Strategies and techniques to increase resectability rate for liver tumors.

STRATEGIES AND TECHNIQUES TO INCREASE RESECTABILITY RATE FOR LIVER TUMORS

STRATEGIE E TECNICHE PER AUMENTARE LA RESECABILITÀ DEI TUMORI EPATICI

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Riassunto. La resecabilità dei tumori epatici può essere aumentata se si ottiene una riduzione delle dimensioni della lesione attraverso la chemioterapia per le metastasi da carcinoma colo-rettale e la chemioembolizzazione per il carcinoma epatocellulare.

Anche metastasi multiple e bi-lobari possono, al giorno d'oggi, talvolta, essere trattate con la strategia delle "staged resections" che abbina resezioni minori (prevalentemente atipiche) ed ablazioni con radiofrequenza a successive resezioni maggiori. Queste possono essere precedute da una embolizzazione di un ramo portale allo scopo di ottenere un'ipertrofia compensatoria del fegato che si prevede di lasciare. Quest'ultima tecnica è indicata infatti quando il volume del fegato residuo risulti inferiore al 20%, per resezioni maggiori su fegato steatosico, fibrotico o francamente cirrotico.

Le ri-resezioni devono essere considerate ogni volta che si abbia una recidiva resecabile in assenza di malattia extraepatica. La sopravvivenza e l'intervallo libero da malattia dopo ri-resezione sono risultate sovrapponibili a quelle dopo il primo intervento resettivo.

Fra le tecniche che consentono di aumentare la percentuale di resecabilità dei tumori epatici sono da ricordare la epatectomie "difficili" quali le epatectomie allargate, l'epatectomia centrale o mesoepatectomia e le segmentectomie, a torto ritenute e classificate come "minori", risultano, se bene eseguite anatomicamente, di difficile esecuzione, come ad esempio la resezione dell'VIII o del I, a causa del non facile isolamento dei peduncoli glissoniani corrispondenti, per l'estensione della trancia di resezione e quindi per le possibili perdite ematiche e/o biliari che si possono verificare. Esiste inoltre la possibilità di resecare e di ricostruire strutture vascolari come la vena cava, le vene sovraepatiche, la vena porta o la via biliare. Le resezioni/ricostruzioni vascolari sono al giorno d'oggi possibili per l'uso di tecniche di controllo del flusso ematico in entrata ed in uscita dal fegato associate o meno ad un clampaggio della vena cava sovra e sottoepatica. Tali tecniche permettono di resecare lesioni che interessano la confluenza cavo-sovraepatica o la biforcazione portale.

Summary

Liver tumour resectability rate may be increased if a tumour shrinkage is obtained using preoperative chemotherapy for liver metastasis from colon-rectal cancer and with chemoembolization for hepatocellular carcinoma.

Multiple and bi-lobar metastasis have been considered for a long time a contraindication for liver resection but nowadays they can be resected, at time, by means of planned subsequent resections (so called "staged") that included minor resections (mostly wedge) and/or thermal ablations first, followed by delayed major resections. These latter may be preceded by a portal branch embolization in order to obtain a compensatory hypertrophy of the part of the liver to be left especially when this looks small (<20%) or there is some degree of parenchymal damage such as steathosis, fibrosis or cirrhosis.

Re-resection is an option that should be considered each time a resectable recurrence of a liver tumour develops. In fact disease free and survival rates after a re-resection are comparable to those after the first resection provided that there are not extra-hepatic disease.

Among the techniques that have allowed to increase liver tumour resectability rate there are some difficult hepatectomies such as extended hepatectomies or tri-segmentectomies, central-hepatectomies or meso-hepatectomies and some segmentectomies. These latter have been considered and classified as "minor" hepatectomies but they actually may result more difficult to perform compared to the major ones as segment VIII or caudate lobe resection. This is due to the difficult isolation of the corresponding glissonean pedicles, to the extension and deepness of the resection area that may allow the increase of blood loss and biliary leakages.

Furthermore, vital structures such as vena cava, hepatic veins, portal vein and its branches, biliary ducts and artery can be resected and reconstructed. Resection and reconstruction of vascular structures are at present made possible thanks to the experience gained with liver transplantation.

Knowledge of liver tolerance to ischemia and the techniques to control blood in and out-flow are others key factors for resections that entail vascular reconstructions. These techniques have allowed to resects lesions once considered un-resectable such as those near the cavo-hepatic junction or those infiltrating the portal bifurcation.

Introduction

Liver surgery has evolved over the last years thanks to improved knowledge in liver anatomy, new technologies and peri-operative management.

