21 Primary Intrahepatic Lithiasis

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- *Primary intrahepatic lithiasis (stones originated inside the intrahepatic biliary tree) is endemic in East Asia and much less common in the West. It is usually associated with intrahepatic biliary strictures and is responsible for recurrent episodes of cholangitis, hepatic atrophy, secondary biliary cirrhosis, and intrahepatic cholangiocarcinoma.*
- *Diagnosis of hepatolithiasis is usually established by non-invasive radiological methods. Accurate location of stones, detection of biliary strictures, identification of hepatic segments involved and/or atrophic, suspicion of cholangiocarcinoma, and/or the presence of cirrhosis and portal hypertension will ultimately lead the therapeutic approach.*
- *Treatment is challenging and sometimes controversial, and aims to prevent recurrent cholangitis and consequences of progression of disease (ultimately cholangiocarcinoma).*
- *Liver resection allows remotion of the stones, of the biliary strictures, and of the atrophic parenchyma, and ultimately diminishes the risk of cholangiocarcinoma. It seems to be the best surgical option for treatment of primary intrahepatic lithiasis.*
- *Well-established indications for hepatic resection of primary intrahepatic lithiasis include: i) lithiasis limited to one lobe, sector, or segment; ii) parenchymal hypo-atrophy; iii) presence of liver abscess; iv) failure of previous treatments; and v) suspected cholangiocarcinoma.*

INTRODUCTION

Intrahepatic lithiasis (or hepatolithiasis) is defined as the presence of stones in the biliary tract proximal to the confluence of the right and left main hepatic ducts, irrespective of the presence of stones in the main bile duct or the gallbladder.

Intrahepatic lithiasis is endemic in East Asia (including Taiwan, China, Hong Kong, Korea, Malaysia, and Japan). While in some Asian countries (such as Taiwan) the prevalence of intrahepatic stones can reach up to 50%, in the West it is much less common - closer to 1%.[1–3] However, the incidence of hepatolithiasis is increasing in the Western world, and it seems to be in decline in some Eastern countries. The etiology of hepatolithiasis probably suffers the contributory influence of genetic, dietary, and environmental factors, and trends in incidence can be at least partially explained by migration from endemic areas and by westernization of lifestyle.

Differential diagnosis between primary and secondary intrahepatic lithiasis is extremely important. Intrahepatic stones secondary to extrahepatic biliary strictures related to previous liver surgery (common bile duct stricture or stricture of hepaticojejunostomy), or secondary to stone migration from the gallbladder, can be classified as **secondary intrahepatic lithiasis** (**Figure 1**). This is the most frequent cause of intrahepatic stones in Western patients. Stones may also originate inside the liver, within single or multiple dilations of the intrahepatic biliary tree, in association or not

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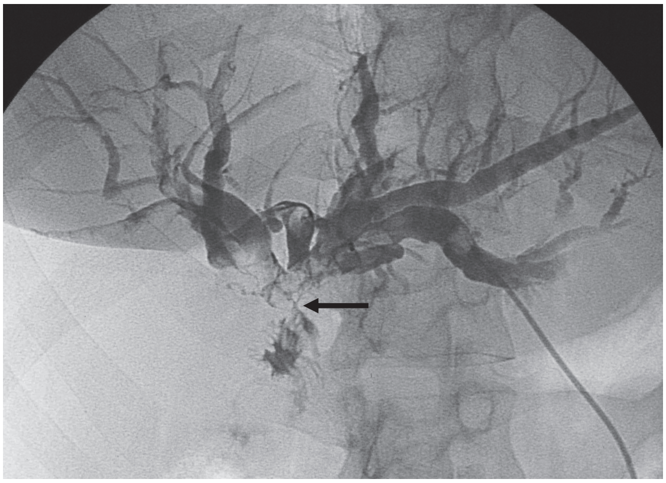


Figure 1. Secondary intrahepatic lithiasis. Percutaneous transhepatic cholangiography (PTC) showing intrahepatic stones above a strictured hepaticojejunostomy (arrow).

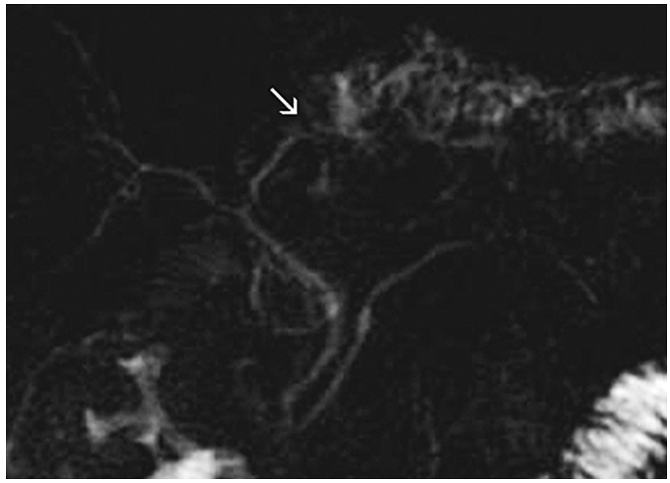


Figure 2. Primary intrahepatic lithiasis (PIL). Magnetic resonance cholangiography (MRC) showing multiple biliary dilations and stones proximal to a stricture on the left biliary hepatic duct (arrow).

with intrahepatic biliary strictures (**Figure 2**). Such cases are classified as **primary intrahepatic lithiasis (PIL)**.

Patients with intrahepatic stones have a typical clinical presentation characterized by abdominal pain and recurrent cholangitis; less commonly, patients present with jaundice, acute pancreatitis, or have asymptomatic disease. Unfortunately, hepatolithiasis is characterized by frequent recurrence, requiring multiple interventions. Therefore, to prevent late complications of the disease (liver abscesses, pyogenic sepsis, hepatic fibrosis resulting in secondary biliary cirrhosis, and cholangiocarcinoma), early aggressive treatment is needed.

Advances in hepatobiliary imaging, especially magnetic resonance imaging (MRI) and magnetic resonance cholangiography (MRC), allow clear diagnosis of hepatolithiasis, precise delineation of the biliary anatomy, and identification of the degree of parenchymal hepatic atrophy. These pieces of information are essential for optimal therapeutic planning.

