Liver resections: complications and survival outcome

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Today, liver resection represents one of the most effective therapies in the treatment of defined liver diseases, particularly for hepatocellular carcinomas, liver metastases and tumors originating from the bile ducts. There have been a number of improvements in the technique but the use of kellyclasia associated with meticulous control of hemostasis and biliostasis appears to be more effective and efficient. The procedure is still burdened with some postoperative complications, the more characteristic of which are liver insufficiency, biliary leakage and ascites. Several neoplastic diseases, both primitive and secondary, can benefit from this therapy with substantial improvement of long-term survival, and a notable change in the natural history of the disease. For these situations, a consultation should always be performed by a surgeon experienced in hepatic surgery.

Expert Rev. Pharmacoeconomics Outcomes Res. 7(3), 269–279 (2007)

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KEYWORDS:
bile duct cancer, hepatocellular carcinoma, liver metastasis, liver resection, liver surgery, postoperative complication, postoperative survival

Removal of a portion of the liver is a challenging surgical procedure that has been performed increasingly often over the past 20 years. Currently, surgery of the liver, biliary tract and pancreas represents a significant portion of the work of general surgeons and has already given rise to specialized hepato–pancreato–biliary surgical units. The question of whether this branch of digestive surgery should become an independent specialty remains open [1].

A short summary of the recent developments in liver surgery is necessary in order to understand the history of this procedure and what lies ahead. In fact, before the 1980s, the approach to the liver was a surgical nightmare. Most physicians practicing at that time, who are now in their sixties, remember that period and probably have a particular attitude toward this surgical procedure. The difficulties in achieving full control of the transacted surface, paucity of the instruments and the lack of knowledge of the intrahepatic vascular anatomy made liver resection very difficult. Furthermore, the impossibility of performing an early diagnosis of potentially treatable diseases gave the procedure an aspect of futility. At that time, most of the hepatic diseases were large, symptomatic tumors or diffuse hepatocellular carcinomas (HCC) found in patients with advanced cirrhosis. The majority of the knowledge regarding these diseases was derived from postmortem examination of patients.

During the 1980s, something changed. First, the increasingly widespread use of abdominal ultrasonography (US) led to the possibility of following those patients at risk of developing malignancies of the liver amenable to surgery. These categories of patients were represented by those carrying hepatitis B or non-A non-B hepatitis (later named hepatitis C) [2] and patients already operated on for colonic cancer; these groups were at risk of developing HCC or liver metastases (LM), respectively.

On the other hand, the Vietnamese surgical school of Thang Tung demonstrated that the liver could be transected using the so-called digitoclasia, fracturing the hepatic parenchyma with the fingers in the search of medium and large vessels to be securely tied and cut [3].

Since the early 1980s, the number of liver resections has dramatically increased as a result of improvements in diagnosis and the study of diseases that are surgically treatable, and in surgical techniques and armamentarium.

During the 1980s it became clear that a defined group of patients are more prone to develop lesions that could be treated with the removal of limited portions of the liver. The

10.1586/14737167.7.3.269

ISSN 1473-7167

first are those with chronic liver diseases, both viral and alcoholic. The carcinogenetic action of the viral or toxic agent is well defined. For this reason, they should be submitted to periodical determination of the blood level of α-fetoprotein and to the performance of abdominal ultrasonography. The debate is ongoing regarding the frequency of the schedule [4,5] and controversy remains over whether screening itself is worthwhile in terms of decreasing the mortality rate related to HCC [6]. In patients with chronic hepatic dysfunction, such management can lead to the discovery of tumors with small dimensions that are still amenable to therapies such as liver resection, liver transplantation or percutaneous ablation.

On the other hand, patients already operated on for the removal of adenocarcinomas located in the colon or rectum must be followed up for the possible insurgence of LM, and the liver is the most frequent target site. This follow-up is usually performed by surgeons or by an oncologist, according to the need for adjuvant chemotherapy, as suggested by the staging of the primary tumor. Unfortunately, a considerable number of these patients miss such a follow-up.

At present, patients are aware of possible differences in indications for surgery and on the modality of performance of surgical treatment of liver diseases. They also know how to search for these differences among qualified centers [7]. Thus, further efforts should be made by the scientific community to obtain a widespread rationalization of the treatments of these diseases.

Pre-operative work-up

Without any doubt, the widespread use of abdominal US among radiologists, gastroenterologists, internal medicine physicians, surgeons and a variety of other health providers has led to an increased detection of focal lesions of the liver. This procedure is easy to perform, noninvasive and has low costs. The potential for portable instruments further increases applicability. The major limit is perhaps represented by operator experience and skill. This instrument has benefited from the addition of the Doppler study software and the possibility of using intravenous vascular contrast media. At present, ultrasonography represents a formidable tool for first-line study of the liver and recognition of possible diseases.

CT scanning and MRI are the fundamental tests used for the determination of a possible indication for surgery. It is beyond the scope of this review to discuss the indications for the performance of both tests. Nevertheless, it should be mentioned that both are able to correctly define the nature of a focal disease within the liver in most instances, enabling the location of the tumor in relation to the glissonian pedicles and hepatic veins to be determined. 3D imaging is increasingly used even in peripheral hospitals. This is of paramount importance for surgeons planning intraoperative strategy. In addition, it is possible to evaluate the volume of the portion of parenchyma to be removed by measuring them through the summation of each 2D area calculation. This could reduce the risk of postoperative liver failure due to insufficient mass of healthy liver remaining after extended hepatectomies.

Intraoperative ultrasonography remains the final step of radiological evaluation and the ultimate tool for staging before the performance of a resection. It has proved to be superior to all other imaging systems in the study of the liver, both in terms of sensitivity and specificity. The method can further define the relationship between tumor and hepatic vessels, detect the presence of missed nodules, and guide the performance of the resection, thus verifying the direction of the transection plane. Therefore, the presence of the instrument is mandatory in every surgical liver center. It remains to be verified whether a further improvement of its performances will be achieved with the addition of contrast media.

Indication for liver resection

The vast majority of liver resections are performed for malignancies. In a series of 1787 liver resections performed at the University of Bologna (Bologna, Italy) since 1981, 1389 (77.7%) were on tumors. The main indications are HCC (646; 36.1%) followed by metastases (626; 35.0%) and tumors originating from the bile ducts (118; 6.6%).

A key point is the presence or absence of chronic hepatic disease in the liver to be operated on. Patients without any hepatic disease, and thus with normal liver and hepatic function, can be submitted with success to a large range of procedures and even to extended or multiple resections. This is possible owing to the well-known capacity for regeneration of the liver [8]. However, particular attention should be placed on the volume of parenchyma remaining after resection. A number of different formulas for calculating the total volume of the liver [9] and the minimum acceptable volume have been evaluated [10,11].