If we look back to the history of liver resection [1] one may note that there are roughly three distinct periods. The first goes from the first reported resection of the liver in 1886 to 1952 year in which the first right lobectomy has been performed. In the second period (fifties to eighties) liver surgery shifted from pionieristic to a challenging procedure but with still sensible morbidity and mortality. With the introduction in clinical practice of liver transplantation, liver surgery has dramatically changed toward a routine operation with mortality approaching 0% notwithstanding the expansion in the indications.

Liver tumours resulted resectable at diagnosis in only 10 to 20% (either for primary or secondary lesions). This is due to

the dimensions and the vicinity of vital structures such as the vena cava, portal vein or the biliary tree, the presence of a liver damage, the multicentricity of the tumour or even the recurrence on a previously resected liver. This low resectability rate may be improved through the application of some strategies and techniques such as the chemotherapeutic down staging, chemoembolization, multiple and staged resections, occlusion of a branch of the portal vein and following resection, re-resections, difficult resections, vascular exclusion techniques and vascular reconstructions.

Downstaging

The vast majority of liver tumours resulted un-resectable at the time of diagnosis. Successful attempts to reduce the tumour volume (shrinkage) have been made using chemotherapy, embolization or chemo-embolization. Each of these therapies were able to reduce the tumour volume in a small portion of patients. In fact only 14% of patients were amenable to be resected after a preoperative chemotherapy for colorectal liver metastasis in a study made by Adam et al. [2]. Furthermore, there is now increasing interest in using preoperative chemotherapy for patients presenting with resectable hepatic colorectal metastases. In fact up to 19% of positive surgical margins have been reported thus jeopardizing the benefit of the surgical procedure whereas only 3% rate of positive surgical margins is obtained using preoperative irinotecan-based chemotherapy with comparable postoperative complications [3].

A downstaging after transarterial chemoembolization has been demonstrated also for hepatocellular carcinoma. In this setting 10% of previously unresectable tumours could be resected after downstaging with improved disease-free survival [4].

Multiple Resections

Number of liver metastases has been considered for a long time a prognostic factor for liver resection(s) [5-7]. The results of a large multi-institutional retrospective study showed that only 3 out 100 patients who survived more than 5 years had 4 or more metastases so they concluded that these patients should not undergo to hepatic resection. In 1994 Kawasaki et al. [8] reported good results in 5 patients operated for bilateral multiple liver metastases (3 to 12 lesions). Ten years later Kokudo et al. [9] showed that patients with 4 or more hepatic metastases had the same survival rates. The peculiarity of this study is, that more than a third of the patients, had more than 7 nodules that they were treated mainly by means of partial resections provided that at least 30 to 40% of liver parenchyma were left. The background for this attitude is that the anatomical resection is necessary and beneficial for hepatocellular carcinoma because of intra-portal metastatization but not for colorectal metastases [10].

Staged Resections

Up to the recent years liver resection has been considered contraindicated if not all the tumours can be completely resected. In the year 2000 Adam et al. [11], clearly demonstrated that a hepatectomy that leaves tumour tissue in place may be justified if a second liver resection could resects the remnant tumour. This technique consists in removing the highest possible number of metastases in the first non curative intervention, even synchronously with the colorectal operation, while the remaining tumours were resected after a period of liver regeneration. This policy allowed to expand the resectability rate to 54% (5% more for the first hepatectomy and 15% for the second) and to reach 35% and 31% of survival rate and disease free survival rate respectively at 3 years in this subgroup of patients.

A second reported approach to treat initially nonresectable multiple and bilobar hepatic metastases comes from Jaeck et al. [12] who demonstrated the efficacy and safety of two staged hepatectomy combined with portal vein embolization. In this study they tried to clear a hemi-liver (usually the left) from metastatic lesions trough multiple wedge resections then, after 14 days in mean, patients underwent a right portal vein embolization and after 8 weeks a formal right hepatectomy. They actually reported even better results with 3 years survival rate of 53%.

Re-Resections

Approximately 60% of patients resected for colorectal metastases as well as for HCC will present a tumour recurrence in the liver [13, 14]. When the recurrence is isolated the treatment of choice is represented by a repeat hepatectomy that has shown the same risks and outcome as first liver resection. Unfortunately a recurrence will be expected in these patients at a rate of again 60% for liver metastases and of 80% for HCC. For patients with a solitary recurrent lesion a third hepatectomy has been performed. In this setting Adam et al. [13] showed that a third hepatectomy is safe, although more technically demanding and provides additional benefit of survival similar to that of first and second resections for liver metastases from colorectal cancer. The third hepatectomy owes a survival benefit of 32% that cumulates with that obtained with previous hepatic resections leading to an expected survival of 65% at 5 years for this group of patients.

