The risk of surgery in patients with cirrhosis

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Abstract

Several reasons result in the finding that patients with cirrhosis need surgery more often than other patients groups. Patients with cirrhosis frequently have comorbidities resulting in gastrointestinal, lung or cervical cancer, among others. Independent of cirrhosis, surgical resection may be the best alternative for a number of those malignancies. Comorbidities may also result in an increased incidence of vascular complications (such as lower extremity atherosclerosis and coronary stenosis) some of them being potential indications for surgery. Patients with alcoholic cirrhosis are more frequently subjected to trauma and bone fractures. Ascites leads to umbilical hernia which can be strangulated or ruptured. Emergency surgery may be needed in this context. Finally, a significant proportion of patients with cirrhosis develop hepatocellular carcinoma (HCC) during the course of the disease. Surgical resection remains a first line option for HCC. While reliable guidelines have been proposed for surgical resection of HCC and liver transplantation, no precise guidelines are available for other aspects of surgical management during cirrhosis. Specific surgical procedures such as hepatectomy and transplantation are concentrated in highly specialised centres, where detailed evaluation is relatively easy to obtain. In contrast, more general surgical procedures, either abdominal or non abdominal, are performed in various centres, making it more difficult to obtain detailed evaluation and draw recommendations. General surveys are still needed to precisely assess the risk of non-specific surgery in patients with cirrhosis, to identify risk factors and to propose reliable guidelines. (Acta gastroenterol. belg., **2008**, 71, **42-46**).

Key words : cirrhosis, surgery, hepatocellular carcinoma, liver failure, intensive care.

1. Surgery and cirrhosis

Several reasons result in the finding that patients with cirrhosis need surgery more often than other patients groups. Patients with cirrhosis frequently have comorbidities resulting in gastrointestinal, lung or cervical cancer, among others. Independent of cirrhosis, surgical resection may be the best alternative for a number of those malignancies. Comorbidities may also result in an increased incidence of vascular complications (such as lower extremity atherosclerosis and coronary stenosis) some of them being potential indications for surgery. Patients with alcoholic cirrhosis are more frequently subjected to trauma and bone fractures. Ascites leads to umbilical hernia which can be strangulated or ruptured. Emergency surgery may be needed in this context. Finally, a significant proportion of patients with cirrhosis develop hepatocellular carcinoma (HCC) during the course of the disease. Surgical resection remains a first line option for HCC.

Unfortunately, cirrhosis by itself represents a significant risk factor for surgical morbidity and mortality. Decreased coagulation factors and platelet count are a source of bleeding. Independent of coagulation factors and platelets, portal hypertension is a source of additional bleeding in case of abdominal surgery. Anaesthesia and, more generally, any sedative agent may induce prolonged encephalopathy. The risk of sepsis is markedly increased in patients with impaired liver function. Patients with compensated cirrhosis are likely to experience decompensation after either abdominal or non-abdominal surgery. Poor nutritional status and muscle waste which are common findings during cirrhosis compromise rehabilitation.

Overall, cirrhosis and associated comorbidities result in relatively frequent indications for either emergency or elective surgery. Surgery is a major risk factor for decompensation of cirrhosis as well as non specific complications. Major surgery is strictly limited to patients with compensated cirrhosis. There is a synergistic interaction between cirrhosis and surgery which may eventually lead to a vicious circle.

2. Mortality and morbidity risks

2.1. *Non-hepatic surgery*

Non-hepatic emergency surgery in cirrhotic patients is associated with the highest risk of mortality and morbidity. Mortality and morbidity rates of 38% and 77%, respectively, have been reported (1). High mortality rates may result from the condition which justifies a surgical procedure, more advanced liver disease in patients undergoing emergency surgery and the impossibility to proceed to optimisation. Non surgical options, when available, should always be preferred to surgical options in this context.

Non-hepatic elective surgery in cirrhotic patients is also associated with high mortality and morbidity rates although drastic selection can be applied. Mortality and

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morbidity rates of 8% and 24%, respectively have been reported (1). Child-Pugh grade B or C cirrhosis and the presence of ascites were shown to be significant risk factors (1). Similarly, abdominal surgery carries significantly higher risks compared to non-abdominal surgery (2). It is important to note that cirrhotic patients undergoing surgery frequently have comorbidities which may have a proper impact on the outcome. Heart failure, chronic pulmonary diseases, diabetes and poor nutritional status are especially frequent in this population (2).

2.2. *Hepatic surgery*

In almost all cases, hepatic surgery in cirrhotic patients consists in hepatectomy for hepatocellular carcinoma. Mortality and morbidity rates after hepatectomy are lower than those reported after non hepatic surgery, at least in part because the patients are highly selected. Only patients with compensated cirrhosis (Child-Pugh grade A) and a relatively small (non central) tumour can undergo surgery.

