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RISK FACTORS FOR BILE LEAKAGE AFTER LIVER RESECTION FOR NEOPLASTIC DISEASE

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INDEX

Abstract

Background

In recent years, hepatobiliary surgery has undergone an important evolution thanks to technological innovations and advances in surgical techniques.

Despite this, biliary leakage (BL) remains the most frequent and feared complication after liver resection (4-17%)

BL can compromise the results of the surgery and can represent a risk to the patient's life.

The study was aimed to detect the possible risk factors for BL occurrence in a set of clinical and surgical variables.

Placement of the abdominal drainage at the end of hepatoresective surgery remains controversial due to the related risks and potential benefits in case of BL. Therefore, in the literature, there is an unanimous consensus in discouraging the routine use of drainage after surgery, but to reserve its placement only for patients that have risk factors for biliary fistula.

Materials and Methods

We enrolled in this observation study all patients undergoing liver resection for neoplastic disease in Ismett from June 2016 to March 2021.

BL was diagnosed, according to the ISGLS definition, when the level of bilirubin in the drainage fluid exceeded three times the blood level.

We have examined: anthropometric characteristics of the patients (sex, age, BM, smoking), type of neoplasia (Hepatocellular Carcinoma (HCC), Biliary Cancer, Colorectal Liver Metastasis(CRLM) , noncolorectal Liver Metastasis), presence of cirrhosis, neoadjuvant chemotherapy, type of intervention (laparotomic or laparoscopic, segments involved in the resection, devices used for parenchyma transection, intraoperative blood loss, duration of surgery and use of amines during surgery).

A preliminary univariate analysis was performed by investigating variables distributions, both on the full sample and conditioned to the presence of the fistula, and performing univariate logistic regressions, in order to assess the association between the outcome (fistula occurrence) and possible predictors. Then, a multivariable logistic model was used to detect the most important predictors of biliary fistula considering significant predictors with $p\text{-value}<0.05$.

Results

379 patients were enrolled in the study. 16 patients developed BL, (4,2 % of cases): 50% grade A fistula, 38% grade B fistula and 12% grade C fistula. Main risk factors for BL are the involvement of segments 4, 5 and 8 (central liver resection), (OR: 18.9 % C.I. 1.1 – 313, p= 0.040); the involvement of segments 6 and 7(right side) (OR: 4,1 95% C.I. 1.0 – 16.8, p=0.050) and the administration of amines (OR: 4.5, 95%C.I.: 1.0-20.1, p= 0.047), both being associated to a probability of BL about four times higher. Two other significant risk factors are BMI (OR: 1.26 , 95%C.I.: 1.07 - 1.49, p=0.005) and blood loss (OR: 1.08 , 95%C.I.: 1.03 - 1.12 p <0.001),. On univariate analysis, there is a strong association between biliary fistula and bilio-digestive anastomosis (OR: 9.75, C.I. 2.7 - 34.7, p <0.001). On the contrary, neoadjuvant chemotherapy before surgery can be considered as a protective factor OR: 0.09, C.I 0.01, - 0.88, p= 0.039

Conclusion

Resections involving the central segments (S4-5-8), resection of right lateral side segment (S6-7), bilio-digestive anastomosis, intraoperative use of the amine, BMI and blood loss are risk factors for the development of BL.

Identifying this risk factors can help in the choice of positioning the drainage at the end of the liver resection.

Summary.

Knowing the risk factors of an event is always important to predict its occurrence, prevent it, if possible, and facilitate its resolution.
This was the goal of the work, an observational study carried out on patients who underwent hepatoresective surgery for primary or secondary malignant liver diseases at ISMETT (Mediterranean Institute for Transplantation and High Specialization Therapies) in Palermo, aimed at identify the factors predicting the development of BL.

BL remains a complication feared by the hepatobiliary surgeon, because it can compromise the operation's success, worsen the patient's outcome and quality of life.

Fortunately, there are few cases in which treatment is required to resolve the fistula. In most cases, resolution is spontaneous.

From the beginning of the hepatic surgical experience, at least one abdominal drain was routinely placed at the end of the operation with the dual purpose of early diagnosing biliary fistula and facilitating its spontaneous resolution avoiding the formation of abdominal collections that can easily become infected or create damage.

For some years now in the literature, in the face of complications related to the drainage itself, there is unanimous agreement to place the drainage only in patients who have a high risk of developing a biliary fistula.

Identifying risk factors can certainly help in the correct selection of patients.

CHAPTER 1

Background

1.1 Introduction

Over the past twenty-five years, hepatic resection has evolved from a high-risk, resource-intensive procedure with limited application to a safe and commonly performed operation, with broad indications. In recent years, thanks to scientific studies and experience in the field, it has been possible to note a significant improvement in the perioperative outcome; such as reducing mortality, blood loss, transfusion rates and hospital stays. (1) These improved perioperative results are largely responsible for the emergence of hepatic resection as a viable and effective treatment option for selected patients with hepatobiliary malignancy. During this period there have indeed been considerable advances in "imaging technology" and greater awareness of the clinical and tumor-related variables that determine the outcome, allowing for a better preoperative assessment of the extent of the disease and a better selection of patients. Improvements in other areas, such as minimally invasive and ablative techniques, also favored treatment options and were considered important in treating patients with malignant hepatobiliary disease. However, resection remains the most effective therapy. (2)

Despite the advances, the appearance of Biliary Leakage (BL) remains the most frequent complication of this type of surgery.

In this study, we will examine the risk factors related to the development of BL in patients undergoing liver resection for malignant liver disease. Knowledge of risk factors gives us the possibility to identify patients with high risk and select a treatment for them to reduce the incidence of fistula or improve its outcome.

Before addressing the problem, it is appropriate to clarify the terms of the question. In particular, we will examine the main malignant pathologies of the liver, the indications for their treatment, the types of liver resection with its problems and its complications.

1.2 Malignant pathologies of the liver

Liver resection is indicated for the treatment of

- **primary malignant liver tumors** (hepatocellular carcinoma, cholangiocarcinoma and biliary cystadenocarcinoma),

- **Secondary liver tumors**: colorectal neoplasia metastases (CRLM), neuroendocrine tumor metastases, and non-colorectal, and non-neuroendocrine (NCNN) tumor metastases

➢ Hepatocellular carcinoma (HCC)

HCC is the most common type of primary liver cancer in adults and is the third major cause of cancer death, with a five-year survival of 18%.
It is generally diagnosed between 50 and 70 years of age, is predominant in Asian and African countries, and is not very common in Northern Europe and North America. (3)
As is known, more than 80% of cases of hepatocellular carcinoma arise on cirrhotic livers.
Furthermore, patients with chronic liver disease who undergo any form of therapy for HCC are at high risk for recurrent disease and progression to liver failure. (4)
One of the most important moments in the onset of an HCC is the possibility to achieve a correct staging of the cancer to choose the best therapeutic option. Currently, the most common staging system for HCC is the Barcelona Clinic Liver Cancer (BCLC) system, which determines cancer stage and patient's prognosis based on tumor burden, the diseases severity, and patient's performance status. (fig. 1) (5-6)
Disease severity is assessed by the classification of Child-Pugh. (fig 2)
There are several therapeutic options for the treatment of localized HCC, but the only potentially curative treatment options are resection and liver transplantation.(7)
Liver transplantation is the best treatment because it effectively treats both the cirrhosis andoncological pathology.
However, this therapeutic option is limited by specific contraindications (age, comorbidities) and by the low number of donors. Transplantation must therefore be based on the concept of "fairness" between the different categories of patients and cannot ignore the calculation of the survival "benefit" compared to the expected results with other possible anticancer treatments. (8-9-10- 13)
Hepatic resection, therefore represents the best therapeutic alternative for patients with HCC. Obviously, the surgical indication must necessarily take into account both the stage of the tumor and the stage of liver disease.
The indication for HCC resection is based on two main issues:
● the lesion must be confined to the liver (11)
● the size and position of the tumor must allow for resection that respects residual liver function.(12)
The goal of liver surgery is to achieve an R0 radical resection. This attempt must always take into account the amount of residual liver (FLR) which must necessarily be adequate.

➢ Cholangiocarcinomas

Cholangiocarcinomas account for about 3% of all gastrointestinal neoplasms; derived from the epithelial cells of the intrahepatic and extrahepatic bile ducts. (14)
Biliary tract tumors are traditionally classified in relation to their primary anatomical site into intrahepatic tumors (10% of cases), gallbladder tumors, tumors of the hepatic hilus (50% of cases), tumors of the distal choledocus (40% of cases). (15)
Cancers arising in the perihilar region are referred to as Klatskin tumors and have been further classified according to their patterns of involvement of the hepatic ducts (the Bismuth-Corlette classification). (Fig 3)
Surgery is the only cure for cholangiocarcinoma if the resectability criteria are present. (Fig.4)
Patients generally have a poor prognosis (five-year survival 5-10%). (16)
Distal cholangiocinomas have a higher resectability (91%), while proximal tumors (both intrahepatic and peri-hilar) are resectable in 60% and 56% of cases, respectively.
Even in the operated cases, it is not easy to obtain tumor-free margins (20-40% of cases in the next tumors and 50% of cases in the distal tumors). These percentages are even lower if we consider R0 a tumor-free margin of only 5 mm. (17)
Surgical exploration for resection is appropriate; radiological studies cannot perform resection, especially in cases of perihilar tumors. (18)
The type of liver resection indicated takes into account the localization of the tumor and the relationships with the anatomical and vascular structures. (Fig 5)

➢ Gallbladder cancer (GBC)

Gallbladder cancer (GBC) is an uncommon but highly fatal malignancy;
The poor prognosis associated with GBC is thought to be related to the advanced stage at diagnosis, which is due both to the anatomic position of the gallbladder, and the vagueness and non-specificity of symptoms.
Patients with GBC may also present with obstructive jaundice, either from direct invasion of the biliary tree or from metastatic disease to the region of the hepatoduodenal ligament. (1)
The type of surgery is closely related to the stage of the disease (Fig.6)

➢ Colorectal Liver Metastases (CRLM)