Difficult Resections

Liver resections are currently classified as atypical, minor (less than 3 segments) and major (more than 3 segments) resection. Atypical resections is usually accomplished for peripheral lesions and are not anatomical. Minor resections entail the resection of up to 3 anatomical segments. The term is misleading because sometimes a segmentectomy is more demanding in terms of surgical technique and expertise such as in case of segment 1 or 8 resection [15-17]. Even the isolated resection of a single segment, whatever is, resulted anatomically demanding because of the difficult isolation of the segmental glissonean pedicle. This may be accomplished in different ways: localizing it with ultrasound, isolating artery and portal vein branches into the glissonean sheet or extraglissoneanly isolating within the liver substance the glissonean pedicle [17-20].

Among the difficult liver resections there are certainly those performed for deeply located, central liver tumours of segment 4, 5 and 8. These locations usually require extended hepatectomies that are technically demanding, remove 60% to 85% of hepatic parenchyma and are associated with complications including hepatic failure. An alternative to the extended hepa-

tectomies is the central or mesohepatectomy. This technique require two parenchymal planes of dissection and preserves Couinaud's segment 2, 3, 6, 7 and sometimes 1 [21].

Other difficult resections for large right tumours may be accomplished using some techniques such as the anterior approach [22] and the liver hanging manoeuvre [23].

Vascular Exclusions

Liver resections may be complicated by unpredictable intraoperative bleeding that requires blood transfusions. This increases postoperative morbidity and mortality as well as tumour recurrence. There are many ways to reduce intraoperative bleeding such as the devascularization of the part of the liver to be removed, a vascular planes to follow during parenchymal transection, the use of dissecting and coagulating devices, the intraoperative ultrasound, the use of low central venous pressure with or without hemodilution and the control of hepatic blood inflow and outflow.

The control on liver blood in and outflow can be accomplished in different ways and is based on the tolerance of the liver to ischemia. Methods of control can be classified into two main categories: inflow vascular occlusion and inflow plus outflow vascular occlusion [24] as reported in Table 1.

Table 1: Types of vascular control during hepatic resections

I. Inflow Vascular Occlusion
A) Hepatic pedicle occlusion
- Continuous Pringle manoeuvre
- Intermittent Pringle manoeuvre

B) Selective inflow occlusion
- Hemihepatic inflow vascular occlusion
- Hemihepatic intermittent vascular occlusion
- Segmental vascular clamping

II. Inflow and Outflow Vascular Occlusion

A) Total hepatic vascular exclusion
B) Selective total hepatic vascular exclusion
C) Selective hemi-hepatic vascular exclusion

(Adapted from Smyrniotis et al., 2005)

Pringle's manoeuvre was the first attempt to control bleeding coming from the ruptured liver parenchyma [25] and is still the most popular technique for vascular control among surgeons. It has the advantage of the simplicity, rapidity and reliability. The main problem with this technique is the duration of the warm ischemia especially on a diseased liver. Is generally accepted that duration of ischemia up to 1 hour for diseased and 90 minutes for normal liver do not increase morbidity and mortality [26]. Duration of 130 and 100 minutes have also been reported with favourable outcomes in the same situations [27, 28]. To further extend these limits has been proposed the intermittent Pringle's manoeuvre which permits to almost doubling the ischemia time up to 120 minutes in both normal and diseased liver [29-33].

Among the selective inflow occlusion techniques hemihepatic vascular clamping owes the advantage of the avoidance of the ischemia on a hemi-liver, avoid intestinal blood stasis and if applied intermittently the clamping time may be further extended safely. This technique has been introduced by Makuuchi et al. [34] and consists in the clamping of the artery and portal vein of a hemi-liver. This could be achieved also detaching the hilar plate and looping right and left portal pedicles [19, 20, 35, 36]. It can be combined with the occlusion of the hepatic veins to get the selective hemi-hepatic vascular exclusion of the liver. Hemi-hepatic vascular clamping is indicated to resects peripheral lesions especially on a diseased liver. When this technique is used in an alternate manner is very useful for central liver resections or mesohepatectomy [24]. When extraglissonean approach to the right and left portal pedicles is accomplished, the isolation of the sectional and segmental pedicle may be achieved by means of a combination of traction and further dissection around the glissonean sheets of the main pedicles. This may allow the sectional or segmental pedicle clamping with exact demarcation of the portion of the liver to be resected either on the right or on the left hemi-livers [20, 37, 38].

