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Special Article

New Method of Hepatic Regeneration☆

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ABSTRACT

Postoperative liver failure (PLF) is the most feared and serious complication after extensive liver resections. We present an innovative surgical technique for the treatment of a patient with colorectal cancer and initially unresectable liver metastases. After completing neoadjuvant chemotherapy, it was decided to perform simultaneous surgery. A left hemicolectomy and cleaning of the metastases in the left liver were performed. As the future liver remnant (FLR) was insufficient, it was decided to perform an *in situ* liver split and a right portal vein ligation. On the 6th day after the surgery a volumetric CT showed an increase greater than 40% of the FLR. The right hepatectomy was completed and the patient was discharged on the 11th day after surgery. The technique induced a rapid growth of the FLR, exceeding that reported using portal occlusion. If these findings are corroborated in future studies, this revolutionary technique could enable surgery to be performed in two stages on patients with initially unresectable liver disease during the same hospital admission and without PLF.

Nuevo Método de Regeneración hepática

Palabras clave:
Regeneración hepática
Hepatectomía
Embolización portal
Tumores hepáticos
Insuficiencia hepática

RESUMEN

La insuficiencia hepática postoperatoria (IHP) es la complicación más temida y severa tras de una resección hepática extensa. Presentamos una técnica quirúrgica innovadora para el tratamiento de una paciente con cáncer colorrectal y secundarismo hepático inicialmente irresecable. Tras de completar quimioterapia neoadyuvante se decide cirugía simultánea. Se realizó hemicolectomía izquierda y limpieza de las metástasis del hígado izquierdo. Debido a que el remanente hepático futuro (RHF) era insuficiente, se realizó partición hepática *in situ* y ligadura portal derecha. Al 6.° día postoperatorio una TC volumétrica evidenció aumento mayor al 40% del RHF. Se le completó la hepatectomía derecha y fue externada al 11.° día postoperatorio. La técnica permitió un rápido crecimiento del RHF, superando lo reportado mediante oclusión portal. De corroborarse estos hallazgos en futuros estudios, esta revolucionaria técnica permitiría el tratamiento quirúrgico en dos

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etapas de pacientes con enfermedad hepática inicialmente irresecable durante una misma internación y sin IHP.

Introduction

Surgical resection of hepatic tumours with a curative intent, whether associated with neoadjuvant chemotherapy or not, is nowadays the treatment option chosen by the majority of patients with primary or secondary disease.[1,2] In order to obtain oncological resection margins, the surgeon must perform an extensive resection of the hepatic parenchyma (5 segments or more) in almost half of all patients, putting the patient at risk for developing postoperative liver failure (PLF), along with added morbidity and mortality associated with the surgical procedure.[1] This can be due to insufficient liver remnant volume or the incapacity to maintain synthesis due to the previous hepatopathy. In order to prevent PLF, studies suggest at least 25% of total liver volume in healthy livers and 40% in diseased livers, or those that have received high doses of chemotherapy.[3]

In candidates for major hepatic resection in which an insufficient future liver remnant (FLR) is predicted, portal occlusion (PO) using percutaneous embolisation or surgical ligation in the liver section that will be resected is a widely used strategy to prevent this insufficiency, since it facilitates increasing the volume of FLR.[2–4] This method has yielded FLR growth of 20%–35% in 30–45 days, expanding the indications for liver tumour resections as well as decreasing the rate of complications, especially liver failure and duration of hospital stay.[1,3,4] Despite these benefits, the focus remains on the potential simultaneous and more accelerated growth of the neoplastic disease, both in the liver remnant (15 times higher)[5] and other organs, during the wait period prior to resection.[1–3,5] Also, PO does not always ensure sufficient hypertrophy of the FLR.

Recently, promising results have been reported from a study using a new two-stage hepatectomy technique that obtains a better and faster growth of FLR (Fig. 1).[6] The objective of this study is to present our experience with the use of this innovative surgical technique for treating patients with initially non-resectable liver disease.