Theoretically, a patient can be submitted to the removal of any part of the liver with the preservation of such a calculated volume and also the glissonian pedicles (including the afferent artery and vein, and the efferent bile duct) and the hepatic veins of the remaining parenchyma. A resection is defined as 'anatomical' when the portion of the liver removed corresponds to one or more units of the segmental anatomy of the liver. A consensus on the definition where anatomical resection was reached in 2000 in Brisbane [12]. A resection is defined as 'nonanatomical' when the resection plane does not follow the segmental anatomy.

Technical aspects

Without any doubt, the preferred abdominal incision for accessing the liver is the J-shaped right subcostal laparotomy that, in selected cases, can be extended to the left subcostal configuring a Mercedes logo-shaped laparotomy.

With the introduction of several technical instruments as tools for the surgeons, liver resection technique has changed dramatically. In fact, digitoclasia has been replaced with the kellyclasia [13], which is a method of fracturing the liver parenchyma using Kelly clamps [14]. Several aspects of the procedure should be taken into consideration: the identification of the tumor; the relationship of the tumor and the intrahepatic vessels; the identification and the suture of the main intrahepatic vessels; and the hemostasis of the cut surface.

There are some obvious technical steps that influence short- and long-term results, in particular for patients operated on for oncological reasons; leaving a free margin of healthy parenchyma around the tumor to be removed in order to reduce the risk of local recurrence is one. Furthermore, a significant improvement in overall survival has recently been reported with the increasingly widespread use of the so-called 'anterior approach' to the right hepatic vein during the right hepatectomy [15]. Compared with the extrahepatic isolation of the vein during the conventional technique, the anterior approach has been associated with significantly lower circulating plasma albumin mRNA, a biological marker for circulating liver cells possibly reflecting tumor cell dissemination during mobilization and surgery at various stages of the resection. For this reason, the anterior approach gives better operative and survival outcomes compared with the conventional approach, and it should be the preferred technique for major right hepatic resections, at least for large HCC.

Kellyclasia probably represents the best way of performing a liver resection, but it requires surgeons who are well trained in the performance of the procedure. The search for extending the number of centers attempting liver surgery has brought about the development of new surgical tools for the performance of such operations. The most popular devices that have been claimed to facilitate bloodless transections include the ultrasonic dissector (Cavitron Ultrasonic Surgical Aspirator [CUSA], Tyco Healthcare, MA, USA) using ultrasonic energy, the Hydro-Jet® (Erbe, Tubingen, Germany) using a pressurized jet of water, and the dissecting sealer (TissueLink, NH, USA) using radiofrequency energy.

In a randomized trial, the clamp-crushing technique with routine inflow occlusion was significantly associated with decreased blood loss and shorter resection time when compared with transection with CUSA, Hydro-Jet or dissecting sealer [16]. Furthermore, the concomitant cost analysis of the use of each respective device indicated that the clamp-crushing technique is the most cost-efficient strategy, regardless of the volume of liver resection performed [16]. Clamp crushing was also superior to ultrasonic dissection in terms of the overall quality of the hepatectomy [17]. A plausible interpretation of this result is that surgeons experienced in hepatic resection will achieve comparable levels of blood loss and transection time whether or not an ultrasonic dissector is used [17].

The cost advantage of the kellyclasia technique is not only attributed to very low equipment costs, but is also related to the shorter resection time and lower blood loss with less need for blood transfusion. The equipment costs of CUSA and Hydro-Jet depend strongly on the number of cases per year, since both devices require a large initial purchase with lower costs for disposable material. The costs of these devices decrease by increasing the number of cases performed. However, CUSA and Hydro-Jet are three- to sixfold and two- to fourfold more expensive compared with the clamp-crushing technique, respectively. By contrast, the dissecting sealer only has costs of the disposable material without the need to purchase a machine, but costs were also three-times higher than the clamp-crushing technique. Thus, the kellyclasia technique has the highest cost-saving potential compared with other devices. Even if the advantageous results of the clamp-crushing technique, such as shorter resection time and lower blood loss are ignored, the cost of the equipment significantly favors the clamp-crushing technique.

Some criticism arises from the fact that Hydro-Jet allows the entrance of air bubbles into the intrahepatic vascular structure during parenchyma transection, contributing to the difficulty in performing intraoperative echography. CUSA, however, can crush a wider range of liver parenchyma, which may lead to the increased possibility of a tumor-positive surgical margin; however, these considerations have not been confirmed by randomized controlled trials.

The most recently developed method, thermal technique by radiofrequency ablation, has also been proposed to prevent blood loss by inducing necrotic clotting of the defined resection plane. Final division of the parenchyma can be performed using a scalpel or scissors. This method has been also claimed to increase the margin of clearance, thus providing some oncological advantage. Using a similar technique, some authors have demonstrated a reduction in intraoperative blood loss. On the other hand, radiofrequency precoagulation may be associated with an increase in postoperative complications related to increased necrosis of the liver parenchyma. It has already been shown that, in effect, the radiofrequency resection technique allows parenchymal resection in a clean surgical field, but it is more expensive and it is associated with a higher rate of postoperative complications [18].

More recently, the harmonic scalpel (Ultracision, Ethicon, Endo-surgery, Ohio, USA) and the Ligasure™ (Atlas, Vallylab, Boulder, Tyco Healthcare) have both been proposed as useful tools in the performance of hepatic resections. At present, there are no data in the literature regarding their true utility. Nevertheless, the feeling is that they will not change the way that surgeons already experienced in liver resections perform these procedures. On the contrary, they could be of some help to general surgeons who are already well trained in their use due to their application in other abdominal procedures (open or laparoscopic).

Vascular control

It has already been demonstrated that reducing blood loss during liver surgery improved short- and long-term results [19]. The liver owns a vascular inflow, represented by the hepatic artery and the portal vein, and a vascular outflow, which is the hepatic vein system. Controlling only the vascular inflow or both the inflow and the outflow systems are the suggested ways of reducing blood losses during parenchyma transection.

The most effective and easy way to apply this theory is by clamping the hepatic pedicle, the so-called 'Pringle maneuver', which completely stops the blood inflow occluding the portal pedicle with the use of a vascular clamp [20]. Even if extremely effective, clamping cannot be applied for a long period due to the warm ischemic damage causing anoxia to the liver cells.

Patients with chronic liver dysfunction are more susceptible to these deleterious effects, and thus alternative ways of clamping are needed.

The modification of continuous clamping with intermittent clamping has been proposed successfully [21]. Intermittent clamping of the portal triad is somehow related to ischemic preconditioning (a brief period of ischemia followed by a short interval of reperfusion), which is a nonpharmacologic strategy to protect the liver from ischemic injuries. The rationale of ischemic preconditioning is that cells are exposed to a limited stress that triggers natural defense mechanisms against subsequent ischemic injuries. In a recent review, intermittent clamping and ischemic preconditioning are reported to be highly and equally effective in minimizing postoperative injuries to the liver, but intermittent clamping appears to be superior for long periods of ischemia (≥75 min) [22].