Total hepatic vascular exclusion is performed using the Pringle's manoeuvre and retro-hepatic vena cava clamping (usually infra and supra hepatic along with the right adrenal vein). The result is the complete isolation of the liver from systemic circulation. This situation produces hemodinamic instability not tolerable in 10% to 20% of patients in whom a veno-venous bypass may be indicated. Using this technique however exposed the patients to a higher complication rates 2.5-folds in a study from Belghiti et al. [39] so it is recommended that should be used in patients with tumours of the cavo-hepatic junction in whom a resection and substitution of the vena cava and/or major hepatic veins is indicated. Total hepatic vascular exclusion is a technically demanding procedure that requires surgical and anaesthetic expertise [24].

Inflow and outflow vascular occlusion of the liver (selective hepatic vascular exclusion) is achieved through the Pringle's manoeuvre along with the extraparenchymal control of the major hepatic veins and it is similar to total vascular exclusion except for the vena cava clamping. So it is not complicated with hemodinamic instability, renal or other general complications. The main problem with this technique is the extraparenchymal isolation of the main hepatic veins. This however may be achieved in up to 90% of the cases [40]. The isolation of the main and accessory right hepatic veins is usually accomplished after the section of some small accessory veins and of the posterior liver ligament [41]. Also the isolation of the middle and left hepatic veins has been reported in detail with the description of the technique [40, 42, 43]. Selective hepatic vascular exclusion can be applied continuously, intermittently [40] or partially [44]. When applied continuously the maximum ischemia time is 58 minutes [45] while intermittently 140 minutes [40]. When applied partially is very useful in defining the anatomic boundaries between right and left hemilivers but we have to keep in mind the different clamping for right and left liver resections, because the risk of increased bleeding, as described by Cherqui et al. [44]. In fact a complete bloodless field is obtained for segment 6 and 7 resections clamping the right portal pedicle and right hepatic vein, segment 5 and 8 are drained by middle hepatic vein as well, which is unclamped. For the same reason in left liver resections, left and middle hepatic veins clamping must follow a complete Pringle's manoeuvre because of the risk of venous stasis [44]. In the Authors' view, selective hepatic vascular exclusion (SHVE) is particularly indicated for central or mesohepatectomy where the right and common trunk of the left-middle

hepatic vein can be injured or torn, because it permits an easy and immediate repairing avoiding bleeding and gas embolism. SHVE or intermittent vascular exclusion (IVEL) are also indicated for tumours near the major hepatic veins, but far enough from cavo-hepatic junction, where they must be preserved or reconstructed [40, 44].

Selective hepatic vascular exclusion has showed to be better tolerated than total with lower complications rate, so it is particularly indicated in patients with impaired renal or liver functions [46].

Vascular Reconstructions

Until not many years ago liver tumours infiltrating the portal vein, major hepatic veins or the vena cava has been considered inoperable. Unlike the resection and reconstruction of portal vein and hepatic artery, which are reported and applied widely for resection of hilar colagiocarcinoma or hepatocellular carcinoma [47-50], resection and reconstruction of the retrohepatic vena cava and hepatic veins remain a challenging procedure with few and scattered reports. With the advent of liver transplantation which entails the reconstruction of the liver vessels, reports on vascular resection and reconstruction of the major liver vessels for tumours are growing in the literature in the more recent years. The techniques for the resection and reconstruction of the vena cava with liver resections have been described using various type of vascular exclusion technique, with or without venous by-pass and different materials used for reconstruction, either autologous/eterologous veins or prosthetic, of the vena cava [51-56] or the hepatic veins [57-60].

These procedures are performed in a small number of patients (0.7% to 5.4% of the resected patients) [52, 54, 58, 60] but they contribute anyway to the increase of the resectability rate. Major drawbacks are represented by the difficulties of the operation, which should be carried out by an experienced surgical and anaesthetic team, and the increased morbidity and mortality rates of approximately two folds [52-54, 58, 60]. Once the perioperative problems are overcome, disease free and overall survival rates were similar to those which do not entail vascular resection/reconstruction thus deserving these complicated procedures.

Conclusions

Liver tumours resectability rate may be increased nowadays through several ways such as: downstaging, multiple resections for multiple tumours, staged resections planned to remove completely the tumour in two operations, iterative surgery or re-resections for liver recurrence after the first, second or even third liver resection, difficult liver resections usually performed with various techniques of vascular control of the liver blood inflow and outflow which permits also vascular reconstructions of the major hepatic vessels invaded by the tumour and once considered a contraindication for liver resection. This has allowed to expand the pool of resectable patients with improving results and better survival rates.

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