less than 50 years, 11 were between 50 and 60 years, and two patients were more than 60 years. Eleven were male patients and four were female patients. In the LDLT group (15 patients), two patients were less than 50 years and 13 patients were between 50 and 60 years. In all, 13 patients were men and two were women. In the RFA group (10 patients), one patient was under 50 years, eight patients were between 50 and 60 years, and one patient was above 60 years. Nine patients were men and one patient was woman. In the TACE group, five patients were between 50 and 60 years and another five patients were above 60 years. Nine patients were men and one was woman.

Hepatitis C infection was positive in our 50 patients, but combined HBV and HCV infection was present in eight patients. Mass size less than or equal to 3 cm was found in 22 patients. In all, 28 patients had mass size more than 3 cm. A total of 35 patients were with single masses and 15 patients with multiple masses. Regarding the site of masses, 31 patients were with right lobe masses, 10 with left lobe masses, and nine patients were with bilateral masses.

Regarding biliary anastomosis in the LDLT group, which is the most common complication in LDLT, we used duct-to-duct technique in biliary anastomosis in seven patients and hepaticojejunostomy in three patients; in addition, we put stents in all our cases.

Biliary anastomosis in the study by Kyoden *et al.* [23] was as follows: of the 310 patients reviewed, hepaticojejunostomy was primarily performed in 87 patients (28%) and duct-to-duct anastomosis was performed in 223 patients (72%). A biliary anastomotic stent tube was placed in 266 patients (86%) at the time of transplantation in this series.

Complications following hepatectomy in cirrhotic patients are common. This is attributed to inadequate liver reserve, bleeding tendency, and usually poor

general condition. Complications may be early in the first 30 days postoperative or late after this period. The most important and common late complication of liver resection is recurrence. Regarding our results, recurrence was in three patients (12%); one patient developed recurrence after 6 months and two patients within 2 years. Recurrence incidence was 8, 52.5, and 71% at 6 months, 1 year, and 2 years, respectively [24]. After a median follow-up period of 34 months, 98 patients (51%) had recurrent cancer; initial tumor recurrence was confined to the liver in 86 patients (88%).

Regarding the LDLT group, early complications were seen in one patient complicated with intraoperative bleeding. Septicemia was present in one patient. Wound infection (seroma) was observed in two patients. Bile leak was present in two patients in which both cases underwent re-exploration with hepaticojejunostomy bile diversion after evacuation of the biloma. Finally, pleural effusion was seen in two patients. Tanaka [25] had encountered 50 complications in 222 right lobe grafts, mostly biliary. Four of the donors in the LDLT group showed complications; two of them complained from wound infection and another two patients showed biliary leak. These results were comparable with the results of Hwang *et al*. [26], as there was no donor mortality in his series.

Treatment policy

Liver resection still plays a key role in the treatment of patients with HCC and a functional hepatic reserve, after fulfilling of strict criteria. In these cases, surgery achieves good survival rates with acceptable perioperative morbidity. Even in nonanatomic resection, there are no adverse effects on the oncologic outcomes of single and small (≤4 cm) HCC in patients with well-preserved liver function (Child–Pugh class A).

Liver transplantation is the only treatment left for many patients with end-stage liver disease. The optimal candidates for transplantation are patients within Milan criteria. There is really no doubt that liver transplantation offers better survival than liver resection provided the patients with early stage tumors, compensated cirrhosis. However, delay in performing liver transplantation may decrease the benefits of liver transplantation and make liver resection an equivalent or preferable option in regions where time to transplant exceeds 6 months.

Treatment with RFA is safe and effective similar to liver resection in single small lesion with good hepatic reserve (Child A). In addition, it is effective as palliative therapy for patients who cannot undergo resection or as a bridge to transplantation.

TACE is considered for patients with nonsurgical hepatocellular carcinoma who are also ineligible for percutaneous ablation, provided there is no extrahepatic tumor spread.

Recommendation

As we have in Egypt a high incidence of HCV infection, which proved to have a direct relationship with occurrence of HCC, we recommend a surveillance program to provide a data-supported approach to the diagnosis, staging, treatment, and management of HCC.

Acknowledgements

Conflicts of interest

None declared.

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