A further step has been to verify the length of the interval of the intermittent clamping [23]. It has then been used to ascertain the safety of selectively clamping only the portion of liver where the resection has to be performed to reduce the ischemic time in the nonresected portion of the liver [24,25].

Pedicle clamping is useful for suddenly reducing the amount of acute bleeding from the resected hepatic surfaces, but it is not a mandatory step in the performance of a liver resection. The maneuver must be in the armamentarium of all general surgeons. Well-trained hepatic surgeons and/or a meticulous technique of division of the liver parenchyma can render this procedure completely unnecessary [26,27].

The control of the vascular outflow during resection is more intriguing. The complete total vascular exclusion of the liver, mainly proposed by Huguet [28], gained popularity in the early 1990s [29]. Its application is challenging from the technical point of view and it quickly became evident that it is also unnecessary in most cases [26]. The complete hepatic vascular exclusion with preservation of the caval flow was also considered to be difficult to perform and did not gain much popularity in the surgical community, even if it has defined application [30]. Rather, a greater consensus has now been reached on keeping the central venous pressure of the patient as low as possible during the division of the parenchyma, thereby reducing the possibility of bleeding from backflow [31].

One of the most controversial aspects of liver resection is the treatment of the raw surface of the organ after the removal of the surgical specimen. A number of hemostatic methods have been evaluated as adjunctive procedures in hepatic resection. Topical hemostatic agents have been used for this reason with varying degrees of success. They include oxidized cellulose, absorbable gelatin sponge, microfibrillar collagen and fibrin sealants produced with pooled plasma blood. Fibrin sealants have become popular for improving perioperative hemostasis, reducing the need for packed red blood cell transfusion, and in preventing bile leakage. Nevertheless, it is thought that the way hepatectomy is performed and the accuracy of the hemostasis reached during parenchymal transaction are the major determinants of the final results.

In fact, a prospective randomized trial reveals that the application of fibrin sealant on the raw surface of the liver does not seem justified [32]. Blood loss, transfusion, incidence of biliary fistula and outcome were comparable to patients without fibrin glue in this study. Therefore, discontinuation of routine use of fibrin sealant would result in significant cost savings.

Complications

The definition of a specific complication in surgery is always difficult to define and to reach a consensus on. For the purpose of this review, we defined a complication as a condition or event unfavorable to the patient's health, causing irreversible damage or requiring a change in therapeutic policy, including prolonged hospital stay, after a liver resection. An accurate classification of surgical complication has been recently reported [33].

As in every surgical procedure, there are two different sets of complications: those related to the performance of laparotomy alone and those specifically related to the performance of a liver resection.

Postoperative liver failure

Under this view, most of the complications of liver resections are directly related with the performance of the procedure itself (TABLE 1). The most life threatening is the hepatic failure. This is a grade IV–V surgical complication according to the already reported classification [33]. The definition of postoperative hepatic failure is not yet fully standardized. Without any doubt, the death of the patient is the most extreme end point to be taken into consideration. Nevertheless, the problem also exists for the categorization of those patients who present transient abnormalities of hepatic function and who eventually recover. Clinical and biological variables, such as ascites, encephalopathy, jaundice, prolonged prothrombin time, hyperbilirubinemia and hypoalbuminemia, are usual markers of impaired liver function. There is neither a standardized definition of postoperative liver failure based on these markers, nor precise data on their correlation with postoperative mortality (TABLE 2). The need for a standardized definition of postoperative liver failure is important for the evaluation of technical improvements in different fields of liver surgery, such as pre-operative portal vein deprivation and the result of different methods of vascular clamping.

Impaired hepatic function after the operation can be secondary to several intraoperative factors: massive bleeding after or during surgery with hypoperfusion of the organ, prolonged clamping of the hepatic pedicle, incorrect fluid replacement during laparotomy with secondary hypovolemia, removal of an excessive amount of parenchyma and irreparable surgical lesion of the vascular inflow or outflow during transection. Sepsis is the leading cause of hepatic failure in the postoperative period.

For patients without any underlying liver disease, the possible causes of a postoperative liver failure are mainly related to an acute event that occurred during the operation or to the excessive amount of parenchyma removed. For patients with a

Table 1. Postoperative complications in hepatic resections.

	HCC group	Other liver malignancy group	Biliary malignancy group	LDLT donor group	Other benign diseases group
1056 hepatic resections					
n	532	262	57	174	31
Patients with complications (%)	208 (39)	108 (41)	31 (54)	43 (25)	10 (32)
Major complications* (%)	15 (3)	20 (8)	16 (28)	8 (5)	0
Surgical intervention (%)	7 (1)	8 (3)	5 (9)	6 (3)	0
Bologna, 1787 resections					
n	646	692	51		398
Patients with complications (%)	229 (35.4)	157 (22.7)	26 (50.9)		90 (22.6)
Major complications* (%)	58 (9.0)	57 (8.2)	11 (21.5)		11 (3.0)
Surgical intervention (%)	22 (3.4)	38 (5.5)	9 (17.6)		9 (2.2)

*Complications that required radiological or surgical interventions. Adapted from [34].
HCC: Hepatocellular carcinoma; LDLT: Living donor liver transplantation.

healthy liver, several indices have been proposed for calculating the maximum amount of parenchyma that may be removed with safety [10,37]. The total liver volume can be verified at CT volumetry with the formula:

$$Total\ liver\ volume\ (cm^3) = -794.41 + (1267.28 \times body\ surface\ area)$$

This formula was evaluated as the most helpful and reliable in a recent meta-analysis [9].

It has been postulated that individuals with normal liver function can undergo resection of up to 60% of nontumorous parenchyma [10,37]; however, this limit can be extended with a certain safety under several circumstances [11]. More data and experience on the liver volume concept have recently been accumulated from the experience gained with the activity of liver transplantation from a living related donor [38,39].

The possibility of performing the pre-operative embolization of a main branch of the portal vein in order to induce the hypertrophy of the controlateral lobe [40–42] or to perform iterative resections [43,44] increases the possibility given to selected patients of undergoing radical resections with a reduced risk of postoperative liver failure.

The problem is more complex for patients with impaired liver function. The etiology of possible postoperative liver failure varies according to the degree of a functional damage already present in the liver for the contemporary presence of the underlying disease. For these reasons, there have been several attempts to identify clinical or mathematical tools capable of predicting the insurgence of the complication.

Historically, the classification used the most for these patients has been the Child-Pugh classification [45,46]. Despite its widespread use, this classification lacks specificity, since two of its components (the presence of ascites and encephalopathy) are dependent on the observer and thus subject to criticism and variability.

