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Transarterial Chemoembolization Prior to Early Hepatocellular Carcinoma Laparoscopic Resection in Patients with Child A Cirrhosis

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1. Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary neoplasia of the liver and its incidence has risen and mainly affects subjects with cirrhosis. Globally, the main risk factor for HCC is hepatitis B virus linked or not to aflatoxin (1). Nevertheless, in industrialised countries, the most frequent risk factors associated with HCC are chronic infection caused by hepatitis C virus and ethanol ingestion (2).

In the treatment of HCC, besides the size and number of nodules, also involved the patient's clinical status assessed by different methods (Child-Pough classification, MELD, ECOG performans status, indocyanine green levels, etc). Recently, the Barcelona Clinic group (3) provides a staging classification using the Child-Pough classification, performans status, Okuda classification, and evaluate the presence of portal hypertension and bilirubin levels. In the initial stages, the treatment options include: resection, liver transplant and ablation. In subjects with compensated cirrhosis, candidates for resection must be selected carefully and the liver function reserve must be tested (4). The best candidates for surgery are those with single tumours, those who present normal bilirubin and no clinically significant portal hypertension (5). HCC vascularisation is predominantly arterial and this establishes a specific vascular pattern characterised by intense contrast uptake in the arterial phase, followed by rapid wash out in the portal phase (6). Nevertheless, given that tumour spread via the veins originates in the area immediately surrounding the tumour, from an oncological point of view, it is worth performing a resection with a margin of 1 cm.

Despite the strict selection process, the recurrence rate for this disease is very high and can reach 70 % after 5 years (4), recurrences of which, 70 % correspond to intrahepatic metastasis, that were not detected when the resection was carried out, and 30% are de novo HCC (7,8). On the basis of this, it was established that when liver transplants are limited to those subjects with single tumours that measure 5 cm or less or with a maximum of 3 nodules which measure less than 3 cm and that do not present vascular invasion or extrahepatic dissemination, a 4-year survival rate of 75 % and a recurrence rate of 8 % is obtained (9).

In subjects with decompensated cirrhosis of the liver, resection is formally contraindicated and a liver transplant must be considered. In subjects with intermediate stage HCC (stage B according to HCC classification), the only treatment that has proven to be beneficial in terms

of survival outcome is transarterial chemoembolization (TACE) (10-13). However, despite the radiological treatment response obtained, in over half the cases, the main disadvantage was that most of the subjects experienced development of the disease despite the initial response. This treatment focuses on the predominantly arterial vascularisation of the HCC. It involves the selective catheterization of the hepatic artery, injecting a chemotherapy agent that is embedded inside a transport medium (usually lipiodol) and occluding the arterial flow afterwards with different embolizing substances.

Moreover, laparoscopic liver resection (LLR) of hepatocellular carcinoma (HCC) on cirrhosis is generally indicated in Child A patients with tumours minor than 5 cm located in the peripheral segments (14) and more rarely in the right posterior segments. Given the special nature of the liver and the cirrhotic patient, LLR involves a high risk of bleeding and could require the use of the Pringle maneuver. Both events (hemorrhage and use of the Pringle maneuver) could cause postoperative liver failure, the main cause of death after liver resection (LR) in child A patients.

Preoperative transarterial chemoembolization (TACE) has until now been used in large HCC with two objectives: (a) to increase resectability or liver transplantation, by achieving understaging, and (b) to increase survival, by decreasing recurrence rates. However, given that HCC is a tumour that is mainly irrigated through the artery, preoperative TACE could decrease vascularization in the segments to be resected, and therefore reduce the risk of hemorrhage during liver resection. Consequently, the use of preoperative TACE could be recommended in early onset tumours, especially when they are going to be resected laparoscopically.

2. Laparoscopic surgical technique

2.1 Pure laparoscopic hepatectomy (PLP)

The patient is placed in the decubitus supine position, independent of the location of the lesion, with the legs apart and slight bent over the pelvis. The surgeon stands between the patient's legs and the first assistant to the left, with the second assistant to the patient's right using a second monitor. Five trocars are used (four 10-mm and one 12-mm), 4 of them following a concave line to the lesion. After creation of the pneumoperitoneum (12 mmHg of CO₂), either with a verres needle or with optiview®, a 10-mm trocar is placed at the umbilicus for insertion of the straight telescope, and the 4 remaining trocars are placed under direct visual guidance.