Mortality rate after resection in patients with cirrhosis and HCC is below 5% in most recent series (3-6) (Table 1). Morbidity is quite variable according to the criteria used for defining postoperative complications. With the advent of transjugular intrahepatic portosystemic shunt (TIPS) in parallel with other improvements in the management of portal hypertension, there are virtually no longer indications for surgical portosystemic shunts in cirrhosis.

3. Assessment of the risk of surgery

Child score was the first score to be used for assessing the prognosis of patients with cirrhosis undergoing surgery (more than 30 years ago). It was originally designed for predicting outcome after surgery of portal hypertension (7). Although it has been empirically designed, Child score proved to be a robust marker of mortality in patients undergoing surgery. Independent of any other factor, the higher Child score is, the higher mortality risk. Child score defines 3 grades of increasing severity (i.e., grades A, B and C) (8). Basically, only patients with Child's grade A cirrhosis can undergo major surgery, either hepatic or non hepatic, with an acceptable chance of success (9,10).

In recent years, MELD score emerged as an attractive alternative to Child score for the assessment of the prognosis of patients with cirrhosis (11). MELD score has several advantages over Child score. In particular, MELD score relies on three objective and readily available variables (i.e., creatinine, bilirubin and INR) while some of the variables of Child score (encephalopathy and ascites) may be influenced by subjective interpretation. While Child score was originally designed for assessing the prognosis of cirrhotic patients undergoing surgery, MELD score was designed for assessing the prognosis of patients undergoing TIPS. Besides TIPS, MELD score proved to be a robust marker of waiting list mortality in candidates for transplantation. Recently, MELD score was also shown to be a good marker of mortality risk in patients with cirrhosis undergoing non hepatic abdominal surgery (2,12). The higher MELD score is, the higher the risk of mortality after surgery. The probability of death within 30 days after surgery exceeds 50% when MELD score is over 20-25 (2,12). A large study has shown that MELD score, age and American Society of Anesthesiologists (ASA) class were independent predictors of mortality (12).

MELD score may be useful for selecting patients for non transplant surgery. It has been suggested that MELD score is a predictor of mortality, independent of emergency surgery compared to elective surgery (12) (Table 2). However, apart from resection of HCC, no clear limit has been identified for a given procedure. Additionally, what represents an acceptable risk for a given procedure needs to be clarified.

4. The particular issue of resection for HCC

4.1. *Patients selection*

As indicated above, only patients with compensated cirrhosis (Child-Pugh class A) and small tumours (below 5 cm) can safely undergo surgical resection. Additional criteria taking into account markers of portal hypertension (no oesophageal varices and hepatic venous pressure gradient below 10 mmHg) have been proposed since mortality and morbidity increases in patients with severe portal hypertension (9). There is no universal consensus on the usefulness of markers of portal hypertension. In addition, measurement of portal pressure gradient needs hepatic vein catheterisation which is not readily available in all centres.

MELD score was also shown to be reliable for assessing the risk of resection in patients with cirrhosis. In patients with cirrhosis and HCC, resection is safe when

Table 1. — **Mortality and morbidity following resection of hepatocellular carcinoma in patients with cirrhosis**

Author	Year	Patients	Child's Grade A	Mortality	Morbidity
Llovet, J.M. (3)	1999	74	100%	4%	–
Fong, Y. (6)	1999	154	91%	4.5%	45%
Grazi, G. (5)	2001	264	79%	5%	–
Régimbeau, J.M. (4)	2002	64	100%	6.5%	50%

MELD score is below 8 (13). Mortality increases over this cut-off value. Independent of MELD score, the small size of the tumour remains an absolute prerequisite.

More specific markers of liver function have been tested in order to refine the selection process. Indocyanine green clearance has been used preoperatively. It has been suggested that indocyanine green retention less than 14% at 15 minutes is a limit for major hepatectomy (more than 3 segments) (14). No more general recommendations have been proposed. Non invasive devices relying on transcutaneous pulse densitometry have been developed for measuring indocyanine green clearance after a single injection in a peripheral vein. This attractive technique has not been clearly validated yet. Finally, most patients with HCV-infection have persistent active hepatitis until the stage of cirrhosis. It has been shown that serum ALT over 3 time normal, which is an indirect marker of activity, is associated with an increased risk (15). In this particular population, only patients with serum ALT below 3 times normal should undergo major resection.