Treatment of primary intrahepatic lithiasis includes surgical (mainly hepatectomy) and non-surgical (such as percutaneous and endoscopic procedures) approaches. Liver resection is the best surgical treatment for PIL. Hepatectomy allows for remotion of stones, of the bile strictures and of atrophic parenchyma, and ultimately prevents the development of cholangiocarcinoma. Very rarely, liver transplantation is considered.[4–9]

This chapter will focus on the management of primary intrahepatic lithiasis (PIL).

ETIOLOGY AND PATHOLOGY

COMPOSITION OF INTRAHEPATIC STONES

Typically there are two types of intrahepatic stones: calcium bilirubinate stones (brown pigment stones) and cholesterol stones.

Calcium bilirubinate stones, overall the most frequent, are mainly composed of bilirubin, cholesterol, fatty acids, and calcium, and represent the majority of intrahepatic stones (**Figure 3A**).[2] Intrahepatic brown pigment stones contain more cholesterol than similar stones of extrahepatic biliary ducts, suggesting the involvement of an associated altered cholesterol metabolism. Calcium bilirubinate stones are probably associated with biliary strictures, stasis,

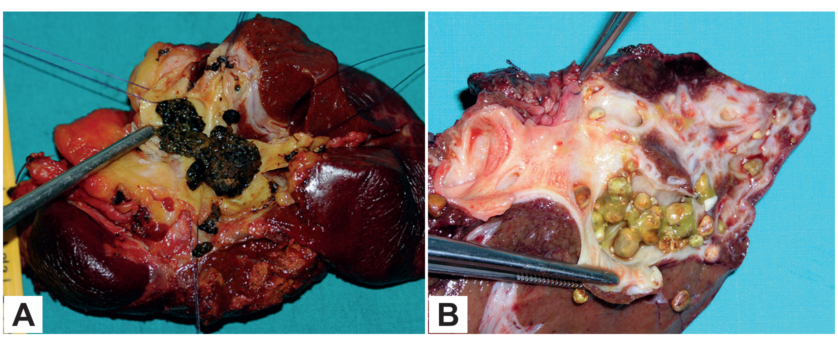


Figure 3. A) Typical calcium bilirubinate stones (brown pigment stones) within the left biliary hepatic ducts in a specimen of left hepatectomy. **B**) Cholesterol stones within the right biliary hepatic ducts in a specimen of right hepatectomy.

and bacterial infection (by β-glucoronidase-producing bacteria).[1,2,10] The histologic changes of the bile ducts containing calcium bilirubinate stones are classified into chronic proliferative cholangitis, suppurative cholangitis, and chronic granulomatous cholangitis.[11] In later stages, atrophic changes are seen, and biliary cirrhosis and portal hypertension can develop if the whole liver is involved. Also, long-standing chronic cholangitis may be related to malignant transformation. In fact, a continuous histologic spectrum may be observed, from papillary growths with low-grade and high-grade dysplasia to carcinoma in situ, and finally invasive cholangiocarcinoma.[12] The prevalence of cholangiocarcinoma in patients with hepatolithiasis is 2.4% to 14%.[10,13–15] Similarly, among patients with cholangiocarcinoma, up to 27% have intrahepatic stones.[16–20]

Intrahepatic cholesterol stones (5.8% to 13.1% of all intrahepatic stones) are more common in Western countries (**Figure 3B**).[2] Cholesterol stones result from an error in biliary phospholipid secretion, which leads to bile supersaturated with cholesterol. They can occur without biliary stenosis or dilations. Pathogenesis of primary intrahepatic cholesterol stones remains unclear. Recent investigations indicate that their formation is based upon the dual defects of up-regulation of cholesterol synthesis and down-regulation of bile-acid synthesis in the liver, possibly in association with defective secretion of phospholipid by its canalicular transporter, multidrug resistance protein (MDR3).[21] Metabolic factors, either acquired or congenital, act synergistically in the development of these intrahepatic stones.[1,22] Bile ducts containing cholesterol stones generally show a milder degree of fibrosis and glandular hyperplasia than ducts containing calcium bilirubinate stones. Foamy cell aggregates and multinucleated giant cells are characteristic findings associated with intrahepatic cholesterol stones.[23] Causal relationship between cholesterol stones and carcinoma is not clear.[24]

BILIARY DUCT FEATURES

Some studies suggest that anatomical features of intrahepatic bile ducts can be involved in the development of hepatolithiasis.

Usual biliary tree anatomy

Intrahepatic stones are more frequent in the left lobe than in the right lobe. The acute angle formed at the junction of the left hepatic duct with common bile duct would tend to induce bile stasis. In fact, a biliary scintigraphy study showed evidence of prolonged time-activity curves in left bile ducts compared to right bile ducts, even in normal livers.[1,25] In the right lobe, the biliary duct of segment 6 seems to be the most frequently involved, and in this case anatomical features could also play a major role. (**Figure 4**).

Biliary tree variations

The confluence of the right posterior bile duct into the left hepatic duct (Norman's anomaly)[26] is likely to be an important factor in the development of PIL (**Figure 5**).[27] However, in a recent comparative study including patients from Taiwan and Japan, anatomic variations of intrahepatic segmental ducts did not seem to play any important role in the pathogenesis of PIL.[28] Although in Western countries anatomic variations of intrahepatic bile ducts are frequently observed in patients with intrahepatic lithiasis, the role of anatomic variations of intrahepatic bile ducts in hepatolithiasis remains unclear.