The first and second (10-mm) to the left and the right of the umbilical trocar; the next (10-mm) in the left flank, on the mid axillary line, to insert the clamp for the Pringle manoeuvre; and the remaining in the subxiphoid areas to insert the liver separation forceps or for a better view of the suprahepatic veins and posterior hepatic ligaments. An intraoperative laparoscopic ultrasonography is performed using a probe inserted through the 10-mm trocar.

After necessary mobilisation of the liver the lesser omentum is dissected for control of the hepatic pedicle. Dissection of the hepatic parenchyma is done with 10-mm Ligasure® Atlas (Tyco©) or harmonic scalpel (Ethicon©). When the hepatectomy is finished, the haemostasis is completed with Tissuelink® (Primm©). Following, any possible bile leaks are sutured, a haemostatic substance is applied to the surgical bed and an aspiration drain is placed on the surgical bed. The tumour specimen is extracted via a Pfannestiel incisión, without fragmenting so that the resection margins can be checked (15,16).

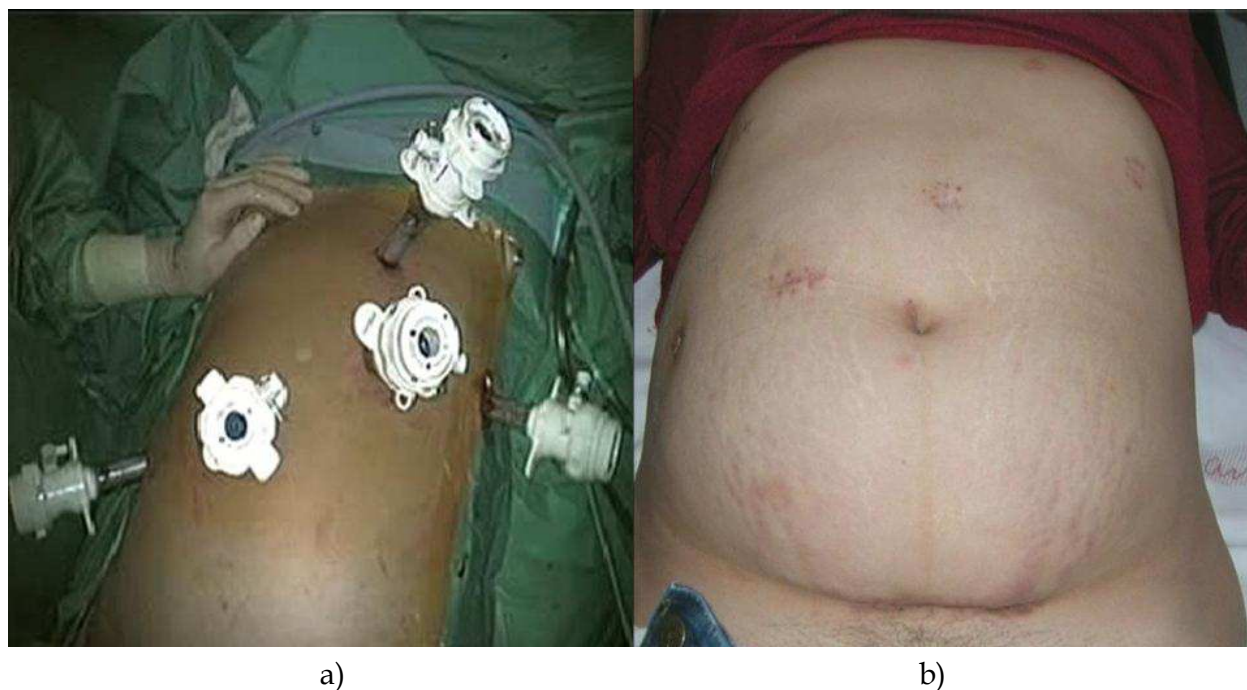


Fig. 1. a) Pure laparoscopic surgery; b) Aesthetic results



Fig. 2. Echography probe a) Laparoscopic probe; b) Hand-assisted probe

2.2 Hand Assisted Laparoscopic Surgery (HALLS)

In cases of conversion to a (15,16), the position of the patient and the assistants is the same as with PLP. The operation is begun with a transverse incision in the right flank, 3-5 fingerwidths from the right costal edge (from the mid axillary line to the anterior axillary line).