4.2. *Optimisation for resection*

Several measures can be applied pre-operatively in order to reduce morbidity and mortality after resection. Pre-operative right or left portal vein branch embolisation can be performed in order to induce an atrophy of the part of the liver which has to be resected (the part which includes the tumour) and, in parallel to induce hypertrophy of the part of the liver which will not be resected. Pre operative embolisation reduces the risk of postoperative liver insufficiency. It must be noted that regeneration capacities are markedly reduced in cirrhotic patients. Therefore, the level of hypertrophy in cirrhotic patients does not reach the level obtained in non cirrhotic patients. However, it has been shown that preoperative portal vein embolisation may reduce postoperative morbidity (16).

Poor nutritional status is frequent in patients with cirrhosis. It may have deleterious consequences on postoperative morbidity and rehabilitation. It has been shown that transient intravenous nutritional support during the week preceding hepatectomy significantly reduces morbidity. In particular, nutritional support significantly reduces the incidence of sepsis (17).

5. Recommendations for the selection and management of cirrhotic patients undergoing surgery

Any patient with cirrhosis carries increased mortality and morbidity risk in case of surgery. Besides post-operative death, the risk is that patients with compensated cirrhosis develop decompensation immediately after surgery with prolonged complications.

Except for hepatectomy and liver transplantation, no general criteria exist for patient selection. However, the decision for surgery should take into account the "hepatic reserve", the existence of non-surgical alternatives, the emergency context.

Only patients with compensated cirrhosis can stand-up major surgery, either abdominal or non-abdominal. As discussed above, only patients with Child's Grade A cirrhosis are suitable candidates for resection. It has been proposed that a MELD score of 8 (which is very low) also represents an acceptable limit for resection, limit over which the risk increases sharply. Occasionally, some patients with more advanced cirrhosis (Child's grade B or C) develop life threatening complications which can only be cured by surgery. In this context, surgery can be viewed as a "last chance" option even if mortality is especially high.

Decreased coagulation factors and decreased platelet count represent a source of bleeding. Both can be corrected by preoperative transfusion of platelets or fresh frozen plasma. In patients with abdominal surgery, portal hypertension leading to a number of collateral vessels also represents a source of bleeding. Careful surgical hemostasis must be done. Occasionally, additional procedures aimed at reducing portal pressure (transient porto-caval anastomosis for example) can be useful.

The risk of bacterial infection is especially high after any surgery, due to altered defences. The most frequent sites of infection are the lungs, ascites, urine and catheters. Bacteremia are also frequent. Gram negative bacteria originating from the digestive flora are predominant. Considering the especially high incidence of bacterial infections and the high incidence of severe sepsis, primary prophylaxis using empirical antibiotics has been proposed in the context of emergency surgery. This approach has been adopted in patients with variceal bleeding since it was shown to reduce mortality (18). However, primary prophylaxis with antibiotics has not been validated in the context of emergency surgery in cirrhotic patients.

Anaesthesia and sedation should be preferentially performed using agents with a rapid elimination. Benzodiazepines are metabolised by the liver. Patients with some degree of liver insufficiency have delayed elimination of benzodiazepines and prolonged sedation even after the drug has been discontinued. Weaning from sedative agents after surgery should be decided at an early stage.

As discussed above, ascites is frequent after major surgery, especially after abdominal surgery. Ascites can be a source of fluid loss and hypovolaemia. It can also be a cause of delayed abdominal wound healing. Aggressive treatment of ascites and oedema with diuretics is not recommended since the risk of pre-renal failure related to hypovolaemia is superior to the proper risk of ascites. Similarly, fluid restriction should be prohibited. Active fluid resuscitation should be performed instead, to maintain adequate renal perfusion until ascites resumes spontaneously (which can need several days or weeks). There is no consensus on the fluid to be

used. There is no evidence that albumin is superior to synthetic colloids or cristalloids in the general setting of intensive care. However, in the particular setting of cirrhosis and low serum albumin, albumin proved to be slightly superior for improving outcome, especially in patients with spontaneous bacterial peritonitis (19-21). Terlipressin was shown to have a beneficial effect on hepatorenal syndrome in cirrhotic patients (22-23). Whether terlipressin is safe and effective in patients developing large volume ascites and renal failure needs to be clarified.

Paracetamol (acetamionophen) and non-steroidal anti inflammatory drugs (NSAIDs) are frequently used after surgery as pain relief agents. Supra-therapeutic doses of paracetamol (over 4 g per day) should obviously be avoided. In addition, therapeutic doses repeated every day for several consecutive days should also be avoided since cumulated doses can result in significant liver cell damage in this context (24). The use of NSAIDs is not recommended because of the risks of deterioration of renal function and upper digestive tract bleeding.