Other functional parameters have been proposed over the years: the conversion of lidocaine to monoethylglycinexylidide (MEGX) test [47], aminopyrine breath test, galactose-elimination capacity, arterial ketone body ratio and indocyanine green (ICG) clearance rate have been widely tested [48]. The latter, in particular, represents the gold standard for evaluation of patients for surgery in Japan.

More recently, the Model for End-stage Liver Disease (MELD) score has been applied with some success in this field [49]. Unfortunately, none of these tests have such a high accuracy in predicting the insurgence of postoperative liver failure.

Table 2. Biochemical parameters used in the definition of postoperative hepatic failure after liver resection.

Study	Bilirubine	Prothrombine time	Period	Ref.
Imamura (2003)	>5.0 mg/dl or >85 µmol/l	<50%	≥3 consecutive days	[34]
Balzan (2005)	>3.0 mg/dl or >50 µmol/l	<50%	Postoperative day 5	[35]
Muller (2007)	>7.0 mg/dl	International normalized ratio >2.0	Postoperative peak	[36]

A hepatic vein pressure gradient of at least 10 mmHg has also been shown to be a predictor of unresolved hepatic decompensation after surgery [50]. The absence of portal hypertension and normal bilirubin could be of some relevance in selecting the best candidates for resection, but these data have not yet been confirmed by other consistent studies.

The incidence of liver failure varies in the published series, depending on the indication for surgery and the presence of cirrhosis. For patients who underwent surgey for hepatic tumors of any kind in noncirrhotic liver the mortality, globally, should be less than 1%. A higher mortality is reported for patients operated on for tumors of bile duct confluence. These latter patients are usually submitted to extended hepatectomies, removal of the caudate lobe and the bile duct with a Roux-en-Y hepaticojejunostomy. In this group of patients, good results have been reported by the Japanese groups, with postoperative mortality as low as 3–9.6% [51,52], while in Western countries, a 7–10% postoperative mortality is quite frequent [53].

In our series of 51 patients operated on for carcinoma of the bile duct confluence, we observed an 11.7% operative mortality (six patients).

For patients with HCC aroused in cirrhosis, a very low mortality (ranging around 1%) can be achieved if restricted indications are followed [54]. When indications have been extended to patients with severe comorbidities that are not amenable to other, less invasive treatments, the postoperative mortality rate quickly increases to 5–7% [55].

Biliary leakage

From a technical standpoint, biliary leakage is the most typical technical complication after liver resection. One of the few definitions for bile leakage is a bilirubin level in the drainage fluid that exceeds 5.0 mg/dl (>85 µmol/l) for more than 7 days or intra-abdominal fluid collection showing a bilirubin level greater than 5.0 mg/dl (>85 µmol/l) after the percutaneous drain [34].

Bile leakage can originate from a separated bile duct with no communication to the main biliary tree. In nonanatomical hepatic resection, interruption of a bile duct can occur during parenchymatous division. Another possibility is bile oozing from crushed and exposed liver parenchymatous cells. A short period of examination cannot detect bile oozing at the capillary level. Such a microscopic bile leak might occur in some transient cases. On the other hand, a delayed bile leak is likely to be related to infection.

Despite a significant decrease in the overall surgical complication rate in hepatic resections, the rate of bile leakage has not changed, with an incidence of 4.8–8.1% reported in recent large series [56]. The incidence of postoperative bile leakage has been reported to be similar among patients with and without hepatitis or liver cirrhosis. High-risk procedure, intraoperative blood loss and surgical time were associated with the development of postoperative bile leakage using univariate analysis [57].

The presence of bile, blood and necrotic tissue in a dead space after hepatic resection provides the ideal environment for bacterial growth; this environment impairs the normal host defense mechanisms and predisposes the patient to sepsis, liver failure and death.

There are at least four recommended methods of preventing biliary complications after liver surgery: intraoperative cholangiography; spreading fibrin glue on the transected raw liver surface; assessing bile duct patency by injecting air under ultrasonographic monitoring; and a bile leakage test. The role of the fibrin glue in liver surgery has already been discussed [32]. A randomized study suggested no advantage in using a bile leakage test to prevent bile leaks and it should, therefore, not be used routinely during hepatic resection [58]. This result came from a high-volume center of liver surgery, but whether this may be reproduced by general surgeons must be evaluated. The best way of preventing postoperative bile leakage remains the meticulous management of the transected liver surface, rather than performing a bile leakage test.

In most patients, bile leakage resolves spontaneously, but sometimes it is unremitting. Patients can usually be treated conservatively. Bile leaks from small biliary stumps with some communication to the main biliary tree will usually close spontaneously, with the restoration of peristalsis and papillary function. Bile leaks from the raw surface often involve concomitant interruption of portal or arterial blood supply, and will also subside with associated partial atrophy of the liver.

If effective drainage is achieved, it is usually sufficient to observe the patient conservatively as long as careful management of the drains against infection is maintained. Surgical intervention is only required when a bile leak originates from injury to a major duct, but re-operation is often complicated by dense adhesions that render dissection and identification of the leakage site difficult. Nonsurgical treatments, such as nasobiliary drainage, are preferable to re-operation. However, biliary decompression will not be effective when the leaking ducts do not communicate with the common bile duct [59]. In these cases, interventional treatment can be necessary (FIGURE 1).

Ascites

Ascites is a frequent complication observed after liver resection. There is no general agreement on even the definition of the insurgence of ascites as a complication. The only consistent definition includes the drainage of ascitic fluid of more than 2 l/day for more than 3 days, drainage requiring paracentesis after the abdominal drain was removed or postoperative hospitalization of more than 30 days owing to ascites control [34].

There are various causes for postoperative ascites: transient impairment of the liver function secondary to the laparotomy with hypoprotidemia and hypoalbuminemia, sections of lymphatic structures, the damage secondary to pedicle clamping and modification of the global area of the portal blood distribution are all factors related to the phenomenon of fluid retention after the operation.

The problem is definitely more frequent after resection in patients with chronic hepatitis or cirrhosis, but it can often be observed in patients with healthy liver after extended hepatectomies.

In our initial series of 264 carefully selected patients, the presence of ascites was verified in 22.7% of the cases [54]. Treatment is usually medical, with infusion of fresh frozen plasma, albumin and diuretics. If the presence of ascites is part of hepatic decompensation, liver transplantation can be necessary when the patient meets the indication.

Survival outcome

Postoperative mortality

The strongest indicator of the short-term clinical efficacy of liver resections is the mortality rate. There are several ways to define this short outcome measure. The classical method is to count the number of patients who died within 30 days of the date of surgery. The parameter has been extremely useful since the management of more complex disease and the extensive use of intensive care therapies led to a further extension of the possibility of patients surviving longer after surgery. For this reason, the 30-day mortality has been widely replaced by the 90-day or in-hospital mortality. These parameters give a more accurate vision of what happens after a liver resection. Unfortunately, none of these parameters have been defined as the gold standard, which is why one or more of them are frequently found in the literature.