Abdominal muscles are dissected to reach the anterior sheath of the rectus, which is generally opened in few centimetres, and the hand-port is inserted. With the surgeon's left hand inside the abdomen a 10-mm trocar is inserted into an adhesion-free area, the pneumoperitoneum is created (12 mmHg CO₂) and the 4 remaining trocars are then placed in the same location and with the same function as in PLP. Subsequently a sonography is performed with an abdominal probe inserted via the hand-port. The surgical specimen is extracted through the hand-port incision in the right flank.



Fig. 3.1 Hand-assisted laparoscopic liver surgery



Fig. 3.2 Aesthetic results

3. Preoperative TACE technique

In 2 cases the procedure involved selective catheterization of the hepatic artery followed by an injection of adriamycin embedded in lipiodol and arterial flow occlusion using spongostan. In the other 8 cases, we used polivinyl alcohol spheres loaded with adriamycin (17).

4. Our experience

We have shown the immediate intra and postoperative results of 10 cirrhotic Child A patients with HCC stages 0 and A according to the *Barcelona Liver Cancer Classification* (3). These patients were given TACE prior to LLR.

Between January 1996 and December 2010 we performed 720 LR on solid liver tumours, of which 100 were by laparoscopy. LLR was carried out on 10 patients with HCC on cirrhosis

using a preoperative TACE, which was applied in order to decrease intraoperative bleeding (Table 1). All patients were Child A cirrhosis, without portal hypertension (normal platelets, gastroscopy without varices and no splenomegaly) and a normal total bilirubin. After 3 weeks of TACE, a routine CT-scan showed tumour response to the treatment and scarce vascularization of embolized segments.