Half of colorectal cancer patients will develop liver metastases. Liver resection is the only cure for these patients (survival after resection: 60%. Perioperative mortality: 20 percent) (19)
The improvement in results and prognosis can be attributed to an increasingly frequent use of neoadjuvant chemotherapy, the result of a better knowledge of tumor biology.
Neoadjuvant chemotherapy made it possible to select patients for surgery (tumors that progress during chemotherapy are biologically aggressive tumors that would not benefit from resection) and in some cases, to reduce the size of the lesions enough to make them

resectable. (RECIST criteria) (Fig. 7) (20)
However, liver damage caused by chemotherapy on the liver parenchyma can cause impairment of its function. This must be taken into consideration during the operative planning. In general, a future residual liver volume> 30% is required for patients undergoing chemotherapy.
Liver metastases can be defined as synchronous or metachronous.
Synchronous if they occur at the same time as primary colorectal cancer (CRC) or shortly thereafter (synchronous metastases may appear within 3, 6, or 12 months of the primary cancer). metachronous metastases, on the other hand, have a more delayed presentation, often after the primary tumor has been treated (21)
In the case of patients with colon cancer and synchronous metastases, treatment involves a multidisciplinary approach. Resection of the primary tumor, metastases, and possible chemotherapy depend mainly on the acuity of the symptoms and the burden of the disease.
If the primary tumor is asymptomatic, in a favorable location (e.g. right colon), and liver metastases are limited, simultaneous resection will be done.
When simultaneous resection is performed, liver resection is performed first. If the liver resection is more extensive than expected, or there is more blood loss than expected, and/or the patient does not tolerate the procedure, the colorectal resection should be postponed.
If the extent of the lesions does not allow a simultaneous approach, a resection will be performed in stages: first the colorectal resection and then the liver resection (classic approach) or first the liver resection and then the colon resection (reverse approach). (Fig 8) (22)

- **NET Liver metastases**

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that are thought to arise from neuroendocrine cells and their precursors located throughout the body. These tumors are characterized by variable but most often indolent biologic behavior. They are also classically characterized by their ability to secrete peptides resulting in distinctive hormonal syndromes. (23)
The majority of patients with advanced gastroenteropancreatic NETs have liver metastases.
Surgery is indicated for patients with resectable liver metastases (absence of extrahepatic metastases, absence of bilobar liver involvement, good functional liver reserve). In cases where metastases are not radically resectable, debulking is controversial and not universally accepted. On the other hand, if liver lesions cannot be resected, it is possible to resort to locoregional treatments or liver transplantation in selected patients. (24)

- **Non Colorectal- Non NET Liver metastases (NCNN)**

Unlike what has been established for colorectal and neuroendocrine tumor metastases, the role of metastasectomy for liver metastases from NCNN tumors is debated. Until recently, patients with metastatic metastases were not considered curable and life expectancy was limited. Although reports to date do not suggest any survival benefit in resection of liver metastases from some cancers (esophagus, stomach, or pancreas) for other cancers, the situation is different.

Survival improvements have been demonstrated for resection of liver metastases from renal cell carcinoma (median survival 26 months for resection vs. six months for conservative treatment only) from breast cancer (survival rates are respectively 53.9% and 24.6%), genitourinary tumors (50.4% and 37.8%) and leiomyosarcoma (63.% and 36%). (1)

The resectability criteria are: (i) absence of extrahepatic disease at the time of detection, (ii) functional liver status and residual liver volume after hepatectomy, (iii) ability to achieve a margin of tumor clearance, and (iv) suitability for resection hepatic.

1.3 Liver resection

Resection is the first-choice treatment in selected patients with primary or metastatic liver cancer.

The type of hepatic resection chosen depends upon the location of the lesion(s), the ability to provide an adequate future liver remnant, and, for malignant disease, a tumor-negative margin.

Hepatic resections are divided into "major" (removal of 3 or more liver segments) and "minor" (removal of less than 3 segments) and "anatomical" and "non-anatomical" (depending on whether they are performed based on the criteria of functional anatomical subdivision of the liver. (Fig 9)

Hepatic resection can be done with a laparotomic, laparoscopic or robotic approach.

Intraoperative ultrasound helped to develop liver surgery.

It confirms the presence of the lesions highlighted on preoperative imaging, highlights the relationship between the tumor and the vascular structures and helps in defining the resection plan. (Fig. 10) (25)

Major liver resections can be performed following the three fundamental techniques proposed by Lortat – Jacob ("hepatectomy with preliminary vascular section"), Ton That Tung ("hepatectomy with immediate parenchymal section”) and Bismuth (“combined technique” involves: isolation and clamping of the Glissonian peduncle , transection of the hepatic parenchyma, the section of the glissonian peduncle and , at the end, the section of the supra-hepatic vein) (Fig 11) (26-27)

The use of clapping of the hepatic peduncle is not systematic, but it is used only if necessary to reduce bleeding during liver transection. (28)

It can be continuous or intermittent: the continuous interruption of blood flow in a healthy liver can be safely prolonged up to 60 minutes, exceeding this limit cytolysis enzymes can increase significantly.

To reduce clamping-related damage, especially in a cirrhotic liver, intermittent clamping of the hepatic peduncle is indicated, alternating 15 – 20 minutes of clamping to 5 minutes of declamping

1.4 Future Liver Remnant (FLR)

A fundamental principle of liver surgery is to maintain adequate liver function at the end of the operation.

Liver function after surgery basically depends on the amount of residual liver (Future Liver Remnants FLR) and on the quality of the liver parenchyma. Most patients undergoing liver resection for malignancy have impaired liver function due to the presence of concomitant chronic liver disease (especially patients with HCC) or recent use of chemotherapy (especially in cases of liver metastases). Preoperative hepatic functional reserve therefore becomes essential to reduce the risk of postoperative hepatic insufficiency. In patients with chronic liver disease, Child-Pugh score, portal hypertension and thrombocytopenia should be considered. (29)

In cases of doubtful functional liver reserve (cirrhotic - radiological evidence of hepatic steatosis - recent chemotherapy ...) it is possible to perform a biopsy of the non-tumor parenchyma. The histological examination allows to have an estimate of steatosis, fibrosis or liver damage associated with chemotherapy, but does not reflect the function and regenerative capacity of the liver.

In order to better evaluate the hepatocellular function it is possible to use the indocyanine green test by evaluating the clearance 15 minutes after intravenous administration.

FLR volume assessment is currently the most reliable approach for predicting outcomes for patients who are candidates for major hepatic resection.

FLR is considered insufficient if it is less than 20% of the total liver (TLV) in patients with healthy liver

FLR is considered adequate if greater than 30% of the TLV for patients with chronic liver injury (e.g. patient undergoing chemotherapy for more than 3 months) and FLR should be at least 40% of the TLV for patients with fibrosis or cirrhosis.

If FLR is insufficient, it is necessary to promote hypertrophy before surgery by embolization of the right branch of the portal vein, (PVE, Fig. 13) or in selected cases by means of two-stage hepatic resection (ALPPs, Fig 15) (30)

1.5 Mininvasive resection- Parenchymal sparing

To reduce the incidence of PHLF, (post hepatectomy liver failure), responsible for 60% of deaths after extended hepatectomy, it is necessary to accurately evaluate the surgical indication and the extent of resection by finding an adequate compromise between oncological radicality and the need to preserve a sufficient amount of parenchyma. (31)

While the BCLC prognostic system, approved by the European and American Association for the Study of the Liver (EASL) and (AASLD), recommends liver resection only for patients at the first stage (Child-Pugh A, without portal hypertension or major vascular invasion), many centers tend to extend the surgical indication also to patients with cirrhosis stage II Sec BCLC as these patients have better survival outcomes than those treated with locoregional therapies (32)

In this effort of the surgical community to extend the limits of liver resection, 2 concepts become relevant: non-invasive surgery and the concept of parenchymal sparing.
A laparoscopic or robotic approach is an alternative to open surgery (33)
A recent meta-analysis compared open liver resection and laparoscopic of "difficult" liver lesions in terms of intraoperative, postoperative outcomes, and oncological radicality showing no significant differences. (34)
In particular, in expert hands, LLRs are associated with a shorter operative time, a significantly lower blood loss, a shorter hospital stay, lower general morbidity and a comparable oncological radicality.
The magnified vision allows better identification of intraparenchymal vascular structures compared to open surgery, pneumoperitoneum pressure reduces venous blood loss (more frequent) and left lateral decubitus (preferred position for this type of resection) places the right hepatic vein in a higher position than the inferior vena cava, reducing bleeding.
The advantages of laparoscopic resection are fewer postoperative complications, a reduced incidence of postoperative ascites, especially for cirrhotic patients, as manipulation is reduced, and early mobilization of the patient due to small skin incisions.
Surgical resection is the only curative option for HCC, with a 5-year survival rate of between 31.8 and 59.0%
However, recurrences after surgery are high (approximately 50% at 2 years) and are associated with a poor prognosis. (34)
Since intrahepatic diffusion occurs mainly through the portal system, anatomical resection over non-anatomical resection is always preferred especially for large lesions (> 5 cm).
In cases where anatomical resection is not possible, the negative resection margin is therefore the fundamental objective. The standard resection margin is> 10 mm if anatomically feasible. Otherwise the resection should still be performed if a minimum margin of> 1 mm can be achieved. (35)
Several studies have in fact shown that overall and disease-free survival is not influenced by the extent of resection, but much more by the characteristics of the tumor (vascular microinvasion, presence of satellites) and by liver function (BCLC stage B) (36-37)

1.6 Prevention and Control of Bleeding

During liver resection, intraoperative blood loss (IBL) is a reported predictor of morbidity, mortality, and recurrence after hepatectomy for liver cancer. Intraoperative bleeding is a relevant issue in minimally invasive surgery cases as it determines the greatest number of laparotomic conversions (8% of cases). (38) Massive IBL is related to the difficulty of resection. (fig.14)
Numerous strategies have been proposed to minimize blood loss during liver transection. The Pringle maneuver is an established technique for reducing IBL by occluding the inflow, maintaining low central venous pressure, increasing the possible pressure limits of new pneumothorax and parenchymal transection devices: ultrasonic aspirators (CUSA) staplers, saline-linked cautery (TissueLink), bipolar electrocoagulation devices, harmonic scalpels, radiofrequency transection devices and microwave coagulators. (39)

1.7 Complications after liver resection

Complications after liver resection are prevalent. Their incidence is proportional to the extent of resection and the degree of liver disease.