Biliary anomalies

It is unclear whether primary intrahepatic stones and intrahepatic congenital bile duct dilation represent different features of the same disease. In Western patients, PIL has been reported to be more frequently associated with the presence of congenital intrahepatic bile duct dilation than in Eastern patients, in whom it seems mainly related to biliary infestations and infections.[29]

Congenital bile duct dilation is a rare disorder, in most cases hereditary, resulting from an embryonic disorder known as ductal plate malformation.[30,31] The estimated frequency of this disease is reported to be 1 in 1,000,000 in the whole population.[31] The ductal plate malformation may comprise different segments of the intrahepatic biliary tree (sectorial bile duct, segmental bile ducts, and peripheral bile ducts) leading to different clinicopathological entities defined according to Todani's classification.[32] Congenital bile duct dilation with intrahepatic-only localization corresponds to Todani Type V.[32] This entity was first described by Caroli et al. in 1958.[33] Later, Guntz et al.[34] classified congenital

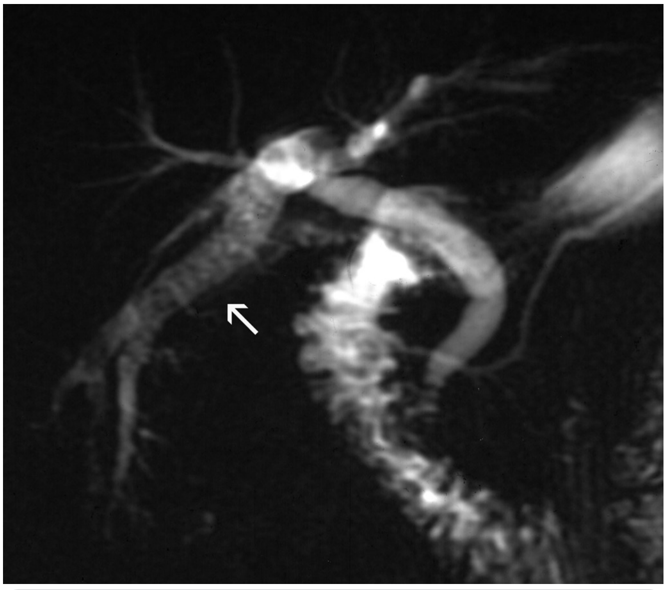


Figure 4. Magnetic resonance cholangiography (MRC) showing dilation of the biliary duct of segment 6 filled with stones (arrow).

intrahepatic bile duct dilations (IHBD) according to the aspect and the extent of dilations: Type 1 (grape-brunch-like saccular communicating dilations of peripheral IHBD); Type 2 (fusiform dilations of large IHBD); and Type 3 (saccular dilations of large IHBD). The original disease described by Caroli corresponds to Type 1, according to Guntz classification.

PARASITIC INFECTION

Biliary parasitic infection (by clonorchis sinensis, ascaris lumbricoides, and opisthorchis) can lead to stone formation (parasite fragments or eggs may act as a nidus). However, evidence of infestation is not commonly found in resected liver specimens.[2]

CLINICAL PRESENTATION

Abdominal pain, either in the right upper quadrant or in the upper abdomen, is the most frequent initial symptom (70% of patients). Other common manifestations of hepatolithiasis include cholangitis, jaundice and acute pancreatitis. Abdominal discomfort and vomiting may occur. However, no clinical manifestation is pathognomonic for intrahepatic stones. Hepatolithiasis may be an incidental finding on abdominal imaging in asymptomatic patients (16%), especially due to advances in diagnostic imaging modalities and their frequent use.

Frequently, patients have a long history of previous biliary operative and/or non-operative treatments and tend to have recurrent pyogenic cholangitis as the most common clinical manifestation. Pyogenic cholangitis may cause further septic complications such as hepatic abscess, and may ultimately result in parenchymal atrophy or secondary sclerosing cholangitis. Indeed, the most frequently observed clinical history of patients with PIL includes several endoscopic treatments by endoscopic retrograde cholangiopancreatography for recurrent stones of the common bile duct. Patients usually first undergo cholecystectomy and then present with recurrent extrahepatic lithiasis misdiagnosed as migration from the gallbladder. For this reason they usually undergo several endoscopic treatments of the common bile duct stones, frequently without any further complete investigation of the entire intrahepatic biliary tree. Rarely, patients with hepatolithiasis may develop thrombocytopenia and enhanced platelet activation, resulting in coagulation and fibrinolysis disorders that might be particularly severe following liver resection.[35]

The Hepatolithiasis Research Group in Japan has proposed a clinical grade classification to quantify the severity of hepatolithiasis: Grade I: absence of symptoms; Grade II: abdominal pain; Grade III: transient jaundice or cholangitis; Grade IV: persistent jaundice, sepsis, or cholangiocarcinoma.[36]

DIAGNOSIS AND TREATMENT-ORIENTED CLASSIFICATION OF PRIMARY INTRAHEPATIC LITHIASIS

Diagnosis of hepatolithiasis is established by non-invasive radiological methods, mainly ultrasonography, computed tomography scan, and magnetic resonance cholangiography. These methods frequently allow accurate location of stones, detection of biliary strictures, and identification of hepatic segments involved. These data, associated with suspicion of cholangiocarcinoma and/or the presence of cirrhosis and portal hypertension, will ultimately lead the surgical approach. On the other hand, direct opacification methods, such as endoscopic retrograde cholangiography and percutaneous cholangiography, are usually used in case of non-surgical invasive treatments.

ULTRASONOGRAPHY

Ultrasonography (US) is frequently the first technique used to examine patients with PIL. Intrahepatic stones

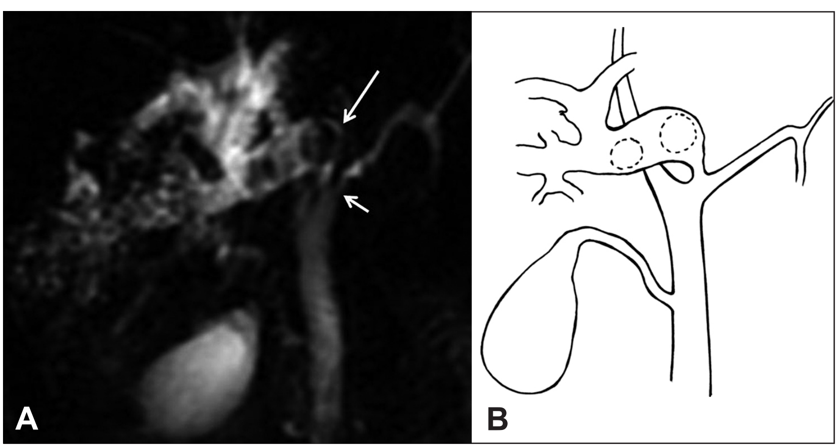


Figure 5. A) Magnetic resonance cholangiography showing primary intrahepatic lithiasis of biliary ducts of the right posterior (RP) sector (long arrow). The RP bile duct drains into the left hepatic duct – Norman's anomaly (short arrow). **B**) Schematic representation of the anomalous drainage of the RP duct into the left hepatic duct.

appear as hyperechogenic spots with a posterior acoustic shadow. Associated biliary dilation is easily identified on US (**Figure 6**). Pneumobilia, as a result of a previous endoscopic procedure with papillotomy or biliary-enteric anastomosis, may make ultrasonography interpretation difficult. Also, stones that do not produce an acoustic shadow cannot be clearly visualized by US, and accurate assessment of biliary strictures might be difficult due to the presence of stones. Liver abscesses can be identified by US.