The mortality of liver resection was considerable when this surgery started becoming common practice. In some early series, the percentage of patients who did not survive surgery ranged from 15 to 20% and, in fact, these data led to the development of alternative strategies for treating specific diseases, such as HCC or cirrhosis. The most efficient has been proven to be percutaneous radioablation. Most of the indications for resection and ablation overlap, thus opening a strong competition between the two different approaches.

In experienced centers, the mortality can, today, be as low as zero, even in the setting of a large number of procedures [34].

In our initial series of HCC, the hospital mortality was 4.9% for patients with cirrhosis and 3.0% for patients without cirrhosis, without any statistically significant difference among the two groups. These values dropped to 2.9 and 1.1%, respectively, after 1992 [60].

In a systematic review of published studies on surgical resections of LM from colorectal cancer, the death rate within 30 days was reported as 0–6.6% (median: 2.8%). More frequent causes of death were hepatic failure (18.4%), postoperative hemorrhage (17.5%), generalized sepsis (16.5%) and cardiac failure (11.7%) [61]. The mortality rates after extended hepatectomies for bile duct cancers have already been reported.

Survival after resection of hepatocellular carcinoma

The natural history of HCC in cirrhosis foresees no survival 3 years after the initial diagnosis [62]. More recent data on the natural history of the same disease revealed that selected patients with extremely favorable prognostic factors can achieve a 3-year survival up to 50% without any treatment [63]. Nevertheless, this is one of the diseases where surgical and interventional therapies have significantly changed prognosis.

The survival rate reported after resection is somewhat heterogeneous. A 5-year survival rate of 50–70% is currently described at several centers [64]. The main problem with surgical resection is neoplastic recurrence, which complicates 70% of cases at 5 years [65]. In fact, about a third of the patients are alive and disease free 5 years after surgery [54]. The data reporting a 100% recurrence came from a single center and it has never been confirmed by others [66].

It is difficult to discriminate between true recurrences (intrahepatic metastases) and the development of *de novo* tumors. From genomic investigations it has been determined that 60–70% of recurrences are intrahepatic metastases undetected at the time of resection, whereas 30–40% are *de novo* tumors [67,68]. True recurrences typically emerge within 2 years of resection, and are usually associated with vascular invasion, satellites and poor differentiation degree [65]. *De novo* tumors habitually occur late (>2 years after resection). At present, there are no strategies (adoptive immunotherapy, chemoembolization or internal radiation) that consistently prevent recurrence.

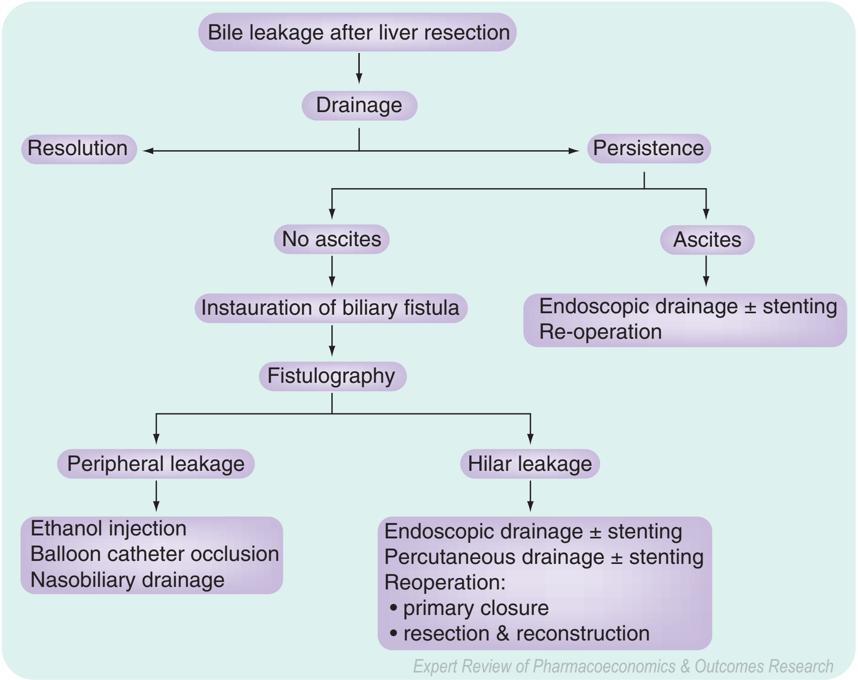

Figure 1. The treatment of a biliary fistular after liver resection.

When recurrence is established, re-resection can be applied in 10–20% of cases, particularly those in which tumors are thought to be *de novo* lesions. Salvage liver transplantation can also be applied. Other treatments include percutaneous ablation and transarterial chemoembolization. The combined treatment of HCC recurrences significantly contributes to the improvement of the results obtained in the most recent years.

Survival after resection of metastases from colorectal cancer

The natural history of LM from colorectal cancers is extremely poor, but only a few studies dealt with the natural history of untreated LM. A prospective study carried out during the 1980s on 484 consecutive patients with untreated LM reported an average survival rate of 31% at 1 year, 2.6% at 3 years and 0.9% at 4 years. Factors independently influencing survival included the extent of liver involvement, the presence of extrahepatic disease, the presence of metastases in the mesenteric lymph nodes, carcinoembryonic antigen (CEA) level and the patient's age [69].

On the contrary, the 5-year survival of patients submitted to liver resection in more recent years ranges from 30 to 50%, largely depending on the selection criteria. Our series, in which 44% of patients had multiple lesions (which are considered to be a negative prognostic factor) reached a 5-year survival of 34% [70].

Even with the introduction of new and more efficient antineoplastic drugs into the health market, the surgical removal of LM remains the best treatment choice for these patients. Therefore, the indication for liver resection for this disease receives the compilation of specific guidelines [71]. There is no other therapy that can achieve such an extension of patient survival. This is, in fact, stated in most scientific literature on this topic [72].

It should also be underlined that the recurrence of the disease, intrahepatic or even extrahepatic, represents the most common cause of death after liver resection. There are no definitive strategies for reducing the percentages of patients who develop recurrence and who have been validated from prospective randomized trials. When recurrence is detected, patients should be evaluated again by a surgeon and treated accordingly either by re-operation or systemic chemotherapy. Survival after repeated resections is as good after the first procedure. In two recently published Japanese series, the percentage of treatable patients with a second resection after the development of an intrahepatic recurrence ranged from 14.3 to 25.4%, and the 5-year survival was 49% [73,74].

Since the greater proportion of patients with metastases do not have chronic diseases, all patients should be evaluated by a surgeon for the indication for resection. Unfortunately, even recent data from the literature reveal that only a minority of patients with colorectal metastases underwent surgical removal of the metastases [75].

Survival after resection of metastases from noncolorectal cancers

The indication for liver surgery in the presence of LM from tumors originating in places other than the colon and rectum is more controversial and less clear.