Significant complications occur in approximately 10-20% of patients and include pulmonary complications, ascites, thrombosis, liver failure, bleeding, biliary leakage (which we will cover separately)

- **Pulmonary complications** - One of the reasons for pulmonary complications is the altered respiratory physiology due to the extension of the incision and the retraction required for surgical exposure. Independent risk factors are: prolonged surgery, right hepatectomy, neoadjuvant chemotherapy, intraoperative blood, transfusion, diabetes, and atrial fibrillation.
- **Ascites -** Ascitic decompensation is common in the postoperative period of patients with liver disease.

If a large amount of ascites is produced, it must be ensured that it is not a consequence of portal thrombosis.

- **Thrombotic complications** - Thrombosis of the portal vein and hepatic artery is considered a rare but serious complication of liver resection.

In case of portal or arterial thrombosis, liver function indices will be elevated the patient will complain of abdominal pain

Right hepatectomy is a risk factor for the development of portal thrombosis (9.1% of cases)

- **Liver failure** - Liver failure is the most severe complication after liver resection (PHLF).

PHLF is the impairment of the liver's ability to maintain its synthetic, excretory, and detoxifying functions. It is characterized by an increase in INR and bilirubin by or after the fifth postoperative day. PHLF-related mortality can reach 70 %.

The main risk factors for PHLF are underlying functional liver disease and insufficient residual liver volume. A determining role is also played by portal hypertension.

- **Bleeding** - Another relevant complication is postoperative intraperitoneal bleeding and it usually occur within 48 hours of surgery

The incidence of intraperitoneal hemorrhage ranges from 4.2% to 10%. The most common reasons for postoperative bleeding are:

(1) bleeding from the sectional surfaces, a consequence of venous congestion or the interruption of an arterial vessel.

(2) Inadequate intraoperative hemostasis

(3) loose or fallen vascular sutures, an event that is usually attributed to an increase in pressure in the vena cava.

1.8 Biliary Leakage

Post-hepatectomy biliary loss occurs in 4-17% of patients undergoing hepatectomy (PHBL) and remains a major complication after liver resection. The onset of a biliary fistula is associated with the need to perform other invasive procedures, with an increase in mortality, morbidity, and hospitalization times. The improvement of instruments and techniques over the years has not led to a reduction in biliary fistulas, which are increasing, according to recent studies. This is due to increasingly complex surgical procedures. (39)

In addition to being related to infectious problems, the fistula inhibits the regenerative capacity of the liver thus influencing the prognosis of patients.

The International Study Group of Liver Surgery (ISGLS) tried to give a unanimous definition and a severity grading to biliary fistula. The definition is based on the documentation in the drain of secretions with a bilirubin rate more than three times higher than the determined plasma one at the same time. There are three degrees of severity:

- **Grade A**: Bile loss requiring no or small changes in the clinical management of patients
- **Grade B**: Bile loss that requires a change in the patient's clinical management (eg, additional diagnostic or interventional procedures) but manageable without relaparotomy, or a Grade A bile loss lasting> 1 week
- **Grade C**: loss of bile requiring invasive intervention. (40)

In other words, when the fistula is low-flow it generally resolves spontaneously or with minimally invasive procedures for radiological or endoscopic detention of the biliary tract. Only in case of failure of the minimally invasive approach a new invasive surgery con be required. The presence of bile in the peritoneal cavity, for its intrinsic quality, very irritating to the tissues, represents a real threat to the patient and constitutes a possible source of severe complications, from sepsis to lesions due to erosion of anatomical structures. Therefore, prompt percutaneous drainage should be performed in the case of evidence of intra-abdominal collections.

The controversial role of post surgical abdominal drainage remains fundamental by the same principle,. It has now been widely demonstrated that in patients at low risk of developing fistulas the presence of abdominal drainage appears futile and often associated with the development of complications (infections, the onset of biliary fistulas that self-maintain due to the reduction of pressure given by the suction of the drainage itself. …) (41)

In reverse, in patients at high risk of developing biliary fistulas, positioning of the surgical drainage after hepatoresective surgery is essential to prevent severe complications. In this perspective, it is essential to know the risk factors related to the onset of biliary fistulas

CHAPTER 2

Materials and Methods

2.1 Patient selection

The study enrolled all patients who had undergone hepatoresective surgery for malignant liver lesions in ISMETT from June 2016 to March 2021.
Patients undergoing liver resection for liver donation, for benign lesions, and patients undergoing laparotomic or laparoscopic thermal ablation were excluded from the study.
The data was collected retrospectively from June 2016 to November 2018 and prospectively from November 2018 onwards.
The data were collected from the IT medical record provided at the ISMETT center in Palermo.
The patients admitted to the study are 379, 256 men and 123 women.
The average age is 67, with an average BMI of 26.
All patients underwent a second level radiological evaluation (CT scan of the abdomen or MRI of the upper abdomen) and, in the cases indicated, percutaneous ultrasound-guided biopsy.
Prior to surgery, anesthetic risk stratification (ASA score) was performed for all patients.
Patients enrolled in the study were, on average, complex due to multiple comorbidities. In fact, 78% had ASA 3-4 risk scores.
224 patients had primary liver tumors, in particular 176 hepatocarcinomas (46%) and 48 cholangiocarcinomas (intrahepatic 54%, perihilar 13%, gallbladder tumors 16%)
One hundred thirty-one patients (35%) had hepatic metastases from colorectal cancer and 24 patients (6%) from primary non-colorectal liver metastases (GIST, NET, medullary thyroid cancer, metastasis from choroid melanoma).
In the group of patients with HCC, 58% had HCV-related liver disease, 10.5% HBV-related liver disease, 16.7% had NASH-related liver disease, 8% cryptogenic, 4.9% alcohol-related liver disease.

2.2 Type of surgery

All hepatopathic patients enrolled in the study had BCLC stage 0, therefore a correct hepatoresective indication was placed in all.
Patients suffering from synchronous hepatic metastases from colorectal neoplasia with primary in site underwent liver first approach in 85% of cases, in 10% of cases with combined surgery (one step resection of metastases and primary tumor), and in 5% of cases to a colon first approach for symptomaticity of the primary tumor.
Neoadjuvant chemotherapy was performed in all patients with primary non-colorectal metastases, approximately 62% of patients with metachronous metastases and 48% of patients with synchronous primary colorectal neoplasms (90 patients in total, 58% of patients metastatic) The recommended times for washout from therapy were respected in all cases.
Fifty-two patients (13%) underwent major hepatic resection (with the removal of at least 3 liver segments), of which 33 underwent right hepatectomy, 17 underwent left hepatectomy and two under another trisegmentectomy.
Sixteen patients underwent resection of the gallbladder bed for histological examination performed after cholecystectomy, of gallbladder cancer (pT1b, pT2 or pT3).
Anatomic segmentectomy was performed in 42 patients, and one or more wedge resections were performed in 234 patients.
The bilio-digestive anastomosis was prepared in 16 patients. Approximately 70% of these patients had a percutaneous biliary catheter placed before surgery.
For all patients undergoing major liver resection, the calculation of volumes (TLV - FLR) was performed to assess the suitability of the FLR. The calculation was performed using special software applied to the preoperative tomographic examination. The assessment of the suitability of the FLR took into account liver function or recent chemotherapy treatment.
For calculating the minimum FLR, the Urata Formula and the Vaulthey formula were used. Taking into account the patient's weight and height, the formulas return an estimate of the minimum sufficient FLR.
In the case of insufficient FLR, percutaneous embolization of the right portal branch was performed and subsequent radiological volumetric re-evaluation after four weeks.
In two patients, both suffering from bilobar liver metastases from colorectal neoplasia, ALPPS was performed, a procedure that involves two-stage hepatectomy. Fig. 15
One hundred eleven cases were performed laparoscopically (about 30%), 246 in laparotomy.. 22 cases were converted from laparoscopy to laparotomy (conversion rate of 16%) due to bleeding or technical difficulties.
The resection of the hepatic parenchyma was performed using of energy devices (aquamantys, CUSA, Thunderbird, Ultracision and bipolar forceps).
In the case of major hepatectomies, a preliminary vascular check of the hilum was always performed (in the right hepatectomy the ligation, and section of the right branch of the hepatic artery and portal vein, in the case of lobectomy-left hepatectomy the ligation and section of the left branch and possibly of the branch for S4 of the hepatic artery and portal

vein) followed by the parenchymal transection and finally by the section using a linear stapler of the hepatic veins.
In the case of minor resections (segmentectomy, wedge resection), extensive liver mobilization was always performed for better control of the surgical field. These conditions minimized the need for intermittent clamping of the hepatic hilum to control bleeding (Pringle's maneuver was performed only 10 times - 2.6% of cases).
In the data collection we also took into account the need to use amines during the surgery due to hemodynamic instability, the duration of surgery and the amount of blood lost during the surgery, in particular by dividing patients with a blood loss less than or greater than 500 ml.

2.3 Device for transection of the parenchyma (fig 16)

Hepatic parenchyma transection was performed using one or more of the following devices:
Aquamantys ™ bipolar sealants use technology that combines radiofrequency (RF) and saline to provide hemostatic soft tissue sealing.
The combination of RF energy and saline allows the device to operate at approximately 100 ˚C, nearly 200 ˚C lower than traditional electrosurgical devices.

Thunderbeat is the first and only advanced energy system that simultaneously provides two established forms of energy. Hybrid technology combines bipolar energy and ultrasound in one device. The dissector is a cutting tool (ultrasonic energy) and a sealing tool (bipolar energy) for vessels.

Ultracision is an energetic device that uses ultrasound. The longitudinal vibration of the blade, with a frequency of 55,500 vibrations per second (55.5 kHz), can easily dissect the parenchyma. The range of motion of the blade is a distance of approximately 50 to 100 micrometers. A system of acoustic transformation of piezoelectric elements in the knife's handle transforms electrical energy into mechanical energy. Lateral energy diffusion is minimal (500 micrometers).
The coagulating effect through the denaturation of proteins is caused by the destruction of the hydrogen bonds in the proteins and by the generation of heat in the vibrating tissues. The cut comes from a saw mechanism in the direction of the high-frequency vibrating blade. The intracellular generation of vacuoles makes the correct dissection of different tissue layers even easier.
Blood vessels up to 2-3 mm in diameter are coagulated upon tissue contact with the vibrating metal. For coagulation of larger vessels, it is necessary to exert pressure with the side or curve of the blade for 3-5 seconds.