COMPUTED TOMOGRAPHY

Computed tomography (CT) is the single most cost-effective imaging modality when hepatolithiasis is suspected. CT provides information about location and composition of stones as well as precise liver anatomy, biliary strictures and dilation, the degree of parenchymal atrophy, and the presence and location of abscesses (**Figure 7**). All of these pieces of information are useful in choosing the best therapeutic approach. Images before contrast injection are especially useful to detect stones with low calcium content. Dilated bile ducts appear as low-density, tubular, tortuous branching structures, and they are best appreciated on contrast-enhanced studies. Unlike on US, pneumobilia does not impair CT evaluation of the biliary tree. Strictures appear as thickened duct segments distal to the dilated bile duct. Inflammatory changes on strictures are responsible for contrast enhancement, and differential diagnosis with cholangiocarcinoma can be challenging. Malignancy should be suspected in case of i) periductal soft-tissue density, ii) higher enhancement (on portal phase) compared to adjacent bile duct, iii) ductal wall thickening, iv) portal vein obliteration, and v) lymph node enlargement. These features are associated with the presence of cholangiocarcinoma.[20]

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI), especially magnetic resonance cholangiography (MRC), is accurate in detecting and locating intrahepatic stones, identifying obstructed intrahepatic bile ducts, and defining bile duct anatomy (**Figures 2 and 8**). In a retrospective study by Sugiyama et al., the sensitivity, specificity and accuracy of MRC for detecting and locating intrahepatic stones in hepatolithiasis

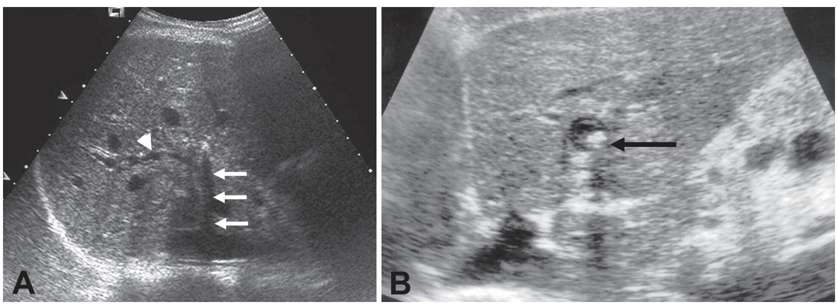


Figure 6. Ultrasonography of primary intrahepatic lithiasis. **A**) Intrahepatic stones appear as echogenic structures that produce acoustic shadow (arrows). Proximal bile duct dilation (arrow head) is frequently identified. **B**) Typical ultrasonographic imaging of stone (arrow) into a dilated bile duct.

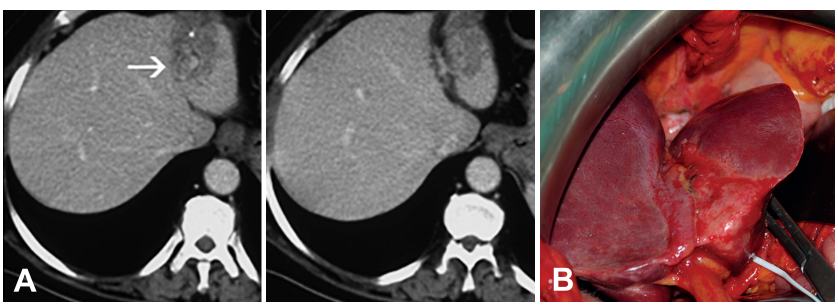


Figure 7. A) Abdominal computed tomography (CT) showing atrophy of the left lateral sector of the liver associated with intrahepatic bile duct dilation and stones (arrow). **B**) Intraoperative view confirming atrophy of the left lateral sector, especially segment 3.

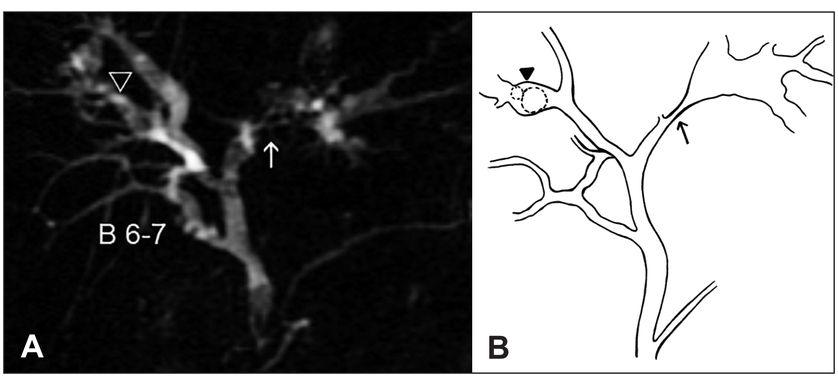


Figure 8. A) Magnetic resonance cholangiography (MRC) showing intrahepatic lithiasis of the left hepatic duct proximal to a biliary stricture (arrow) and of the right anterior biliary duct (arrow head). The right posterior biliary duct (B 6-7) joins the common bile duct, below the main biliary confluence. **B**) Schematic representation of the biliary anomaly. RP: right posterior biliary duct, RA: right anterior biliary duct, L: left hepatic biliary duct.

were 97%, 99%, and 98%, respectively.[37] The sensitivity, specificity and accuracy of MRC for detecting and locating intrahepatic bile duct strictures were 93%, 97%, and 97%, respectively.[37] Similarly to CT, MRI is a valuable tool to detect liver abscesses. However, as with CT, detection of cholangiocarcinoma associated with hepatolithiasis can be difficult with MRI and MRC. Also, pneumobilia can be misinterpreted with intrahepatic stones on MRI. MRC allows the accurate location of intrahepatic stones and of accompanying biliary strictures and it has replaced diagnostic endoscopic retrograde cholangiography in patients with hepatolithiasis.