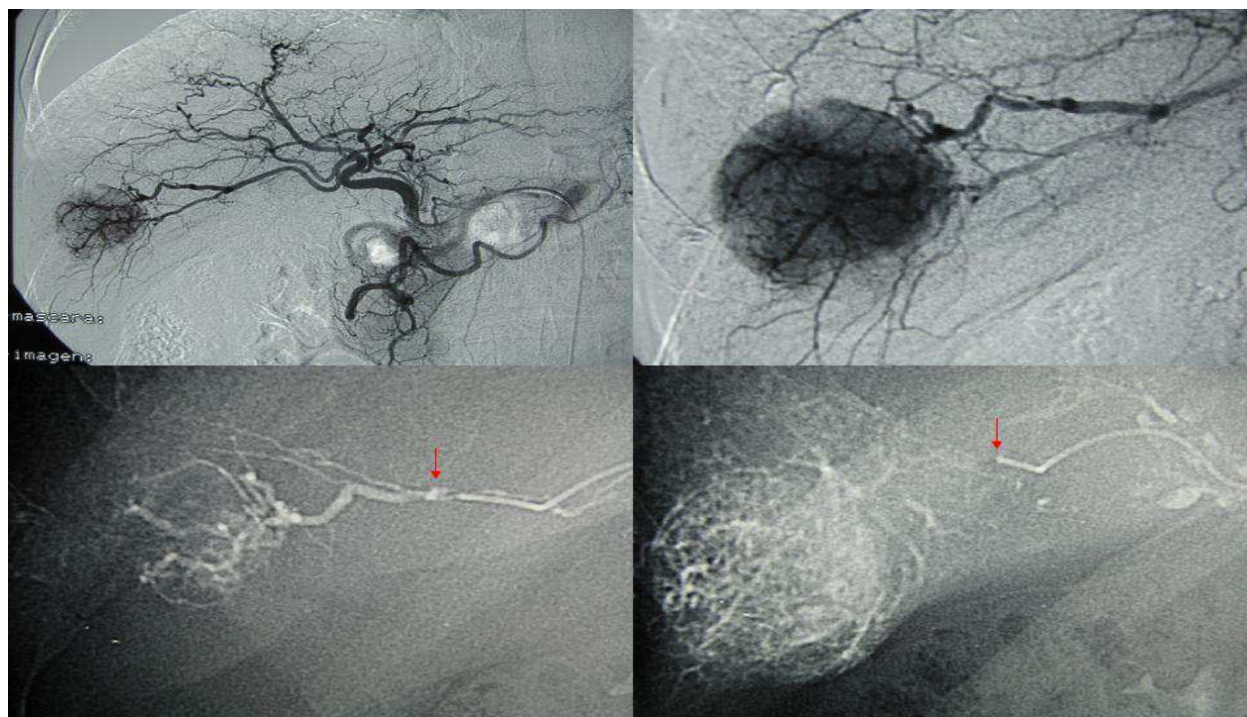


Fig. 4. TACE: we can see the tumor and where arterial occlusion is performed

Sex , years	Etiology	Nodules	Size (cm)	Location	Technique	Conversion to HALLS	Surgical time/minutes	Blood loss	Morbidity
Male, 75	C Virus	1	4	VI-VII	VI-VII	No	210	150	No
Male, 66	Alcohol	1	3	III	III	No	240	100	No
Male, 60	Alcohol	2	3 and 2	VI + VII	VI + RF VII	Yes, for RF S. VIII	240	200	No
Female, 53	C Virus	1	5	V	V	Yes, for adherencial block	150	150	No
Male, 60	Alcohol	1	3	Left lobe	LLS	No	180	300	Ascitis
Male, 82	Alcohol	1	5	VI	VI	No	150	500	Ascitis
Female, 60	B Virus	1	4	VI-VII	VI-VII	No	120	100	No
Male, 71	Alcohol	1	3	III	III	No	180	70	No
Male, 72	Alcohol	1	3	III	III	No	150	100	No
Male, 74	Alcohol	1	2	VI	VI	No	120	50	No

Table 1. Characteristics of the 10 patients with the TACE protocol prior to laparoscopic resection until December 2010

RF. Radiofrequency

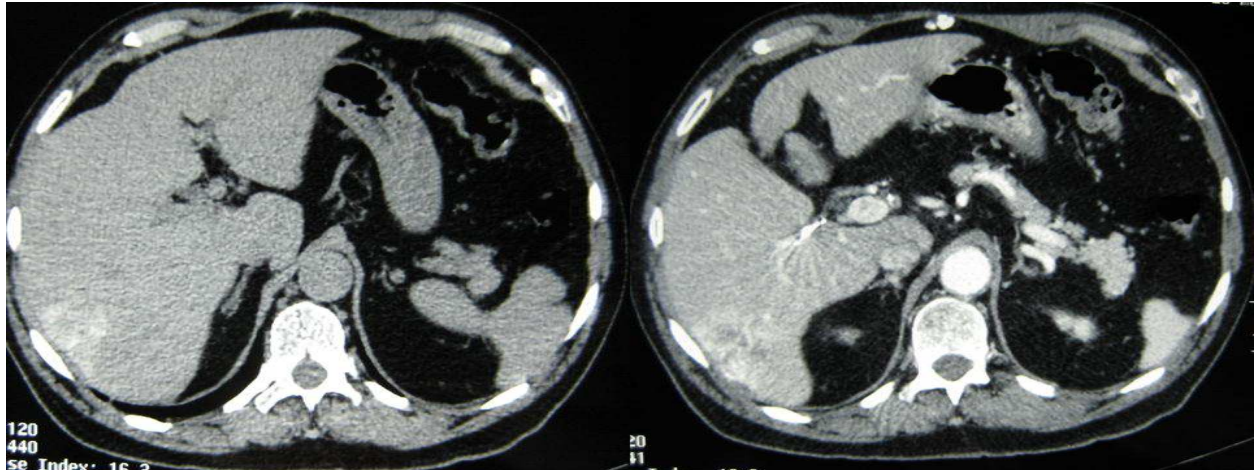


Fig. 5. The CT scan shows tumor necrosis and ischemia of the right lateral sector

The surgical technique performed was: bisegmentectomy VI-VII in 2 cases, segmentectomy VI in 3 cases (in 1 case we associated radiofrequency of a tumour located in segment VII, near to right hepatic vein), segmentectomy III in 3 cases, in 1 case segmentectomy V and left lateral sectionectomy in 1 case. No Pringle maneuver was used. No patients were transfused. There was no postoperative mortality. Two patients presented postoperative ascites that was resolved with medical treatment. The mean hospital stay was 3.7 days (range 2-12 days).

5. Comments

For most authors, HCC involves several surgical difficulties for laparoscopic approach (14-16, 18-27), especially in the cirrhotic liver (14,18,19, 24,25) due to the increased hardness of the liver, portal hypertension and alterations in blood clotting. These difficulties make conversion to laparotomy, mainly because of hemorrhages. In 27 patients with HCC resected by laparoscopy [Cherqui et al. (14)], there was a 26% conversion rate (7 patients, 5 of which were due to hemorrhage); 6 patients had blood losses greater than 1000 ml and 3 of these were given a blood transfusion (15%). Given the risk from bleeding, the authors systematically carry out the intermittent Pringle maneuver (taking a mean time of 55 min) and this could explain why they report a longer mean surgical time (240 min) (14). The technical difficulties were greater in the resection of tumours located in right lobe (even when patients were in the left lateral decubitus position) compared to tumours located in the left lateral segments (II and III segments).