CUSA® Excel is the first ultrasonic surgical suction system indicated for liver resection.
it allows you to limit bleeding, preserving vessels and other healthy tissues

In fact, CUSA allows increasing selectivity and control when removing tissue near critical structures such as bile ducts, arteries or vessels.
It uses pulsed energy and controlled power reserve that create a rebound effect on the tip when it encounters a collagen-rich structure such as a blood vessel.
The tactile feedback improves Liver Surgeons' ability to differentiate between targeted tissue and critical structures and may allow them to move the tip before harming healthy tissue, therefore, creating a wider margin of control.
All devices can be used in both laparotomy and laparoscopy.

2.4 Biliary leakage management

Biliary fistulas occurred in 16 cases (4% of cases), 8 grade A fistulas, resolved spontaneously by maintaining abdominal drainage for at least one week, 6 grade B fistulas treated and resolved with minimally invasive procedures (endoscopic and/or radiological), and 2 cases of Grade C fistulae requiring a second surgery.
At least one abdominal drain was placed near the resection slice in all patients.
In cases where the drainage had characteristics suspected of biliary fistula, total bilirubin was measured in the drained fluid.
We defined the biliary fistula, in accordance with ISGLR, the presence of a bilirubin level at least three times higher than that of serum, and we removed the drains starting from the third postoperative day if it is serous or serum and if its output is less than about 200 cc per day.
Patients with evidence of biliary fistula underwent periodic abdominal ultrasound scans to evaluate any intraperitoneal collections and daily qualitative and quantitative monitoring of the drained fluid.
In the case of high-flow fistulas or infectious complications, minimally invasive endoscopic procedures were performed (ERCP, sphincterotomy, positioning of a plastic biliary stent to detente the biliary tree) and/or radiological procedures (positioning of ultrasound-guided pigtails to drain the collections infected and / or PTC and placement of external-internal biliary catheters). Fig 17
In cases where minimally invasive procedures failed, a second surgery was performed.
All patients with infectious complications underwent blood cultures and drainage fluid cultures.
These patients underwent empirical broad-spectrum antibiotic therapy, which was subsequently modulated according to the microbiological isolations.
The bilio-digestive anastomosis was made in the two patients who developed a grade C fistula. In the second surgery, therefore, the anastomosis was repackaged.
Percutaneous biliary catheters were placed in both cases prior to reoperation. In the 16 cases found, resolution of the fistula occurred in 100% of cases (0% mortality).

2.5 Statistical analysis

The study was aimed to detect the possible risk factors for fistula occurrence in a set of clinical and surgical variables. A preliminary univariate analysis was performed by investigating variables distributions, both on the full sample and conditioned to the presence of the fistula (Table 1), and performing univariate logistic regressions, in order to assess the association between the outcome (fistula occurrence) and possible predictors (Table 2). Then, a multivariable logistic model was used to detect the most important predictors of biliary fistula (Table 3), considering significant predictors with a p-value<0.05. A forward stepwise selection of predictors was made, based on the AIC minimization criterion, and the goodness of fit was performed using indexes AUC, Sensitivity, Specificity and Accuracy (Table 4). The R functions glm and step were used to perform logistic regression and stepwise selection, respectively, while performance indexes were obtained using the pROC package in R.

Table 1. Characteristics of the study population, conditioned to biliary fistula occurrence.

	Fistula No (0) (N=363)	Fistula Yes (1) (N=16)	Total (N=379)
Age	67 (59, 72)	62 (54, 67)	67 (58, 72)
Male Sex	248 (68%)	8 (50%)	256 (68%)
BMI	26 (24, 28)	28 (24, 31)	26 (24, 28)
Smoke	122 (39%)	4 (27%)	126 (38%)
DIAGNOSIS.TYPE			
- Biliary Cancer	44 (12%)	4 (25%)	48 (13%)
- Colorectal Liver Metastasis	124 (34%)	7 (44%)	131 (35%)
- HCC	172 (47%)	4 (25%)	176 (46%)
- Non colorectal liver metastasis	23 (6%)	1 (6%)	24 (6%)
Laparotomic resection	255 (70%)	15 (94%)	270 (71%)
Major resection	45 (12%)	7 (44%)	52 (14%)
Anatomic resection	117 (32%)	13 (81%)	130 (34%)
LeftLobe	124 (34%)	8 (50%)	132 (35%)
Central Liver (S4-5-8)	217 (60%)	15 (94%)	232 (61%)
Right Side (S6-7)	159 (44%)	8 (50%)	167 (44%)
Biliary Anastomosis	12 (3%)	4 (25%)	16 (4%)
Concomitance surgery	24 (7%)	2 (12%)	26 (7%)
CUSA	96 (27%)	8 (50%)	104 (28%)
AQUAMANTYS	133 (37%)	7 (44%)	140 (37%)
Ultracision	156 (43%)	5 (31%)	161 (42%)
Thunderbeat	117 (32%)	1 (6%)	118 (31%)
Duration of surgery (h)	3.42 (3, 5)	5 (4.58, 6.92)	4 (3, 5)
Cirrhosis	83 (23%)	3 (19%)	86 (23%)
Neoadjuvant chemotherapy	104 (32%)	1 (7%)	105 (30%)
Amine	47 (13%)	7 (44%)	54 (14%)
Blood loss (cl)	25 (20, 30)	40 (30, 50)	25 (20, 30)
Type of resection			
- Bed of gallbladder	16 (4%)	0 (0%)	16 (4%)
- Bisegmentectomy	12 (3%)	2 (12%)	14 (4%)
- Left Hepatectomy	13 (4%)	4 (25%)	17 (4%)
- Left Lobectomy	20 (6%)	1 (6%)	21 (6%)
- Right Hepatectomy	31 (9%)	2 (12%)	33 (9%)
- Segmentectomy	39 (11%)	3 (19%)	42 (11%)
- Trisegmentectomy	1 (0%)	1 (6%)	2 (1%)
- wedge (1 nodule)	172 (47%)	1 (6%)	173 (46%)
- wedge (2 nodules)	31 (9%)	1 (6%)	32 (8%)
- wedge (3+ nodules)	28 (8%)	1 (6%)	29 (8%)

Table 1.b Fistola grade in study population

	0 (N=363)	1 (N=16)	Total (N=379)
Fistola grade			
- 0	363 (100%)	0 (0%)	363 (96%)
- A	0 (0%)	8 (50%)	8 (2%)
- B	0 (0%)	6 (38%)	6 (2%)
- C	0 (0%)	2 (12%)	2 (1%)

Table 2. Univariate Odds Ratio (OR) with 95% Confidence Intervals (CI) and p-values for variables associated with fistula status

Predictors	Odds ratio (CI95%)	P-value
Age	0.96 (0.92, 1.01)	0.064
Male Sex	0.46 (0.17, 1.27)	0.134
BMI	1.19 (1.03, 1.36)	**0.015**
DIAGNOSIS.TYPE		
- HCC	1	-
- Liver Metastasis	2.34 (0.69, 7.93)	0.172
- Biliary Cancer	3.91 (0.94, 16.25)	0.061
HCC	0.38 (0.12, 1.21)	0.102
Laparotomic resection	6.35 (0.83, 48.70)	0.075
Major resection	5.50 (1.95, 15.49)	**0.001**
Anatomic Resection	9.07 (2.54, 32.46)	**<0.001**
LeftLobe	1.93 (0.71, 5.23)	0.200
centralLiver (S4-S5-S8)	10.09 (1.32, 77.21)	**0.026**
rightSide (S6-S7)	1.28 (0.47, 3.49)	0.626
Biliary Anastomosis	9.75 (2.74, 34.70)	**<0.001**
Concomitance surgery	2.02 (0.43, 9.40)	0.371
CUSA	2.77 (1.01, 7.59)	**0.047**
AQUAMANTYS	1.35 (0.49, 3.69)	0.565
BipolarForceps	0.60 (0.21, 1.77)	0.358
Thunderbeat	0.14 (0.02, 1.07)	0.059
Duration of surgery	1.51 (1.19, 1.90)	**<0.001**
Cirrhosis	0.76 (0.21, 2.73)	0.673
Neoadjuvant chemotherapy	0.16 (0.02, 1.20)	0.074

Smoke	0.58 (0.18, 1.86)	0.357
Amine	5.20 (1.85, 14.62)	**0.002**
Blood loss	1.10 (1.05, 1.14)	**<0.001**

Table 3. Multivariable logistic regression

Predictors	Odds ratio (CI95%)	P-value
Age	0.95 (0.89, 1.01)	0.085
BMI	1.26 (1.07, 1.49)	**0.005**
HCC	0.27 (0.06, 1.30)	0.102
Anatomic Resection	4.47 (0.97, 20.55)	0.054
centralLiver	18.88 (1.14, 313.18)	**0.040**
rightSide	4.10 (1.00, 16.83)	**0.050**
Neoadjuvant chemotherapy	0.09 (0.01, 0.88)	**0.039**
Amine	4.53 (1.02, 20.10)	**0.047**
Blood loss	1.08 (1.03, 1.12)	**<0.001**

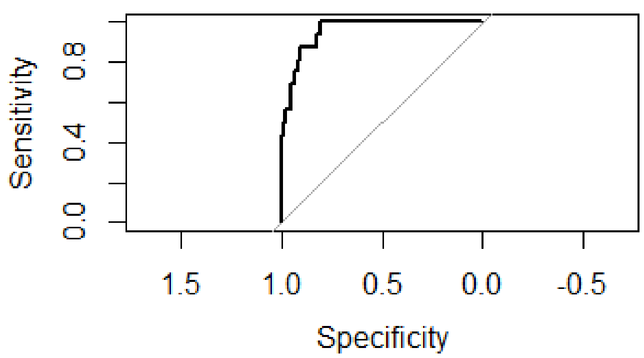
Table 4. Summary of performance indexes for multivariable logistic regression

AUC (CI95%)	Sensitivity	Specificity	Accuracy (CI95%)
0.95 (0.92, 98)	0.44	0.99	0.97 (0.95, 0.99)

Table 5. Confusion matrix from multivariable logistic regression

Values predicted by the model	Real values	
	0	1
0	361	9
1	2	7

ROC curve



CHAPTER 3

Results

The study was developed on a sample of 379 patients for which 24 clinical and surgical variables were collected, including the presence of BL. Table 1 shows their distribution for both the full sample and the two groups of patients with and without fistula, respectively with N=16 and N=363. Specifically, the two groups are similar for patients' median ages (67 for patients without BL and 62 for those with BL) and percentages of male sex patients (68% without fistula and 50% with fistula). In both groups one of the most frequent diagnosis types is Colorectal liver Metastasis, registered respectively in 34% of patients without fistula and 44% of patients with fistula. Still, the most frequent diagnosis type in the group without fistula is HCC (47%). Moreover, most patients had a laparotomic resection (70% without fistula and 94% with fistula), while the minority had another intervention in the same time (7% without fistula and 12% with fistula). For about half of patients in each group segments 6 and 7 (right side) were involved (44% without fistula and 50% with fistula).