DIRECT CHOLANGIOGRAPHY

Direct cholangiography can be performed by endoscopic retrograde cholangiography (ERC) (**Figure 9**) or percutaneous transhepatic cholangiography (PTC) (**Figure 10C**), both being invasive techniques that carry considerable morbidity rates (between 1% and 7%). PTC has excellent sensitivity for intrahepatic stones and it provides precise segmental and subsegmental anatomy of the intrahepatic bile ducts and strictures. ERC provides similar diagnostic results if the whole biliary system is opacified; however, biliary obstacles (stones or strictures) can prevent adequate visualization of proximal bile ducts. PTC provides access to therapeutic percutaneous transhepatic cholangioscopy (PTCS) and percutaneous transhepatic biliary drainage (PTBD), both important tools for treatment of cholangitis, stone extraction, stenting of strictures, and biopsy of intraductal lesions. ERC also provides access to therapeutic modalities, such as biliary stent insertion. However, the risks of ERC (especially cholangitis), when compared to the advantages of PTC, make the latter the current method of choice for direct cholangiography in case of hepatolithiasis.

Percutaneous procedures may result in vascular intrahepatic injury, especially in case of non-dilated bile ducts (**Figure 10D**). Selective puncture of bile ducts (including the affected peripheral branches) can be performed percutaneously aided by US, making PTC more useful than ERC for demonstrating peripheral intrahepatic stones with or without biliary strictures.[2,23] Percutaneous cholangioscopy can be performed during PTC with direct visualization of biliary ducts, achieving more detailed information about location and severity of strictures, impacted stones and features of biliary mucosa.[23]

The significant progress in non-invasive radiological methods, especially MRI and MRC, has led to a more restricted use of invasive techniques as diagnostic tools. However, invasive methods remain helpful for therapeutic aims and when non-invasive methods are inconclusive.

TREATMENT-ORIENTED CLASSIFICATION OF PRIMARY INTRAHEPATIC LITHIASIS

The hallmark of PIL is an abnormal bile duct feature characterized by dilation alone or by the association of stricture with proximal dilation. Several classifications of PIL, especially from Eastern countries, have been proposed over the years.

The most simple classification was proposed by the Japan Research Group for the Study of Hepatolithiasis,[23] and divides patients into two groups: patients with stones confined to intrahepatic bile ducts (Type I), and those with stones in intrahepatic and extrahepatic bile ducts (Type IE). The patients are further classified according to the location of stones within the liver: on the right side (Type R), on the left side (Type L), on both sides (Type LR), and on the caudate lobe (Type C).

Tsunoda's classification includes intrahepatic dilation and biliary strictures: Type I, no marked dilation or strictures of intrahepatic ducts; Type II, diffuse dilation of intrahepatic ducts without strictures; Type III, unilateral solitary or multiple cystic intrahepatic dilation accompanied by strictures; and Type IV, similar to Type III but with bilateral involvement.[38] Types I and II correspond originally to secondary hepatolithiasis.

In the classification system recently proposed by Cheon et al.[39], patients with intrahepatic lithiasis were divided into three groups according to stone distribution and presence of associated bile duct stricture: Type A, unilateral solitary or multiple stones with or without intrahepatic dilation and strictures of the intrahepatic bile ducts of the same lobe;

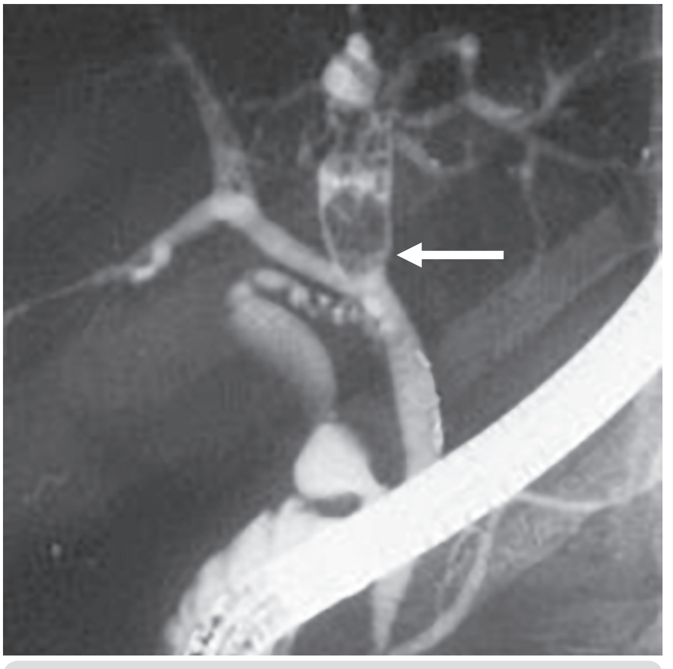


Figure 9. Endoscopic retrograde cholangiography (ERC) showing lithiasis and consequent obstruction of the left biliary duct (arrow).