There is no doubt that an aggressive treatment of LM from the neuroendocrine neoplasm can improve patient survival [76]. The small number of patients affected by this disease prevents the identification of the long-term results that may be achieved with liver resection.

On the other hand, in a series of 142 consecutive patients submitted to curative liver resection for noncolorectal non-neuroendocrine LM, we have reported a 5-year survival close to 35% and a 5-year disease-free survival of 24% with no postoperative mortality, compared with the dismal prognosis of patients undergoing palliative procedures and almost no survivors 3 years after diagnosis. A 5-year survival rate between 20 and 37% might be expected in these patients after curative liver resection [77]. Similar results have been recently reported that confirm that liver resections on these heterogeneous diseases are safe and effective and can offer long-term survival in selected patients [78,79]. Patients operated on for LM from urologic and genital tumors can achieve a 50% survival 5 years after surgery. Furthermore, LM from pancreatic cancers are no longer an absolute contraindication for surgery, with a sustained long-term survival after hepatectomy.

Survival after resection of tumors of the biliary tract

Tumors from the biliary tract are difficult to manage owing to their aggressive behavior, in particular those arising from the confluence of the main bile ducts. These latter tumors are difficult to recognize and stage. Furthermore, because of their relative paucity, there are very few referring centers and institutions.

Common treatment of these patients is limited to the insertion of plastic or metallic stents to relieve jaundice. The survival of these patients is usually limited to 1 year.

Surgical treatment of tumors of the main bile ducts, the so-called Klatskin tumors, usually required right or left extended hepatectomies, removal of the caudate lobe and the bile duct and eventually a Roux-en-Y hepaticojejunostomy. This is a complex surgical procedure that is usually performed in tertiary referring centers.

Considering all of the 51 patients operated on at our institution, as well as those that died shortly after the operation, the 3- and 5-year survivals are 47.3 and 34.1%, respectively.

Survival after resection of benign diseases

The surgical removal of benign diseases from the liver should be carried out only in very carefully selected cases. The most common instances are the documented growth of the lesion, presence of symptoms and intraparenchymal or intraperitoneal rupture or the diagnostic dilemma. Since these are truly benign lesions, their ideal treatment should include no mortality and the lowest rate of postoperative morbidity.

Expert commentary & five-year view

Liver resection is currently an established therapy for a large number of hepatic diseases, particularly for those with malignant origin. The study of a patient carrying a neoplastic disease amenable to treatment with surgery requires a thorough evaluation, including hepatologic balance, oncological view when needed and precise radiological mapping of the tumor and its relationship with the major structures of the liver. The future will thus drive the creation of specialized teams which, formally or not, will cover a large spectrum of patients carrying liver diseases, irrespective of the need for medical or surgical therapy. This will be facilitated by the strong relationships among the different aspects of these illnesses.

The performance of a liver resection, particularly one that is extended or complex, requires well-trained hepatic surgeons with specific competence and skill in the performance of intraoperative echography, parenchymal division, vascular control and hemostasis. This can be achieved only after very specific and direct training, which renders the procedure even more specialized.

The further improvement in indications and technique will increase the safety of surgical intervention. The expertise and necessary, specific competence to place indication for the intervention will highlight the necesity of the creation of dedicated departments exclusively devoted to the surgery and transplantation of liver, which will have established and continuous collaborations with dedicated hepatologists, radiologists and oncologists.

In certain countries hepato–pancreato–biliary units are already a reality, but their number will hopefully increase over the next few years. An alternative is provided by specific recognition and certification of the hepato–pancreato–biliary surgical activity performed by individuals or institutions by the relevant scientific societies.

Key issues

- Liver resection is an established therapy for several neoplastic and benign hepatic diseases.
- Patients at risk of developing hepatocellular carcinoma and liver metastases should be submitted to regular radiological evaluation with abdominal ultrasound and CT scan.
- CT scan and MRI are indispensable tools in the evaluation of patients for surgery and in planning the performance of a liver resection.
- Among all the technical tools proposed for a safe division of the hepatic parenchyma, the so-called kellyclasia still appears to be most efficient, safe and cost saving.
- Vascular control of hepatic in- and outflow can reduce the amount of bleeding during resection.
- Postoperative liver failure remains the most life-threatening complication. The removal of an excessive amount of parenchyma and infections are the main causes of this complication.
- Biliary leakage is the most common technical complication, with an incidence of 4.8–8.1%.
- The possibility of performing portal vein embolization, simultaneous multiple resections and iterative resections has expanded the number of patients who are amenable to liver resections.
- A postoperative mortality rate of 0–5% is widely reported but, in experienced centers, the postoperative mortality can be as low as 0%.
- The 5-year survival after liver resection can be expected to be around 50% for hepatocellular carcinoma.
- The 5-year survival after liver resection for metastases from colorectal carcinoma ranges from 30 to 50%.
- The 5-year survival after extended liver resection for tumors of the main bile ducts ranges from 30 to 40%.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Gozzetti G, Mazziotti A, Grazi GL. HPB Surgery: an independent specialty or a branch of digestive surgery? *HPB Surg.* 8, 111–113 (1994).

2 Bolondi L. Screening for hepatocellular carcinoma in cirrhosis. *J. Hepatol.* 39(6), 1076–1084 (2003).

3 Ton That Tung. Le cancer primaire du foie au Viet-nam. *Chirurgie* 99, 427–436 (1973).

4 Bolondi L, Sofia S, Siringo S *et al.* Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. *Gut* 48(2), 251–259 (2001).

5 Trevisani F, De Notariis S, Rapaccini G *et al.* Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). *Am. J. Gastroenterology* 97(3), 734–744 (2002).

6 Bruix J, Sherman M. Management of hepatocellular carcinoma. Practice Guidelines Committee, American Association for the Study of Liver Diseases. *Hepatology* 42(5), 1208–1236 (2005).

7 Grazi GL. Web relationships between physicians and individuals seeking information on hepatopancreatobiliary diseases. *Arch. Surg.* 141(12), 1176–1182 (2006).

•• One of the first reports on what patients are viewing on the internet.

8 Yokoyama Y, Nagino M, Nimura Y. Mechanisms of hepatic regeneration following portal vein embolization and partial hepatectomy: a review. *World J. Surg.* 31(2), 367–374 (2007).

9 Johnson TN, Tucker GT, Tanner MS, Rostami-Hodjegan A. Changes in liver volume from birth to adulthood: a meta-analysis. *Liver Transpl.* 11(12), 1481–1493 (2005).

10 Kubota K, Makuuchi M, Kusaka K *et al.* Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology* 26(5), 1176–1181 (1997).

11 Truant S, Oberlin O, Sergent G *et al.* Remnant liver volume to body weight ratio ≥ 0.5%: a new cut-off to estimate postoperative risks after extended resection in noncirrhotic liver. *J. Am. Coll. Surg.* 204(1), 22–33 (2007).