Due to the greater risk of bleeding during LLR for HCC, we propose the use of TACE. As the tumour is mainly irrigated through the artery, selective TACE of the segments to be resected could lead to less vascularization, and therefore, less bleeding during LR. Consequently, there might be less need to occlude the hepatic hilum (this would prevent secondary hepatic ischemia, and therefore there could be less risk of postoperative liver failure), less surgical time and less transfusion. This seems to have been confirmed in the 10 patients in our series. In spite of several tumours being located in a position that makes tumour resection technically more difficult, when LLR was used, mean surgical time was

low (174 min, range 120-240 min), mean blood loss was scarce (220 ml, range 50-500 ml) and the Pringle maneuver was not needed.

In our series, unlike other authors (14-16), the patient was placed in supine position even when the lesions were in the right lobe. In two cases we had to convert to HALLS but this was not due to bleeding, which is a factor that commonly leads to conversion in other series (24,25,28). In the first case the patient was converted in order to mobilize the right hepatic lobe enabling radiofrequency of a 2 cm nodule located posterior to the right hepatic vein (resection of segment VI had been carried out previously); and, in the second case, conversion to HALLS was necessary because of complete blockage of adhesions of the subhepatic space due to a cholecystectomy 20 years earlier.

In other series, intraoperative bleeding is lower than the levels published by Cherqui et al. (14). Belli et al. (19) carried out a retrospective study comparing 23 patients with HCC on cirrhosis treated using LLR compared to another 23 treated using open surgery (OS). Blood loss (260 ml vs. 376 ml by OS), transfusion (0% vs. 17% by OS) and the Pringle maneuver (0% vs. 21% by OS) were lower in the LLR group, although surgical time was higher (148 min vs. 125 min with OS). Furthermore, only 1 patient out of 23 was converted (4.3%), the tumour was located in S VI and there were difficulties in finding the tumour for resection, in spite of the patient being in lateral decubitus position. Perhaps these good results are related to the location of the tumour (50% in the left lobe) and due to greater patient selection given that all the tumours were subcapsular and exophytic. In this kind of tumour that is so peripheral, it would probably be inadvisable to carry out TACE.

There have been many retrospective studies of open surgery (30-32) comparing patients operated on by LR for HCC on cirrhosis with and without TACE. For Choi et al. (31) there are no differences in the 5 year survival rates between both groups and for Chen et al. (32) survival at 5 years was greater in the group with TACE. What is more, Choi et al. (31) compared the operative results of both groups, revealing slightly higher blood loss rates in the group with TACE, without statistical differences. These results are in contrast to our results and we believe that this is because the groups are not comparable because the TACE was carried out on central tumours > 5 cm and a greater % of major LR was carried out.

To conclude, selective TACE of the tumour and of the segments to be resected by laparoscopy, in patients in the early stages of HCC on Child A cirrhosis without portal hypertension, seems to reduce blood losses and the need for occluding the hilum, and any consequent complications of occlusion. Prospective randomized studies are needed with a greater number of patients comparing laparoscopic resection with and without TACE in selected cases of HCC on cirrhosis, in order to analyze the advantages in the immediate postoperative period and the possible effects on long term survival.

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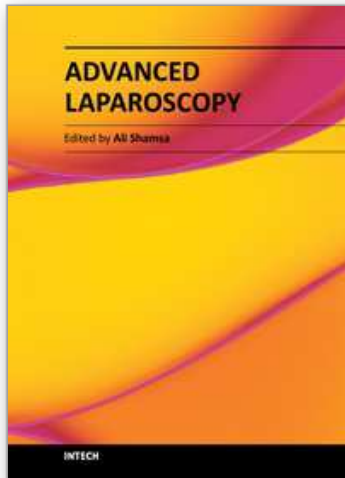
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Edited by Prof. Ali Shamsa

ISBN 978-953-307-674-4

Hard cover, 190 pages

Publisher InTech

Published online 30, September, 2011

Published in print edition September, 2011

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Ricardo Robles, Caridad Marín and Pascual Parrilla (2011). Transarterial Chemoembolization Prior to Early Hepatocellular Carcinoma Laparoscopic Resection in Patients with Child A Cirrhosis, *Advanced Laparoscopy*, Prof. Ali Shamsa (Ed.), ISBN: 978-953-307-674-4, InTech, Available from:

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