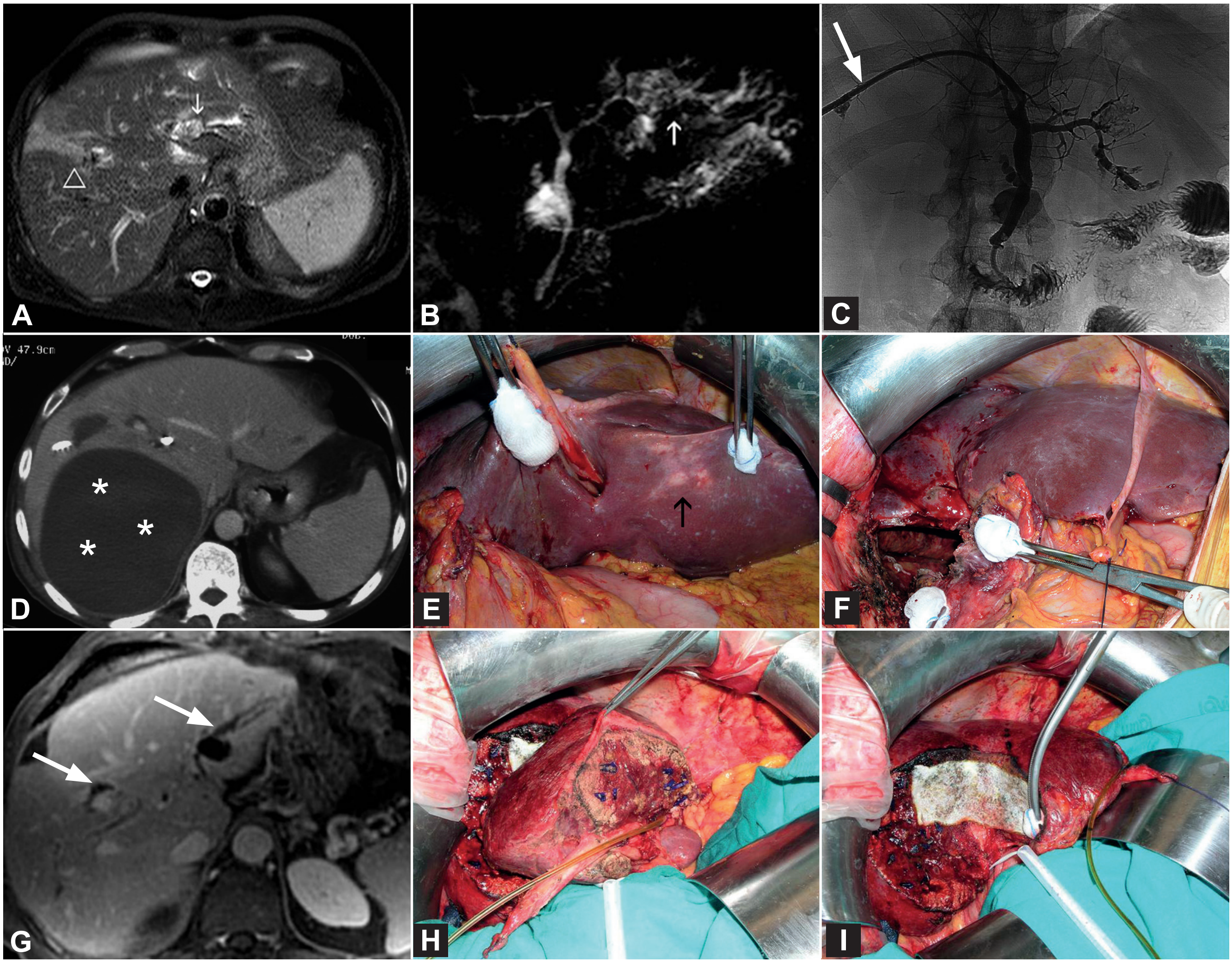
Type B, bilateral multiple stones associated with unilateral stricture of the intrahepatic duct; and Type C, bilateral multiple stones associated with bilateral strictures of the intrahepatic duct (**Figure 11**).[39]

Dong's classification divides localized (Type I) and diffuse (Type II) intrahepatic stones.[40] Additionally, it considers the presence of extrahepatic stones and the functioning of the sphincter of Oddi.

Unfortunately, the various classification systems and the absence of a consensus hampers the possibility of accurately evaluating the outcome of different treatments and series.

PIL TREATMENT ISSUES

The primary goals in the treatment of PIL are to avoid attacks of cholangitis and to prevent progression and sequelae of the disease. Optimal treatment of PIL remains difficult and



Figures 10. 60-year-old male patient who underwent cholecystectomy and endoscopic retrograde cholangiography for treatment of gallbladder and common bile duct (CBD) stones. Endoscopic removal of recurrent CBD stones three months later. Subsequent recurrent episodes of cholangitis. **A**) Magnetic resonance imaging (MRI) demonstrating primary intrahepatic lithiasis of biliary ducts of segments 2 and 3 (arrow) and of segment 5 (arrow head). **B**) Magnetic resonance cholangiography (MRC) confirming these findings. **C**) Percutaneous transhepatic cholangiography (PTC) and percutaneous transhepatic biliary drainage (PTBD) through segment 5 biliary duct after extraction of stones. (Arrow identifies percutaneous biliary drain.) **D**) Computed tomography after PTBD reveals large hematoma on right liver (asterisks). The hematoma caused a large hepatic abscess, responsible for sepsis. **E**) Intraoperative view during laparotomy for surgical drainage of hepatic abscess. Signs of recurrent cholangitis are seen on segment 3 (arrow). **F**) Intraoperative view of remnant cavity after abscess drainage. Patient was discharged in good condition on postoperative day 20. **G**) CT scan five months after surgical drainage, revealing complete resolution of abscess but persistence of intrahepatic lithiasis and dilation of biliary duct of segments 2 and 3 and segment 5 (arrows). **H**) Definitive treatment with surgical resection of segments 2 and 3 (left image) and segment 5 (right image).

controversial. Several surgical, endoscopic, and percutaneous procedures have been reported in the literature, but high recurrence rates are often reported for all of them.

The main steps to be taken in the treatment of PIL to reach its primary goals include: i) complete extraction of stones, ii) elimination of bile duct strictures, iii) removal of affected bile duct drainage areas, and iv) removal of atrophic segments. These procedures will ultimately minimize the risk of repeated cholangitis, liver atrophy, secondary biliary cirrhosis, and cholangiocarcinoma.[41] The procedure most likely to achieve the above-noted goals is resection of affected liver segments. Occasionally, patients with diffuse hepatolithiasis and secondary biliary cirrhosis might be considered for liver transplantation as definitive treatment. On the other hand, less aggressive procedures (surgical or non-surgical) might be helpful in selected cases.

The best approach should be individualized, but some factors - such as the presence of acute cholangitis, stone distribution (hepatic segments involved), presence of bile duct dilations and/or strictures, parenchymal liver atrophy, anatomical biliary variations, suspicion of cholangiocarcinoma, and presence of cirrhosis - affect the choice of treatment.