12 Pang YY, Strasberg SM. The Brisbane 2000 terminology of liver anatomy and resections. *J. Hepatobiliary Pancreat. Surg.* 2, 333–339 (2000).

13 Lin T, Tsu K, Mien C *et al.* Study on lobectomy of the liver. *J. Formosa Med. Assoc.* 57, 742–759 (1958).

14 Lin TY. A simplified technique for hepatic resection: the crush method. *Ann. Surg.* 180, 285–290 (1974).

15 Liu CL, Fan ST, Cheung ST, Lo CM, Ng IO, Wong J. Anterior approach versus conventional approach right hepatic resection for large hepatocellular carcinoma: a prospective randomized controlled study. *Ann. Surg.* 244(2), 194–203 (2006).

16 Lesurtel M, Selzner M, Petrowsky H, McCormack L, Clavien PA. How should transection of the liver be performed? A prospective randomized study in 100 consecutive patients: comparing four different transection strategies. *Ann. Surg.* 242, 814–823 (2005).

•• Good method for comparing different techniques in surgery.

17 Takayama T, Makuuchi M, Kubota K *et al.* Randomized comparison of ultrasonic vs clamp transection of the liver. *Arch. Surg.* 136, 922–928 (2001).

18 Lupo L, Gallerani A, Panzera P, Tandoi F, Di Palma G, Memeo V. Randomized clinical trial of radiofrequency-assisted versus clamp-crushing liver resection. *Br. J. Surg.* 94, 287–291 (2007).

19 Gozzetti G, Mazziotti A, Grazi GL *et al.* Liver resection without blood transfusion. *Br. J. Surg.* 82, 1105–1110 (1995).

20 Pringle JH. Note on the arrest of hepatic hemorrhage due to trauma. *Ann. Surg.* 48, 541–549 (1908).

21 Belghiti J, Noun R, Malafosse R *et al.* Continuous versus intermittent portal triad clamping for liver resection: a controlled study. *Ann. Surg.* 229(3), 369–375 (1999).

22 Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. *N. Engl. J. Med.* 356(15), 1545–1559 (2007).

23 Esaki M, Sano T, Shimada K *et al.* Randomized clinical trial of hepatectomy using intermittent pedicle occlusion with ischaemic intervals of 15 versus 30 minutes. *Br. J. Surg.* 93(8), 944–951 (2006).

24 Makuuchi M, Mori T, Gunvén P, Yamazaki S, Hasegawa H. Safety of hemihepatic vascular occlusion during resection of the liver. *Surg. Gynecol. Obstet.* 164(2), 155–158 (1987).

25 Figueras J, Llado L, Ruiz D *et al.* Complete versus selective portal triad clamping for minor liver resections: a prospective randomized trial. *Ann. Surg.* 241(4), 582–590 (2005).

26 Grazi GL, Mazziotti A, Jovine E *et al.* Total vascular exclusion of the liver during hepatic surgery: selective use, extensive use or abuse. *Arch. Surg.* 132, 1104–1110 (1997).

27 Capussotti L, Muratore A, Ferrero A, Massucco P, Ribero D, Polastri R. Randomized clinical trial of liver resection with and without hepatic pedicle clamping. *Br. J. Surg.* 93(6), 685–689 (2006).

28 Huguet C, Nordlinger B, Galopin JJ, Bloch P, Gallot D. Normothermic hepatic vascular exclusion for extensive hepatectomy. *Surg. Gynecol. Obstet.* 147(5), 689–693 (1978).

29 Delva E, Camus Y, Nordlinger B *et al.* Vascular occlusions for liver resections: operative management and tolerance to hepatic ischemia. *Ann. Surg.* 209, 211–218 (1989).

30 Cherqui D, Malassagne B, Colau PH *et al.* Hepatic vascular exclusion with preservation of the caval flow for liver resections. *Ann. Surg.* 230(1), 24–30 (1999).

31 Melendez JA, Arslan V, Fischer ME *et al.* Perioperative outcomes of major hepatic resections under low central venous pressure anesthesia: blood loss, blood transfusion, and the risk of postoperative renal dysfunction. *J. Am. Coll. Surg.* 187(6), 620–625 (1998).

32 Figueras J, Llado L, Miro M *et al.* Application of fibrin glue sealant after hepatectomy does not seem justified. Results of a randomized study in 300 patients. *Ann. Surg.* (2007) (In Press).

33 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann. Surg.* 240(2), 205–213 (2004).

•• Important paper for all physicians dealing with quality healthcare.

34 Imamura H, Seyama Y, Kokudo N *et al.* One thousand fifty-six hepatectomies without mortality in 8 years. *Arch. Surg.* 138(11), 1198–1206 (2003).

35 Balzan S, Belghiti J, Farges O *et al.* The “50–50 criteria” on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann. Surg.* 242(6), 824–828 (2005).

36 Mullen JT, Ribero D, Reddy SK *et al.* Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. *J. Am. Coll. Surg.* 204(5), 854–862 (2007).

37 Vauthey JN, Chaoui A, Do KA *et al.* Standardized measurement of the future liver remnant before extended liver resection: methodology and clinical associations. *Surgery* 127, 512–519 (2000).

38 Kiuchi T, Kasahara M, Uryuhara K *et al.* Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. *Transplantation* 67(2), 321–327 (1999).

39 Fan ST, Lo CM, Liu CL, Yong BH, Chan JK, Ng IO. Safety of donors in live donor liver transplantation using right lobe grafts. *Arch. Surg.* 135(3), 336–340 (2000).

40 Makuuchi M, Thai BL, Takayasu K *et al.* Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. *Surgery* 107(5), 521–527 (1990).

41 Imamura H, Shimada R, Kubota M *et al.* Preoperative portal vein embolization: an audit of 84 patients. *Hepatology* 29(4), 1099–1105 (1999).

42 Azoulay D, Castaing D, Krissat J *et al.* Percutaneous portal vein embolization increases the feasibility and safety of major liver resection for hepatocellular carcinoma in injured liver. *Ann. Surg.* 232(5), 665–672 (2000).

43 Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: a planned strategy to treat irresectable liver tumors. *Ann. Surg.* 232(6), 777–785 (2000).

44 Ercolani G, Principe A, Ravaioli M, Cescon M, Grazi GL. Long-term survival after two-stage hepatectomy for colorectal metastases: a case report. *Hepatogastroenterology* 51(56), 592–594 (2004).

45 Child CG II, Turcotte JG. Surgery and portal hypertension. In: *The Liver and Portal Hypertension.* Child CG III (Ed.). Saunders, PA, USA, 50–58 (1964).

46 Pugh RN, Murray-Lyon IM, Dawson JL *et al.* Transection of the oesophagus for bleeding oesophageal varices. *Br. J. Surg.* 60, 646–649 (1973).