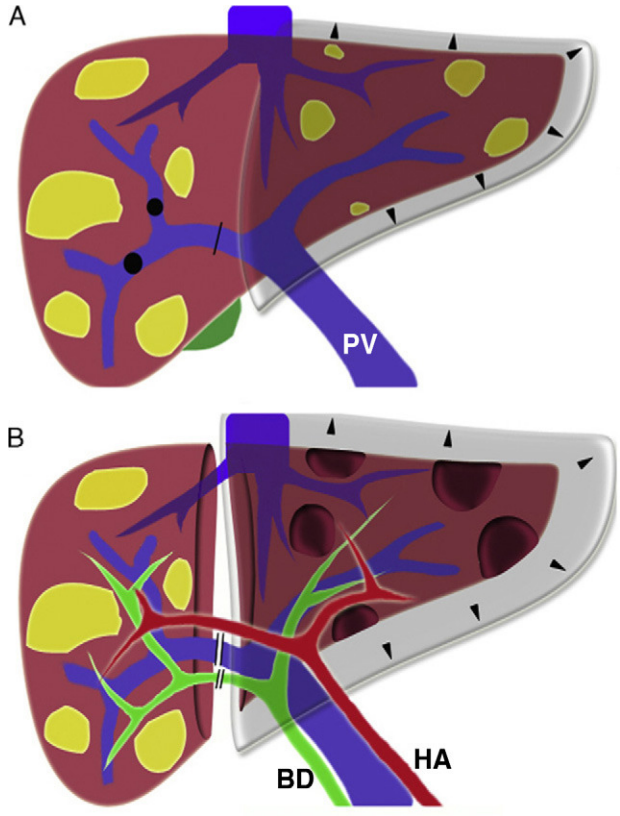

Fig. 1 – (A) Contralateral liver hypertrophy following ligation or portal embolisation. (B) Surgical technique involving two-stage hepatectomy with *in situ* liver partitioning, conserving only the arterial vascularisation and suprahepatic drainage of the right liver. Increased future liver remnant values using this new method have been reported of 40%–160% in 6 days. HA: hepatic artery; BD: bile duct; PV: portal vein.

Case Report

Our patient was a 40-year-old female with no relevant clinical history that sought treatment for proctorrhagia, asthenia, and 7 kg of weight loss in 1 month (current weight at the moment of consultation: 45 kg). Laboratory analysis revealed anaemia (haemoglobin: 11.7) and alkaline phosphatase at 594. Tumour marker levels demonstrated elevated carcinoembrionic antigen (CEA: 351). We decided to administer a video colonoscopy, which detected a high ulcerous lesion 18 cm from the anal margin with a positive biopsy for adenocarcinoma. A CT scan showed the primary tumour in the sigmoid colon with multiple massive hepatic metastases in both lobes. A PET scan confirmed the findings and ruled out disease in other organs (Fig. 2). After 9 months of neoadjuvant chemotherapy (k-ras mutation) with 6 cycles of capecitabine, oxaliplatin, and bevacizumab, and 7 cycles of irinotecan and bevacizumab, we observed a decrease in CEA (value of 3). A second CT scan revealed a significant oncological response (Fig. 3). We decided upon a simultaneous surgical resection, performing a left hemicolectomy and removal of the tumour from the left liver and caudate lobe. Since FLR was insufficient, we performed an *in situ* liver partitioning with portal ligation and ligation of the right bile duct (Fig. 4). A histopathological analysis indicated a low-grade adenocarcinoma down to the submucosa, with