However, the two groups had different percentages of patients having a major resection (12% of patients without fistula and 44% with fistula) and an anatomic resection (32% without fistula and 81% with fistula). They were different between the two groups also the involvement of segments 4, 5, and 8 (centralLiver) (60% without fistula and 94% with fistula), the presence of biliary anastomosis (3% without fistula and 25% with fistula) and the administration of amines (13% and 44%). The median duration of surgery was 3.42 hours for patients without fistula and 5 hours for patients with fistula, with different amounts of (estimated) blood loss (25 cl without fistula and 40 cl with fistula).

Table 2., results of univariate logistic regression, shows a significant association between fistula onset and BMI (specifically the probability of developing a fistula increases proportionally with increasing BMI), major liver resection, anatomical resections, resection involving central segments (S4 -S5-S8), the presence of biliodigestive anastomosis, the use of amines during surgery and the duration of the surgery and intraoperative blood loss in a directly proportional sense.

Table 3. shows the results of multivariable logistic regression, including only predictors selected with stepwise method. Specifically, the most influent risk factors for biliary fistula occurrence are the involvement of segments 4, 5 and 8 (centraliver), which is associated with an increase for biliary fistula probability of a factor of almost 19; the involvement of

segments 6 and 7 and the administration of amines, both being associated to a probability of biliary fistula about four times higher. Two other significant risk factors are BMI and blood loss, associated with the increase of biliary fistula probability respectively of 26% and 8%, when increasing 1 unit (that is, 1 level of BMI and 1 cl of blood loss). On the contrary, the administration of neoadjuvant chemotherapy before surgery can be considered as a protective factor since it reduces the probability of biliary fistula by 91%. Performance indexes in Table 4 show a good model fitting, with AUC and Accuracy near to 1 (respectively, 0.95 and 0.97).

CHAPTER 4

Discussion

The advances in surgical technique, anesthetic and technological innovations have allowed a notable development of hepatic surgery in recent years making it increasingly safe and effective.

Despite this, BL remains the most frequent and most feared complication with an incidence between 4 – 17 %, according to a recent meta-analysis. BL can have quite serious consequences: it reduces the regeneration of the liver parenchyma and can be associated with abdominal sepsis, prolongs hospitalization, and costs.

Our study showed that the main risk factors related to the development of BL are:

BMI, resection of the central segment (S4, S5, S8), resection of posterior segments of the liver on the right(Right side: S6-S7), the use of amines, intraoperative blood loss, bilio-digestive anastomosis.

The BMI (body mass index) is proportional sense to the onset of fistulas (the probability of developing a fistula increases as the BMI increases).

In recent years, many studies have evaluated the impact of body composition on the outcome of patients undergoing liver surgery.

Obesity and even more so obesity-sarcopenia together (a typical condition of cancer patients) are known to be related to the risk of postoperative complications (42)

Obesity, as is known, causes important metabolic and hormonal disorders with important repercussions on the liver parenchyma; the term metabolic dysfunction-associated fatty liver disease (MAFLD) has recently been coined to describe them. (43)

This condition, associated with microcirculatory disorders caused by metabolic disorders can damage the residual liver after hepatectomy and affect healing of the cut surface tissue, which may increase the risk of postoperative bile leakage. (44)

Intraoperative blood loss is also a risk factor related to the onset of fistula. Anemization associated with clamping of the hepatic pedicle (Pringle's maneuver), sometimes necessary to dominate massive bleeding, could cause ischemia of the liver and reperfusion injury with effects on liver function and fistula development.

Another risk factor is the use of amines during surgery, a condition that underlies hypotension and hemodynamic instability often associated with blood loss or sepsis. The amines act on the microcirculation, helping to create ischemia of the liver which is correlated with a disorder of parenchyma scarring and the onset of biliary fistula. (44)

The study showed a strong correlation between the type of resection performed and the onset of the fistula.
In particular, resections involving segments 4-5-8 (called central segments) and the posterior segments of the right (6-7) are at a higher risk of fistula.
Due to their anatomical position, during the resection of the central segments, the main Glisson system around the hilum is easily damaged, thus causing bile leakage.
Central hepatectomy involves a larger resection area, and no tissue coverage may also be one of the reasons for post-operative bile leakage.
Resection involving the right lateral segments (S6-S7) is also strongly associated with the onset of the fistula: this is probably due to pumping action of the right diaphragm that increases the residual right hepatic bile duct pressure and increases bile leakage. (44)
From the analysis of the data, a strong association (evaluated univariate) emerged between the presence of biliary anastomosis and the onset of the fistula.
This association is well known in the literature. The use of preoperative endoscopic or percutaneous biliary drainage remains controversial. On the one hand, it facilitates the recognition of biliary structures, which can be maintained in the transanastomotic site to guarantee the anastomosis itself. Still, on the other, it exposes the patient to an infectious risk.
Although the routine use of preoperative biliary drainage is not recommended, it has been shown that the outcome is better in selected patients (jaundice patients, cholangitis) (45-46)
It is important to underline the strong association between anatomical resection and the onset of the fistula (at least documented in the univariate analysis).
Anatomical liver resection requires too much manipulation of the Glisson ligaments, and resection of the central area of the hepatic portal region may increase the occurrence of bile leakage.
This association could play an important role in the risk-benefit assessment related to anatomic resection, certainly more advantageous from a prognostic point of view, but riskier. We have insufficient evidence, and more studies are needed to verify this conjecture in the future further.
We did not find a significant association between BL and the devices used nor differences between laparoscopy and laparotomy, as is known in the literature. (47)
A fact that emerges from the analysis carried out is the protective role of neoadjuvant chemotherapy. Although its hepatotoxic effects are known (steatohepatitis related to irinotecan and damage to the liver sinusoids related to oxaliplatin) when respecting the recommended washout, neoadjuvant chemotherapy has proved to be a safe and effective treatment. (48)
Knowing the risk factors for the development of biliary lekage is important to prevent its appearance and possibly facilitate its spontaneous resolution.
Experience has shown that most biliary fistulas resolve spontaneously. In these cases drainage plays a fundamental role because it avoids the formation of abdominal collections that can easily become infected and cause sepsis.
In the literature, however, the routine use of abdominal drainage at the end of liver resection is controversial (49)

The table (fig 17) which summarizes a meta-analysis on biliary fistulas shows how the main studies published on the subject share neither the positioning nor drainage management after surgery. (50)

Drainage, on the one hand, allows for early detection of any complications such as bleeding and biliary fistula; on the other hand it is associated with the onset of complications such as increased ascitic production, retrograde infections, pain, intestinal injuries, increased costs, slowing of rehabilitation of the patient and prolongation of hospitalization. (51)

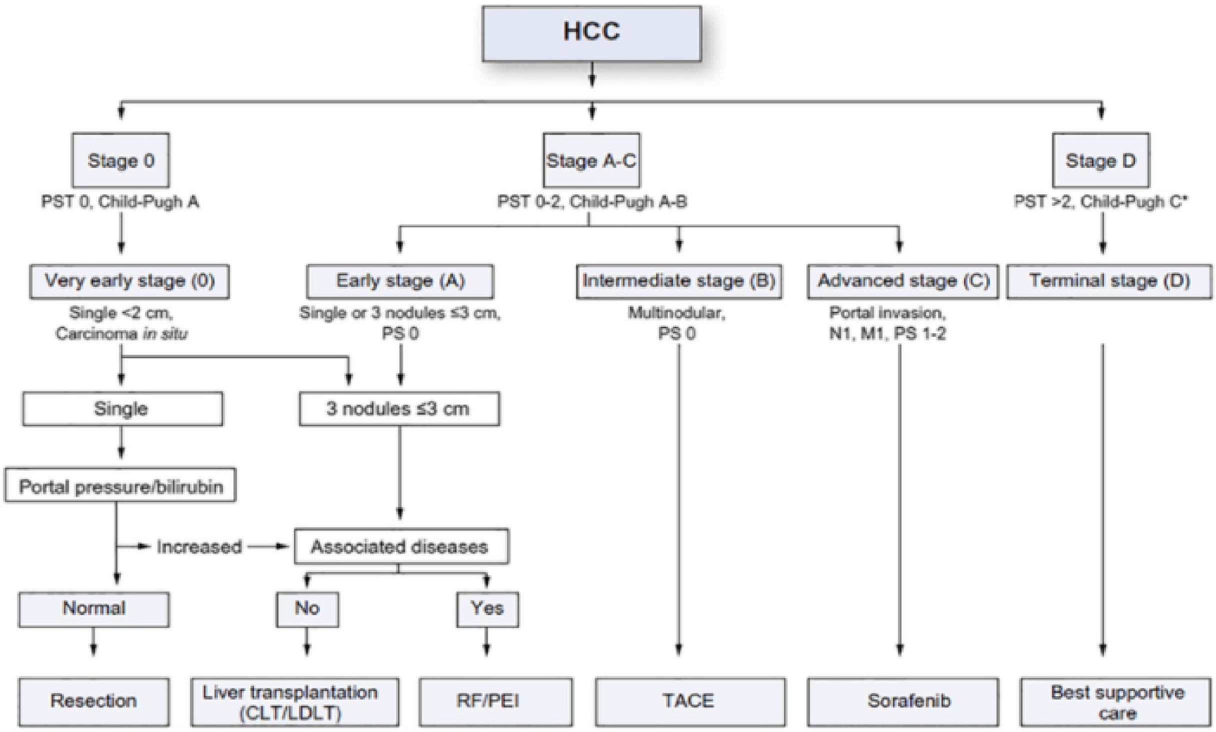
In the literature there is an unanimous consensus in discouraging the routine use of drainage after surgery, but to reserve its placement only for selected patients, who indeed have risk factors for the development of biliary fistula. (52)

Therefore, knowledge of risk factors becomes fundamental for the selection of these patients.