47 Ercolani G, Grazi GL, Callivà R *et al.* The lidocaine (MEGX) test as an index of hepatic function: its clinical usefulness in liver surgery. *Surgery* 127(4), 464–471 (2000).

48 Mullin EJ, Metcalfe MS, Maddern GJ. How much liver resection is too much? *Am. J. Surg.* 190, 87–97 (2005).

49 Cucchetti A, Ercolani G, Vivarelli M *et al.* Impact of Model for End-Stage Liver Disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. *Liver Transpl.* 12, 966–971 (2006).

50 Bruix J, Castells A, Bosch J *et al.* Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. *Gastroenterology* 111(4), 1018–1022 (1996).

51 Ebata T, Nagino M, Kamiya J, Uesaka K, Nagasaka T, Nimura Y. Hepatectomy with portal vein resection for hilar cholangiocarcinoma: audit of 52 consecutive cases. *Ann. Surg.* 238(5), 720–727 (2003).

52 Nagino M, Kamiya J, Arai T, Nishio H, Ebata T, Nimura Y. One hundred consecutive hepatobiliary resections for biliary hilar malignancy: preoperative blood donation, blood loss, transfusion, and outcome. *Surgery* 137(2), 148–155 (2005).

53 Tsao JI, Nimura Y, Kamiya J *et al.* Management of hilar cholangiocarcinoma: comparison of an American and a Japanese experience. *Ann. Surg.* 232(2), 166–174 (2000).

54 Grazi GL, Ercolani G, Pierangeli F *et al.* Improved results of liver resection for hepatocellular carcinoma on cirrhosis give the procedure added value. *Ann. Surg.* 234, 71–78 (2001).

55 Cucchetti A, Ercolani G, Cescon M *et al.* Recovery from liver failure after hepatectomy for hepatocellular carcinoma in cirrhosis: meaning of the model for end-stage liver disease. *J. Am. Coll. Surg.* 203(5), 670–676 (2006).

• Application of the transplant Model for End-stage Liver Disease (MELD) score to conventional liver surgery.

56 Hayashibe A, Sakamoto K, Shinbo M, Makimoto S, Nakamoto T. New method for prevention of bile leakage after hepatic resection. *J. Surg. Oncol.* 94(1), 57–60 (2006).

57 Yamashita Y, Hamatsu T, Rikimaru T *et al.* Bile leakage after hepatic resection. *Ann. Surg.* 233(1), 45–50 (2001).

58 Ijichi M, Takayama T, Toyoda H, Sano K, Kubota K, Makuuchi M. Randomized trial of the usefulness of a bile leakage test during hepatic resection. *Arch. Surg.* 135(12), 1395–1400 (2000).

59 Tanaka S, Hirohashi K, Tanaka H *et al.* Incidence and management of bile leakage after hepatic resection for malignant hepatic tumors. *J. Am. Coll. Surg.* 195(4), 484–489 (2002).

60 Grazi GL, Cescon M, Ravaioli M *et al.* Liver resection for hepatocellular carcinoma in cirrhotics and noncirrhotics. Evaluation of clinicopathologic features and comparison of risk factors for long-term survival and tumour recurrence in a single centre. *Aliment. Pharmacol. Ther.* 17(Suppl. 2), 119–129 (2003).

61 Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br. J. Cancer* 94, 982–999 (2006).

62 Ebara M, Ohto M, Shinagawa T *et al.* Natural history of minute hepatocellular carcinoma smaller than three centimeters complicating cirrhosis. A study in 22 patients. *Gastroenterology* 90(2), 289–298 (1986).

63 Llovet JM, Bustamante J, Castells A *et al.* Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 29(1), 62–67 (1999).

64 Llovet JM, Schwartz M, MazzaferroV. Resection and liver transplantation for hepatocellular carcinoma. *Semin. Liver Dis.* 25(2), 181–200 (2005).

65 Ercolani G, Grazi GL, Ravaioli M *et al.* Liver resection for hepatocellular carcinoma on cirrhosis: a univariate and multivariate analysis of risk factors for intrahepatic recurrence. *Ann. Surg.* 237(4), 536–543 (2003).

66 Belghiti J, Panis Y, Farges O, Benhamou JP, Fekete F. Intrahepatic recurrence after resection of hepatocellular carcinoma complicating cirrhosis. *Ann. Surg.* 214(2), 114–117 (1991).

67 Chen YJ, Yeh SH, Chen JT *et al.* Chromosomal changes and clonality relationship between primary and recurrent hepatocellular carcinoma. *Gastroenterology* 119, 431–440 (2000).

68 Ng IO, Guan XY, Poon RT, Fan ST, Lee JM. Determination of the molecular relationship between multiple tumor nodules in hepatocellular carcinoma differentiates multicentric origin from intrahepatic metastasis. *J. Pathol.* 199(3), 345–353 (2003).

69 Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. *Lancet* 343, 1405–1410 (1994).

70 Ercolani G, Grazi GL, Ravaioli M *et al.* Liver resection for multiple colorectal metastases: parenchymal involvement and total tumor volume, not number or location, significantly affect long term survival. *Arch. Surg.* 137(10), 1187–1192 (2002).

71 Garden OJ, Rees M, Poston GJ *et al.* Guidelines for resection of colorectal cancer liver metastases. *Gut* 55, 1–8 (2006).

•• Current opinion on the surgical treatment of liver metastases.

72 Biasco G, Derenzini E, Grazi GL *et al.* Treatment of hepatic metastases from colorectal cancer: many doubts, some certainties. *Cancer Treat. Rev.* 32(3), 214–228 (2006).

73 Sugawara G, Isogai M, Kaneoka Y, Suzuki M, Yamaguchi A. Repeat hepatectomy for recurrent colorectal metastases. *Surg. Today* 35, 282–289 (2005).

74 Yan TD, Lian KQ, Chang D, Morris DL. Management of intrahepatic recurrence after curative treatment of colorectal liver metastases. *Br. J. Surg.* 93, 854–859 (2006).

75 Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. *Ann. Surg.* 244(2), 254–259 (2006).

76 Grazi GL, Cescon M, Pierangeli F, Ercolani M, Gardini A, Cavallari A. Highly aggressive policy of hepatic resections for neuroendocrine liver metastases. *Hepatogastroenterology* 47(32), 481–486 (2000).

77 Ercolani G, Grazi GL, Ravaioli M *et al.* The role of liver resections for noncolorectal, nonneuroendocrine metastases: experience with 142 observed cases. *Ann. Surg. Oncol.* 12(6), 459–466 (2005).

78 Weitz J, Blumgart LH, Fong Y *et al.* Partial hepatectomy for metastases from noncolorectal, nonneuroendocrine carcinoma. *Ann. Surg.* 241(2), 269–276 (2005).

79 Adam R, Chiche L, Aloia T *et al.* Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1,452 patients and development of a prognostic model. *Ann. Surg.* 244(4), 524–535 (2006).

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