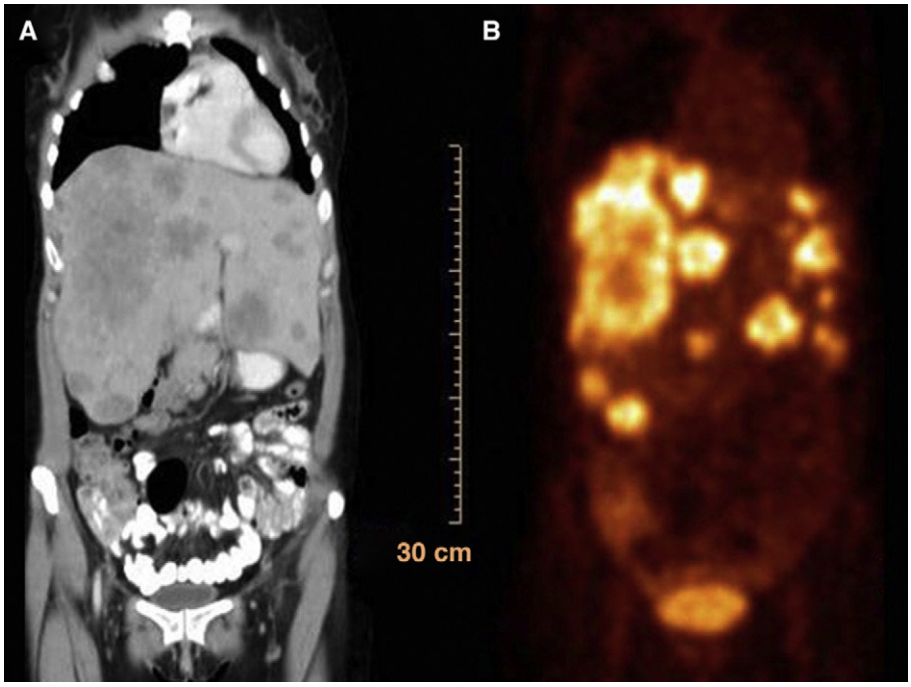

Fig. 2 – (A) CT image showing the hepatic parenchyma replaced by lesions indicative of metastasis. (B) PET scan confirming multiple metabolic hyperactivity centres in the liver.

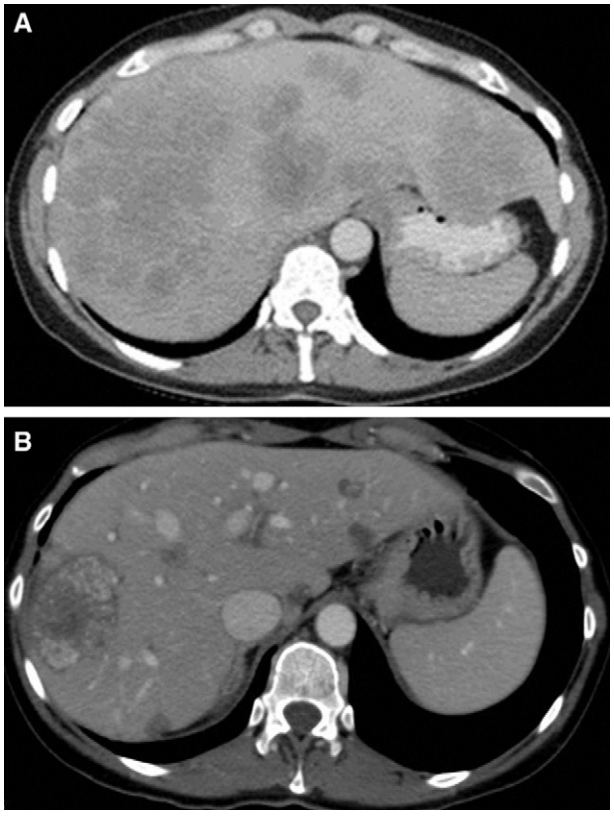

Fig. 3 – CT staging. (A) CT scan from before chemotherapy. (B) Post-neoadjuvant therapy control scan showing a significant response with decreased number and size of hepatic metastases.

10 negative lymph nodes, 8 liver nodes with necrosis varying between 30% and 100%, and negative lymph node dissection of the hepatic pedicle (T1-N0-M1, stage IV/Dworak regression grade III). The patient had favourable evolution with no complications and only a minimally altered hepatogram. A new hepatic volumetric CT was performed on the 6th day after the procedure, with a 92% prothrombin time (Fig. 5). Volumetric CT of the left liver (segments II, III, IV) and the caudate lobe showed over 40% higher volume than preoperative values, predominantly in segments I, II, and III. We performed a second surgical exploration on the 7th day following the first operation, completing the right hepatectomy (Fig. 6). The histopathological analysis resulted in 6 metastatic lymph nodes with necrosis of 30% and 90%. The patient had a favourable recovery, with no signs of liver failure, and was discharged 11 days after the first operation with no complications. A new CT scan taken in the outpatient setting 14 days after the first procedure revealed a >64% increase in the liver remnant and no new metastases.