Approach to patients with **acute suppurative cholangitis** due to PIL is similar to that of cholangitis secondary to gallstones. Antibiotics and biliary drainage are cornerstones in the control of sepsis. PTBD is the most useful method of drainage in case of intrahepatic biliary obstruction, and it is preferable to operative and endoscopic transpapillary drainage approaches (**Figure 10C**).

Concerning **distribution of stones**, most cases of hepatolithiasis are unilateral (61%) and the left side of the liver is more frequently affected (ranging from 58% to 86% of cases) (**Figure 12**).[14,16,31,42–45] As described below, in unilobar disease (especially left liver disease), hepatectomy seems to be the best treatment. On the other hand, treatment of bilateral hepatolithiasis remains controversial. Surgical approaches depend of precise location of stones and strictures and vary from hepaticojejunostomy to bilateral liver resections. Resection of all hepatic segments affected is the best option to reach the ultimate goals in the treatment of PIL. Therefore, once mandatory requirements for a safe resection are met (see **Chapter 22** for further details), resection is the first-choice approach. Frequently, segments to be resected are atrophic and the remnant liver volume is enough. If complete resection of the affected segments is not possible, surgical options include a variety of procedures that can be used alone or in combination, such as resection of the most affected side (generally the left liver) in addition to the complete clearance of remnant bile ducts (by intraoperative cholangioscopy or other perioperative non-surgical procedure), stone clearance and hepaticojejunostomy or hepaticocutaneous jejunostomy or common bile duct T-tube insertion (for postoperative stones extraction), surgical strictureplasty, and even more aggressive approaches with liver transplantation in very selected cases.

Common bile duct stones are present in 27% and gall-

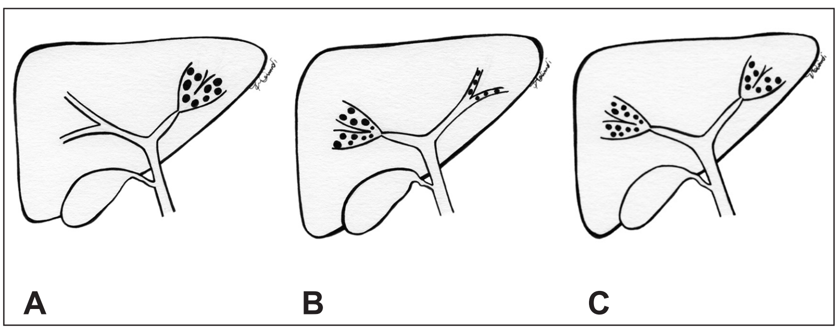


Figure 11. Classification of primary intrahepatic lithiasis based on stone distribution (unilateral or bilateral) and presence of intrahepatic biliary strictures according to Cheon et al. **A**) Type A: unilateral stones with or without intrahepatic biliary dilation and stenosis of the same hemiliver. **B**) Type B: bilateral stones with unilateral biliary stenosis. **C**) Type C: bilateral stones with bilateral biliary stenosis. (Prevalence of Type A, B, and C was 63%, 22%, and 15%, respectively, in a report by Cheon et al.) (Adapted from Cheon et al.[39])

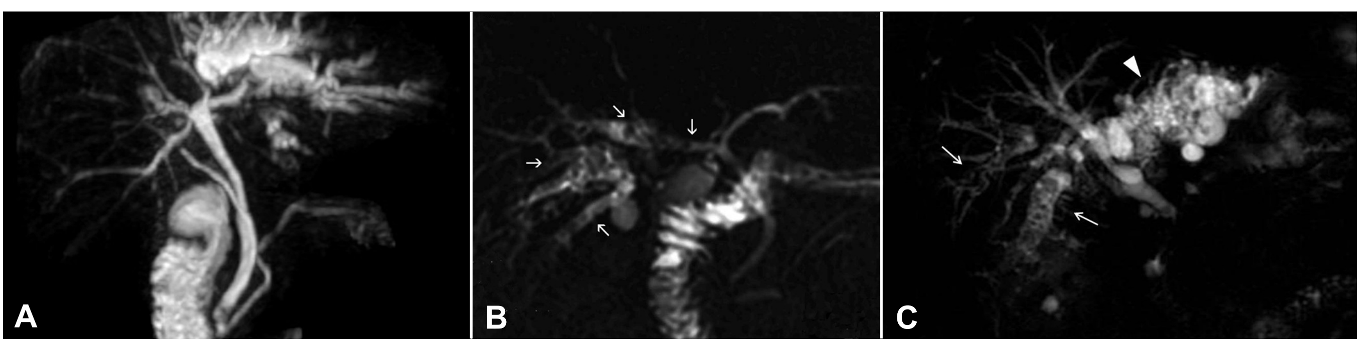


Figure 12. Distribution of stones on primary intrahepatic lithiasis (PIL), demonstrated with magnetic resonance cholangiography (MRC). **A**) Left-sided PIL (biliary dilation and stones on the left hepatic duct). **B**) Right-sided PIL (biliary dilation and stones on the right bile ducts). **C**) Bilateral PIL involving the left bile ducts (arrowhead) and right posterior sector (arrows).

stones in 44% of patients with PIL (**Figure 13**). To avoid the need for a potentially difficult second operation, Lee et al.[9] suggest prophylactic cholecystectomy concomitant to surgical treatment of PIL.

Intrahepatic biliary strictures are frequent (in 27% to 54% of cases)[4,31,39,46–49] and represent a major cause of treatment failure. Residual stones, acute cholangitis, and stone recurrence are more frequent in patients with biliary duct strictures, mainly intrahepatic strictures.[4,6,39,50] Thus, in addition to complete stone clearance, the elimination of biliary duct strictures is necessary to prevent recurrent hepatobiliary complications. More conservative treatment of strictures with balloon dilation does not seem to affect long-term outcomes in patients with biliary strictures.[36]

Repeated episodes of cholangitis lead to **liver atrophy**, **secondary biliary cirrhosis**, and finally end-stage liver disease. Atrophic hepatic segments are usually non-functional and resection of these areas is safe (**Figure 14**). Patients with diffuse hepatolithiasis and secondary biliary cirrhosis should be considered for liver transplantation, which treats the hepatocellular dysfunction and eliminates the possibility of developing cholangiocarcinoma.