CHAPTER 5

Tables and Figure

Fig. 1- Barcellona Clinic Liver Cancer (BCLC)



The Barcelona Clinic Liver Cancer (BCLC) staging system for hepatocellular carcinoma, revised 2011. PST performance status; CLT/LDLT cadaver liver transplant/living donor liver transplant; RF/PEI radiofrequency ablation/percutaneous ethanol injection; TACE transarterial chemoembolization 29.

Fig. 2- Child Pugh Score for Hepatic Functional Reserve

PARAMETER	POINTS		
	0	1	2
Albumin (g/dl)	> 3.5	2.8- 3.5	< 2.8
Bilirubin (mg/dl)	<2	2 – 3	>3
PT (sec > normal)	<4	4-6	>6
Ascites	None	Mild	Moderate
Encephalopathy (grade)	0	I-II	III-IV

Child Pugh **class A**= 5 – 6 points, **B=** 7 – 9 points, **C=** 10- 15 points

Fig 3 Bismuth-Corlette classification

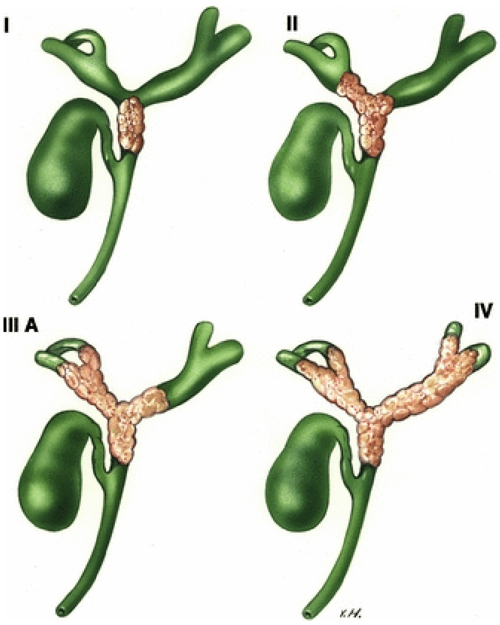


Image taken from the UptoDate website

●**Type I :** Tumors below the confluence of the left and right hepatic ducts

●**Type II** :Tumors reaching the confluence

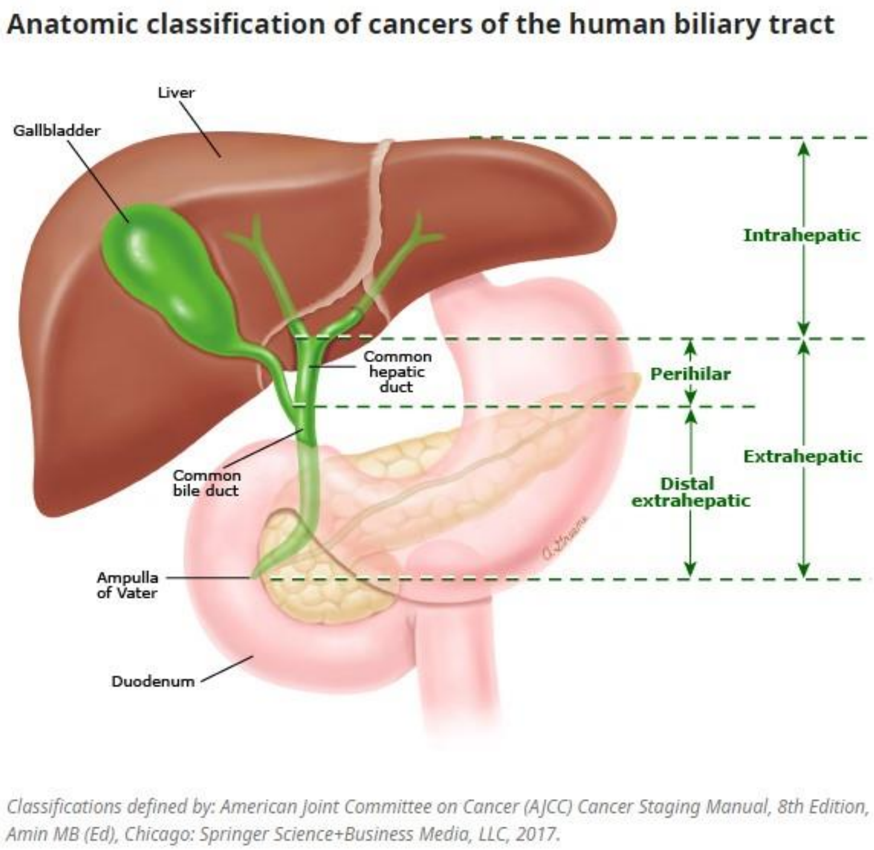
●**Types IIIa and IIIb**, respectively : Tumors occluding the common hepatic duct and either the right or left hepatic duct

●**Type IV** : Tumors that are multicentric, or that involve the confluence and both the right or left hepatic duct

Fig 4 Criteria for resecability of Cholangiocarcinomas

Criteria for resectability
• Absence of distant hepatic metastases, retropancreatic and paracelic lymph nodes • Absence of infiltration of the main hepatic artery and / or main portal vein • Absence of extrahepatic invasion of adjacent organs • Absence of peritoneal carcinosis • Bilateral involvement of the hepatic duct up to the secondary rootlets • Atrophy of a hepatic lobe with infiltration of the contralateral branch of the portal vein, arterial or bile duct up to the secondary ducts.

Fig 5. A) Anatomic classification of cancer of thw biliary tract; B) treatment for Klatskin I-II; C) treatment for Klatskin III A and IIIB



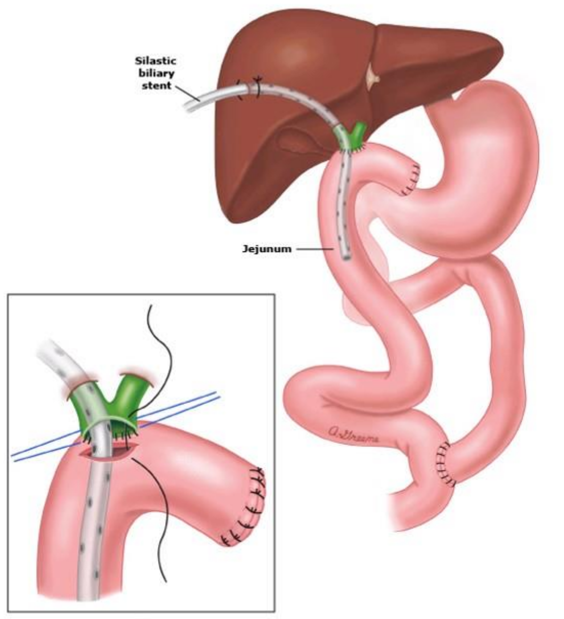
A

Image taken from the UptoDate website

- **Klatskin I- II**

For type I and II lesions, the procedure is **en bloc resection of the extrahepatic bile ducts and gallbladder with 5 to 10 mm bile duct margins and a regional lymphadenectomy with Roux-en-Y hepaticojejunostomy reconstruction**

Biliary reconstruction with Roux-en-Y hepaticojejunostomy



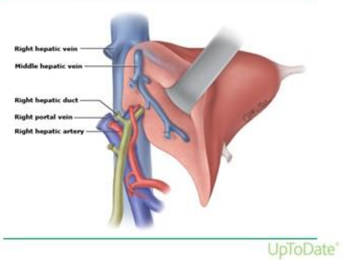
The most common reconstruction for proximal bile duct injury is Roux-en-Y hepaticojejunostomy. Biliary stent placement helps reduce stricture at the anastomosis. Once a silastic stent has been positioned to replace the prior drainage catheter, the small bowel is divided and the distal small bowel (Roux limb) brought up and sutured to the bile duct (end-to-side hepaticojejunostomy). An end-to-side bowel-bowel anastomosis completes the Roux-en-Y reconstruction.

B.

Image taken from the UptoDate website

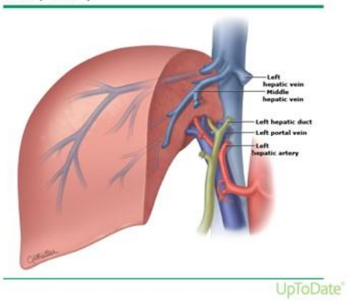
- **Klatskin IIIA**

Right hepatectomy



- **Klatskin IIIB**

Left hepatectomy



Type III and type IV tumors are amenable to potentially curative resection in centers with expertise in these procedures. Aggressive techniques such as multiple hepatic segment resection with portal vein resection (hilar en bloc resection) **to achieve negative margins should not be a contraindication to resection. Highly selected patients with type II, III, and IV tumors that are not resectable** due to vascular invasion or primary sclerosing cholangitis **may be candidates for liver transplantation**

Image taken from the UptoDate website

C

Fig. 6 Fig. 6 a) staging; b) type of resection; c) extent of radical cholecystectomy

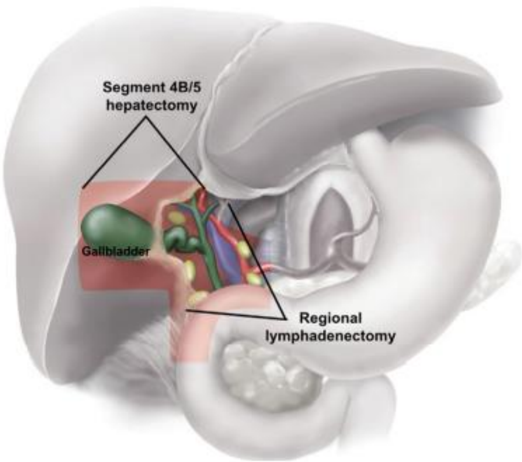
American Joint Commission on Cancer, 8th edition Gallbladder Primary Tumor Staging

T stage	Description
T1a	Tumor invades the lamina propria
T1b	Tumor invades into but not through the muscularis
T2	Tumor invades the perimuscular connective tissue without involving the serosa [for peritoneal-sided tumors (T2a)] or the adjacent liver tissue [for hepatic-sided tumors (T2b)]
T3	Tumor violates the peritoneum (for peritoneal-sided tumors), invades the liver and/or one adjacent extrahepatic major organ or bile duct
T4	Tumor invades major vascular structures (portal vein, hepatic artery) or invades more than one extrahepatic major organ or bile duct

a

T stage	**Type of resection**
T1a	cholecystectomy alone without further radical surgical resection
T1b- T2 – T3	Extent of radical cholecystectomy, en bloc resection with regional lymphadenopathy is appropriate. Extension of disease proximally to the bile duct may require bile duct excision with reconstruction for biliary drainage.

b



Extent of radical cholecystectomy, including lymph node clearance for early-stage disease.