Discussion

The liver is the human organ with the greatest capacity for regeneration, which occurs at the expense of hyperplasia and cellular hypertrophy. Liver regeneration reaches its maximum peak at 2 weeks, reaching a growth of 12–21 cm^3 per day in healthy livers.[7] However, in the postoperative period, patients can die due to the inability of the remaining hepatic parenchyma to cover the metabolic needs of the organism.

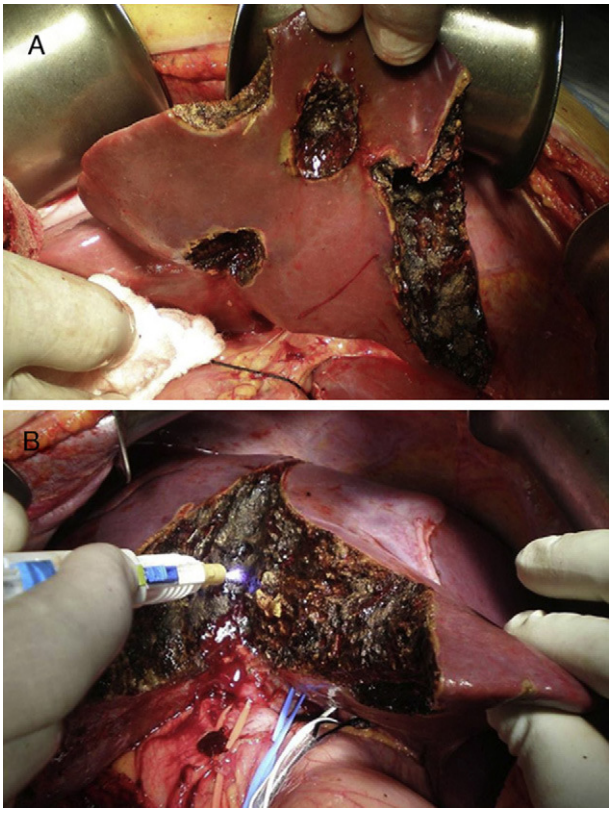

Fig. 4 – Intraoperative photographs. (A) Resection of metastasis from the left liver. (B) Hepatic transection.

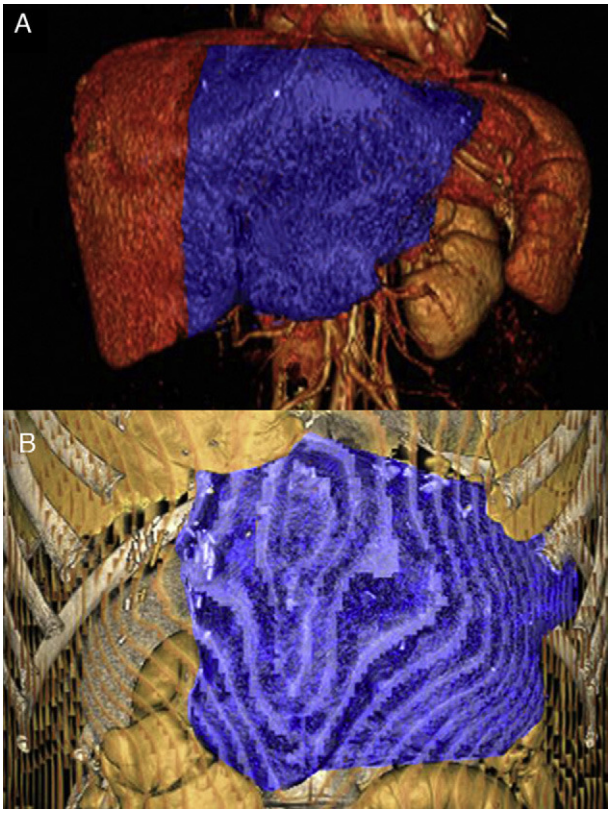

Fig. 5 – (A) Preoperative liver volumetric CT at 492 ml. (B) Volume at 690 ml on the 6th day following the procedure.