As indicated above, some studies suggest that perioperative nutritional support may reduce post operative morbidity after hepatectomy (17). The benefit seems to be independent of changes in objective markers of nutritional status. Indeed, these markers are unlikely to be significantly affected by a short course of nutritional support. No precise guidelines have been proposed in patients with cirrhosis.

A number of studies concerning cholecystectomy in cirrhotic patients have been published (25-28). These studies show that laparoscopic cholecystectomy is feasible in this population and that it should be preferred to open cholecystectomy. However, it must be noted that symptomatic gallstone disease is very rare in cirrhotic patients. Indications for cholecystectomy are uncommon during the course of cirrhosis ; the justification for this procedure is frequently questionable.

6. Liver failure after major hepatic resection

6.1. *Manifestations and predisposing factors*

Occasionally, liver failure may occur in the early post operative course after major hepatic resection. In this context, liver failure is manifested by the persistence of low coagulation factors (prothrombin index below 50% of normal and INR over 1.7), increased serum transaminases, a rise in serum bilirubin, delayed recovery from general anesthesia and/or persistent encephalopathy. In addition, patients with cirrhosis frequently have large volume of ascites (over 2 L per day). If liver function does not rapidly improve, extra hepatic organ dysfunction including renal insufficiency, hypotension related to vasoplegia (and poorly responsive to fluid resuscitation) and respiratory dysfunction occur. At this stage, sepsis (pulmonary infection in particular) is especially frequent. Metabolic acidosis and high lactate level are also a common finding.

Post-operative liver failure is basically due to the inability of the liver to undergo sufficient regeneration. The risk of post-operative liver failure is directly related to the extent of parenchymal resection. It is also related to the existence of underlying chronic liver lesions or other concomitant factors which may impair regeneration.

In patients with normal liver parenchyma, a remnant liver volume corresponding to 30% of the whole liver volume is sufficient to provide rapid regeneration. This threshold can be higher in patients with underlying liver lesions such as massive steatosis, steatohepatitis, vascular lesions secondary to chemotherapy and fibrosis. The risk is even higher in patients with cirrhosis since they have very limited regeneration capacities. Besides the extent of resection, massive blood loss, prolonged hypotension, prolonged clamping of the portal triad and sepsis represent additional risk factors for post operative liver failure.

In patients who develop multi organ failure, the prognosis is especially poor. In this indication, albumin dialysis showed to be poorly effective (29).

6.2. *"Rescue" transplantation*

Emergency transplantation can be an option in patients with liver failure following major hepatectomy. However, there are a number of contraindications related to the original disease. Indeed, transplantation is contraindicated in patients who had resection for large HCC (over Milan (30) or UCSF criteria (31)), cholangiocarcinoma (except in highly selected patients), metastases of colorectal cancer and other malignancies (except rare tumours with a slow progression). In these patients, the risk of recurrence of malignancy after transplantation would be too high (even if the original tumor has been resected).

In the minority of patients who do not have contraindication, a difficult issue is the criteria for making on a decision of transplantation and the optimal timing. It can be anticipated that decision criteria for transplantation in patients with acute liver failure due to acetaminophen overdose or other causes of acute liver disease are not applicable in this context because, in contrast to patients with acute liver disease, patients who had liver resection have a more limited potential for regeneration. It has been shown recently that the coexistence of serum bilirubin over 50 µmol/L and prothrombin index below 50% of normal (INR over 1.7) on post operative day 5 after hepatectomy is predictive of a mortality rate exceeding 50% (32). Even if these criteria do not represent a clear limit for making on a decision for transplantation, they should lead strongly consider this option.

7. Conclusions and perspectives

The interactions between surgery and cirrhosis frequently result in a vicious circle. Patients with cirrhosis

Table 2. — **30-day mortality rates for non-transplant and non-liver surgery in patients with cirrhosis according to MELD score**

Author	Year	Patients	Digestive surgery (%)	30-day mortality per MELD					
				10	15	20	25	30	35
Northup P.G. (2)	2005	142	48%	7%	11%	17%	26%	36%	50%
Teh S.H. (12)	2007	772	76%	10%	25%	44%	53%	90%	–

are more likely to need surgery. By turn, surgery is more likely to result in significant morbidity and mortality. While reliable guidelines have been proposed for surgical resection of HCC and liver transplantation, no precise guidelines are available for other aspects of surgical management during cirrhosis. Specific surgical procedures such as hepatectomy and transplantation are concentrated in highly specialised centres, where detailed evaluation is relatively easy to obtain. In contrast, more general surgical procedures, either abdominal or non abdominal, are performed in various centres, making it more difficult to obtain detailed evaluation and draw recommendations. General surveys are still needed to precisely assess the risk of non-specific surgery in patients with cirrhosis, to identify risk factors and to propose reliable guidelines.

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