.c.

Image taken from the UptoDate website

Fig 7- RECIST CRITERIA Definitions of Response Classification

Response Class	Definition
Complete response	Disappearance of all target lesions; any pathologic lymph nodes (whether target or nontarget lesions) must have reduction in short axis to less than 10 mm
Partial response	At least a 30% decrease in the sum of diameters of target lesions; reference the baseline sum diameters
Stable disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study
Progressive disease	At least a 20% increase in the sum of diameters of target lesions; reference is the smallest sum on study (this includes the baseline sum if that is the smallest on study); in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm; any appearance of one or more new lesions is also considered progression

Fig 8. - Treatment of synchronous CRLM

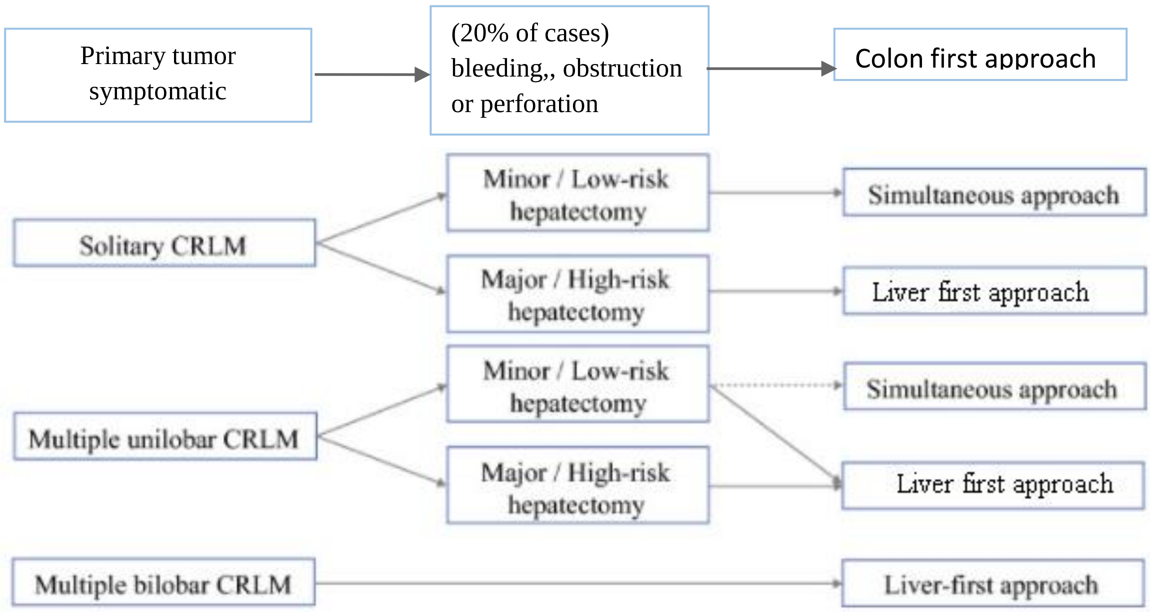
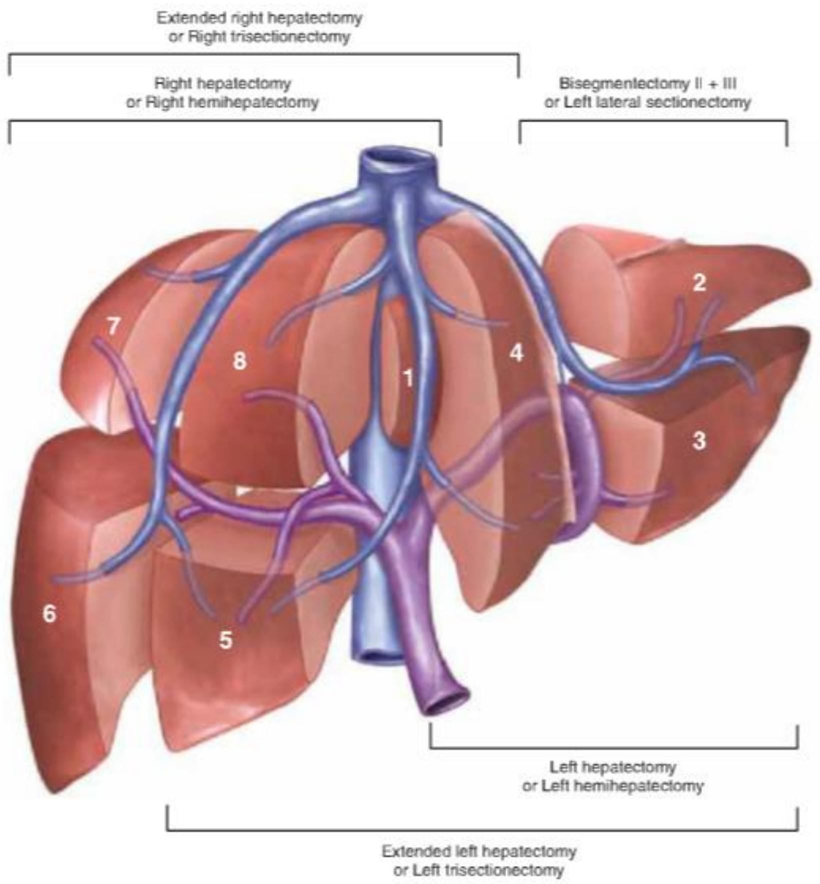


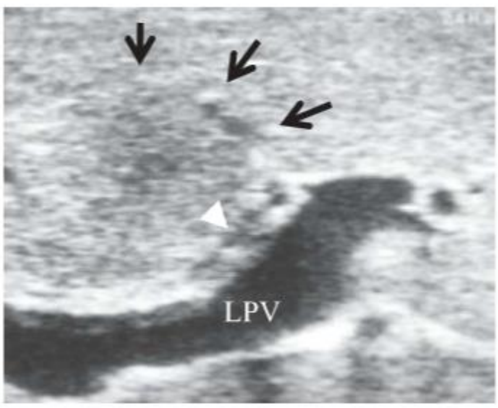
Fig. 9 liver resection



Brisbane 2000 terminology for liver resection. Adapted from Abdalla EK, et al. *Surgery* 2004;135:404–410, with permission.

Image taken from - Hepatobiliary and pancreatic surgery- Lillemoe HA- Lippincott Williams & Wilkins

Fig.10 - Intraoperative ultrasaud



Intraoperative ultrasound view showing metastatic tumor at the base of segment IVB, just anterior to the left portal pedicle. The tumor (*dark arrows*) has begun to exert mass effect on the left hepatic duct (*white arrowhead*), which is slightly dilated; this was not apparent on the preoperative CT scan.

Image taken from - Hepatobiliary and pancreatic surgery- Lillemoe HA- Lippincott Williams & Wilkins

Fig. 11- Type of liver resection

Type of resection	Decription	Advantages	Ddisadvantages
Hepatectomy with preliminary vascular section	All vascular elements are bound and dissected before resecting the hepatic parenchyma,	Early vascular control of the hilus allows the visualization of the hepatic transection line through ischemic demarcation of the surface of the hepatic parenchyma guiding the plane of transaction Reduction of blood loss during parenchyma transection	possible presence of an anatomical variant of the vascular structures of the hilus, which could lead to ischemia of liver segments not involved in resection
Hepatectomy with immediate parenchymal section	Primary section of the parenchyma along the ideal planes of the portal cleavages. The vascular peduncles are identified during transection and then bound and dissected, while the supra-hepatic vein will be bound and dissected at the end.	It is possible to perform resections only according to the localization of liver lesions it is not possible to damage the vascular peduncles of other segments not affected by resection;	Greater blood loss during the parenchymal section, and therefore the need to perform resection faster or possibly with an intermittent clamping of the hilus
Combined technique	Isolation and clamping of the Glissonian peduncle , transection of the hepatic parenchyma, the section of the glissonian peduncle and , at the end, the section of the supra-hepatic vein.	Allows optimal vascular control with minimal blood loss, and reduces the risk of iatrogenic vascular lesions for unknown anatomical abnormalities.	Cytolysis enzymes can increase significantly if the clamping lasts more than 1 hour

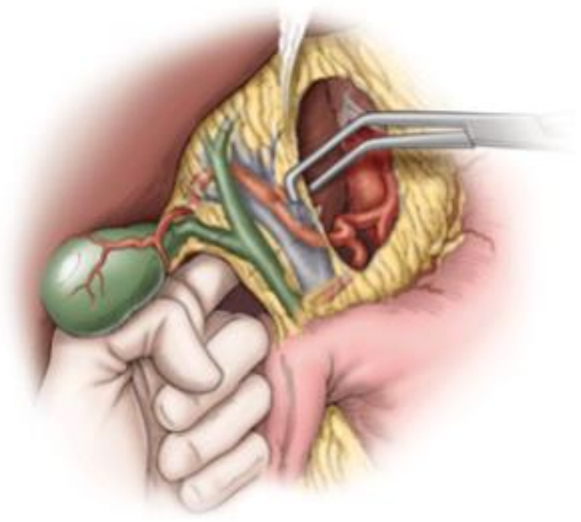


Fig. 12 - Pringle maneuver

Image taken from - Hepatobiliary and pancreatic surgery- Lillemoe HA- Lippincott Williams & Wilkins