Additionally, patients with colorectal metastatic disease that have received modern preoperative chemotherapy regimens can develop adverse effects such as sinusoidal veno-occlusive disease and non-alcoholic steatohepatitis, with the consequent increased risk of dysfunction and failure of the liver remnant.[8]

PO prior to resection surgery with curative intent has been demonstrated to be a safe, well-tolerated procedure with an important therapeutic role, and is currently an indispensable resource for reaching higher FLR and avoiding the mortality associated with PLF.[1]

Using the *in situ* liver partitioning technique, Baumgart et al.[6] described FLR increases of 40%–160% in just 6 days. In our patient, we observed an increase >40% of FLR in 6 days, and more than 64% in 14 days after the procedure, since the initial preoperative volumetric analysis did not take into account the volume corresponding to the metastases located in segments I–IV.

Stopping portal flow to a liver segment causes atrophy and contralateral compensatory hypertrophy provoked by the body's redirecting portal flow rich in hepatotrophic factors and the release of mediators that stimulate growth. Among these are extra-hepatic factors such as insulin and intra-hepatic molecules such as hepatocyte growth factor (HGF) and interleukin-6, among others.[1,7,9] Given the lack of clinical experience and the absence of research on the subject, the physiological mechanisms behind the extreme hypertrophy caused by this technique (up to four times higher and faster than in previously described methods) are still unknown. To our knowledge, the most important factor in this phenomenon is *in situ* liver transection, which provokes an interruption of intra-hepatic porto-portal collateral vessels and impedes their development in the interval between operations, achieving a greater deprivation of the portal flow to the excluded segment. However, we still do not know the role of simultaneous ligation of the homolateral bile duct, nor if it even has any effect on the contralateral hypertrophy.

The results obtained with this new method are clearly superior to those reported in the medical literature using embolisation or portal ligation.[1–4] To our knowledge, this is the sixth case reported in the world regarding the use of this new and revolutionary surgical technique.

In conclusion, the surgical technique of two-stage hepatectomy with *in situ* liver partitioning and portal and biliary ligation described in this study was quite feasible, obtaining favourable results. This procedure induced a rapid regeneration and hypertrophy of the left liver, allowing for curative treatment of the primary tumour and metastases in two stages without PLF and during the same hospitalisation period. If these findings were corroborated in future studies, this method may be useful in patients selected for the resection of large tumours or initially non-resectable advanced liver disease.

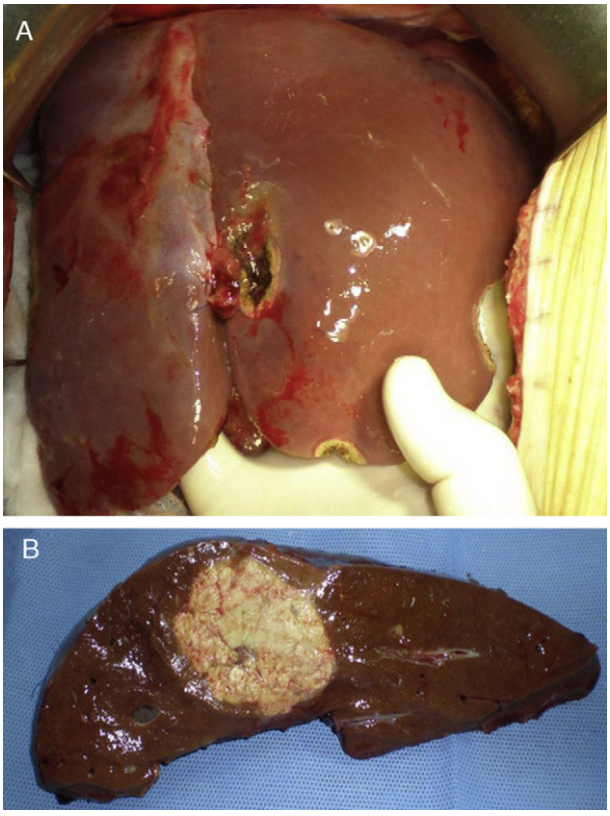

Fig. 6 – (A) Hypertrophied liver remnant, with growth greater than 40% by the 7th day. (B) Surgical specimen from the right hepatectomy.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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