Fig. 13- A) Portal vein embolization (PVE); B) volume of the FLR before and after PVE

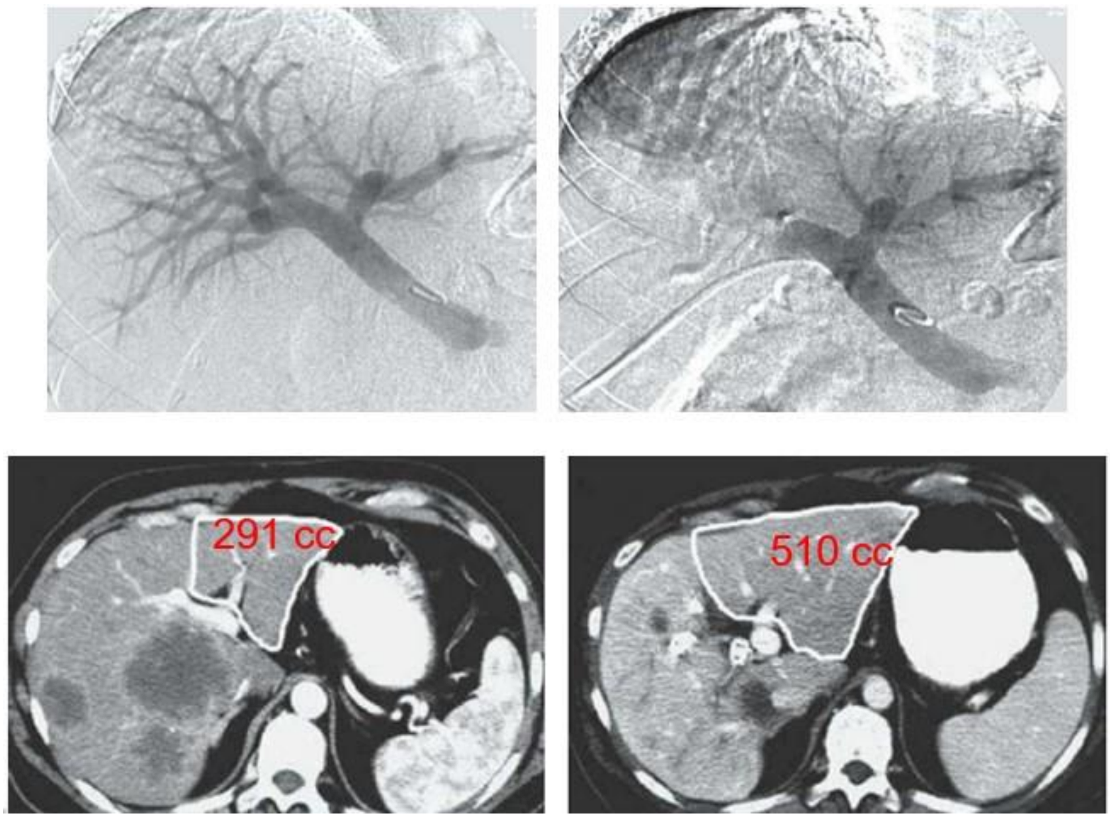


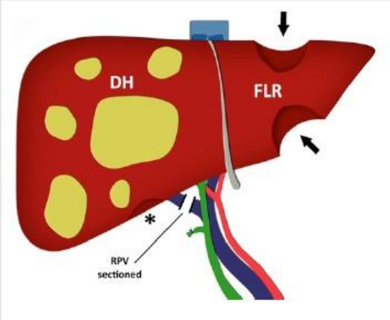
Fig 14. Definition of massive blood loss (38)

Level of difficulty	Type of resection	Blood loss
grade 1 (low level of difficulty)	wedge resection and left lateral sectionectomy	200 ml
grade 2; (intermediate level of difficulty)	anterolateral segmentectomy (segments 2, 3, 4b, 5 or 6) and left hepatectomy	300 ml
grade 3 (high difficulty level)	postero-superior segmentectomy (segments 1, 4a, 7, or 8), right posterior sectionectomy, right hepatectomy, right extended hepatectomy, central hepatectomy, and left hepatectomy extended.	500 ml

Fig. 15 ALPPS (Associating Liver Partition and Portal vein ligation for Staged hepatectomy)

STEP 1

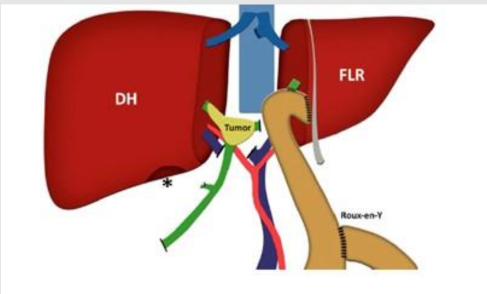
During the first surgery are performed Surgical remediation of the FLR, section and suture of the right portal branch and cholecystectomy (Figure 1)

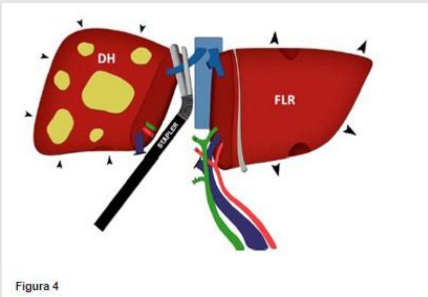


Subtotal hepatic transection with preservation of the hepatic veins and the right hepatic artery (In situ splitting), collection of the vascular structures, positioning of a plastic envelope around the hemi-liver to be removed in the 2nd step (Figure 2).

STEP 2

In the subsequent relaparotomy (7 days after the first step) the completion surgical resection is performed: Extended liver resection, section of the right bile duct with free margin and its en-bloc exeresis with the surgical piece, packing of biliodigestive anastomosis (Figure 3);





Evidence of atrophy of the "deportalized" right lobe with relative hypertrophy of the residual hepatic lobe, section of the right hepatic artery and hepatic veins with mechanical stapler (Figure 4);

Image taken from web site

Fig. 16. Devive for transection of parenchyma –
A) Aquamantys; B) Thunderbeat; C) Ultracision; D) CUSA

A) Aquamantys

B) Thunderbeat

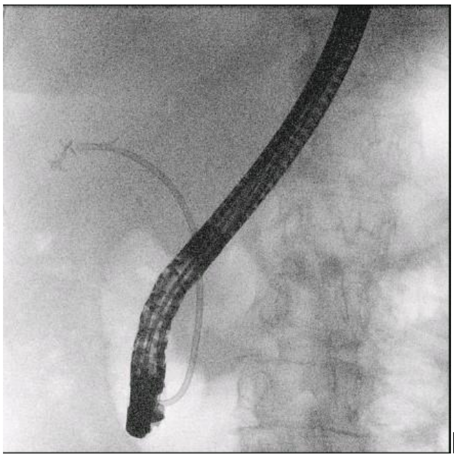
C) Ultracision

D) CUSA

Image taken from web site

Fig 17. Biliary fistula treatment.
a. Cholangiogram
b. Endoscopic stent placement
c. PTC and biliary catheter placement.


A
The cholangiogram shows the presence of the biliary fistula. The arrow indicates the spreading of the contrast medium


B
Endoscopic biliary stent placement for biliary fistula treatment

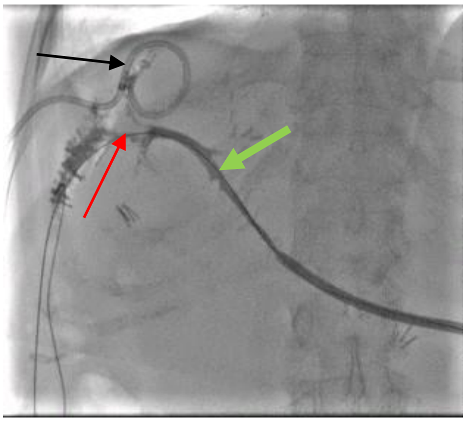

C Patient undergoing liver resection and biliodigestive anastomosis packaging. Black arrow indicates pigtail positioned to drain abdominal collection, Green arrow indicates biliary catheter. The red arrow indicates the biliodigestive anastomosis

Fig. 18 Review of literature on bile leaks definitions and postoperative results (50)

Author	*N*	Bile leak definition	POD of drain removal	Bile leakage (%)	Interventional procedure (%)
Belghiti et al.	42	If daily drainage was less than 100 ml, the drain was removed	3–5	4.8	35.7
Fong et al.	60	Presence of ongoing bilious drainage for more than 1 week postoperatively	4	5	8.3
Liu et al.	52	Macroscopic evaluation not otherwise specified. Drains removed if discharge >200 ml/day	5	3.8	3.8
Sun et al.	60	Macroscopic evaluation of drainage fluid not otherwise specified	3–5	0	5
Viganò et al.	593	Drainage of 50 ml or more of bile from the surgical drain, or from drainage of an abdominal collection, across 3 days or more	4	5.7	1.3
Kyoden et al.	1.269	(i) Drain discharge obviously bile stained, (ii) bilirubin level in the aspirated fluid >5.0 mg/dl at least twice and at least once after POD 7, and (iii) bile-stained intraabdominal fluid collection and/or the bilirubin level >5.0 mg/dl	7	8.7	2
Koch et al.	70	ISGLS. Drain fluid-to-serum total bilirubin concentration ratio ≥3.0 on POD 3 or the need for radiological intervention (i.e. interventional drainage) owing to biliary collections or re-laparotomy due to biliary peritonitis	5	16	10
Rahbari et al.	265	ISGLS definition	3	27.2	18.5
Yamazaki et al.	316	ISGLS definition	3	4.4	0.3
Guillad et al.	1001	(i) Bile in the abdominal drains, (ii) percutaneous or surgical drainage of a biloma, and (iii) biliary ascites or peritonitis found at laparotomy	5	8	5.6
Taguchi et al.	241	ISGLS definition	7 or earlier	25.7	6.6
Brooke-Smith et al.	603	ISGLS definition	Not standardized	11	9.2
Present study	475	Bilirubin concentration in the drain fluid >171 µmol/l (=10 mg/dl) in two or more consecutive measurements. Such measurements were systematically performed on the third, fifth and seventh postoperative days (PODs)	7	8.2	1.7

POD postoperative day, *ISGLS* International Study Group of Liver Surgery

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