The presence of **anatomical biliary variations**, especially with right-sided hepatolithiasis, can make cholangioscopic biliary access difficult. Cranial shift of the right sectorial ducts proximal to the hepatic confluence may be considered an independent risk factor for right hepatolithiasis in the right lobe. It has also been demonstrated that a sharp ductal angle (less than 90º in different views of cholangiography) co-existing with biliary strictures in right-sided hepatolithiasis increases the risk of complications, including severe and/or recurrent cholangitis, liver abscesses, and sepsis.[51] In addition, some anatomical biliary variations can increase the risk of biliary complications in hepatic resections **(Figures 5**, **8 and 14**).

The risk of development of **intrahepatic cholangiocarcinoma** in patients with PIL is well known (prevalence of cholangiocarcinoma in patients with PIL can reach 25%).[16,51] Cholangiocarcinoma associated with hepatolithiasis can be synchronous (depicted preoperatively, intraoperatively by frozen biopsy, or postoperatively as an occasional finding in surgical specimens), or occurs during follow-up after initial treatment (occurring in 1.6% to 12.9% of patients after initial treatment of PIL).[19,52] In fact, most cases of synchronous cholangiocarcinoma are unexpected findings (**Table 1**) (**Figure 15**). The presence of residual stones and bilateral involvement are factors associated with the occurrence of carcinoma.[19]

Preoperative diagnosis of associate cholangiocarcinoma is usually difficult because of hepatolithiasis itself and the related inflammation that hinders clear visualization of bile ducts by imaging techniques. Therefore, especially in patients with biliary strictures where it is very difficult to rule out a malignant stricture, liver resection should always be considered. Cholangioscopy with biopsy can be useful for the diagnosis of malignancies in severe strictures. If malignant stricture cannot be excluded with certainty, liver resection should always be considered. Radical oncological surgery with lymph node dissection is the target treatment when cholangiocarcinoma is suspected or confirmed preoperatively or intraoperatively. Similarly, if malignancy is found postoperatively in the surgical specimen, reoperation to perform a more radical procedure (extended parenchymal resection, resection of main biliary confluence, and lymphadenectomy) should be considered.[53] The prognosis of cholangiocarcinoma secondary to hepatolithiasis is poorer than cholangiocarcinoma alone.[17,39,54]

Regular follow-up after initial treatment (surgical or non-surgical) of PIL could allow early detection of malignancy and it may include tumor markers (such as carbohydrate antigen 19-9 and carcinoembryonic antigen) and imaging modalities (such as US and/or RMI).

HEPATIC RESECTION FOR PIL

Hepatectomy is the most effective treatment for hepatolithiasis. It represents the only treatment that allows com-

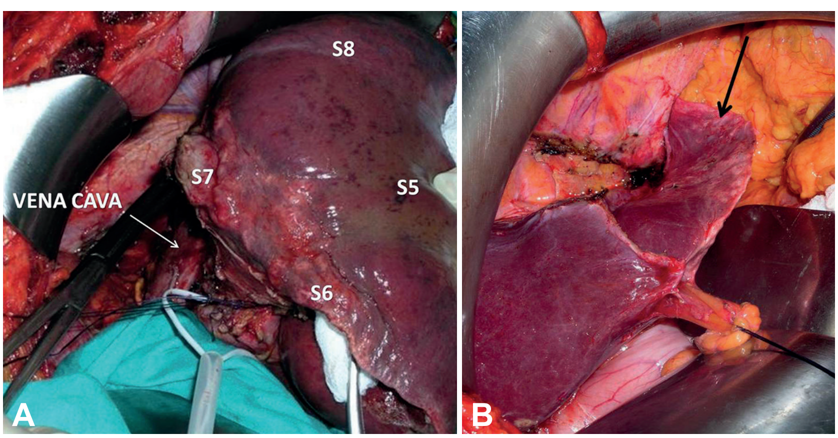


Figure 13. Parenchymal atrophy secondary to primary intrahepatic lithiasis. **A**) Intraoperative view showing atrophy of the right posterior sector (S6 and S7). **B**) Intraoperative view showing atrophy of the left lateral sector (arrow). S5, S6, S7, and S8: hepatic segments 5, 6, 7, and 8, respectively.

plete removal of intrahepatic stones and intrahepatic biliary strictures simultaneously.[5,55,56] Liver resection seems to result in more effective stone clearance (83% to 100%)[16,39] than percutaneous or intraoperative lithotripsy without hepatectomy (20% to 64%).[4,39,50,57–60] Moreover, hepatectomy results in lower rates of stone recurrence (5.7% to 13.9%) than more conservative treatments (31.5% to 52%).[9,46,61–63]

Liver resections in patients with PIL have been frequently reported by Eastern centers with a high prevalence of the disease (**Table 2**), while fewer instances of patients undergoing liver resections have been reported by Western centers (**Table 3**). This is related mainly to the lower incidence of intrahepatic lithiasis in the Western world. However, relative unawareness of this disease, along with the risks associated with hepatectomy for this condition, has further limited the Western data set.

Well-established indications for hepatic resection of PIL include: i) lithiasis limited to one lobe, sector, or segment; ii) parenchymal hypo-atrophy; iii) presence of liver abscess; iv) failure of previous treatments; and v) suspected cholangiocarcinoma. Indication of hepatectomy in patients with incidental finding of PIL is controversial; however, for young patients with low surgical risk, liver resection - especially in localized forms of PIL - should be encouraged to minimize the early and long-term complication risks of PIL.

Table 1. Rate of cholangiocarcinoma in patients with primary intrahepatic lithiasis.

Author	Synchronous cholangiocarcinoma (%)	Unexpected cholangiocarcinoma (%)	Metachronous cholangiocarcinoma (%)
Chen [16]	9.7	60	3.3
Kim [56]	11.1	82	2.1
Lee [65]	3.2	100	1.6
Uenishi [90]	11.6	70	2.7
Lee [9]	7.8	60	-
Kassahun [73]	9.7	33	-
Catena [14]	11.7	100	-
Bockhorn [44]	25.0	100	-
Vetrone [60]	5.3	100	-
Mabrut [31]	7.4	-	-
Clemente [67]	12.2	66	-
Yang [8]	-	-	3.7
Jarufe [41]	-	-	0

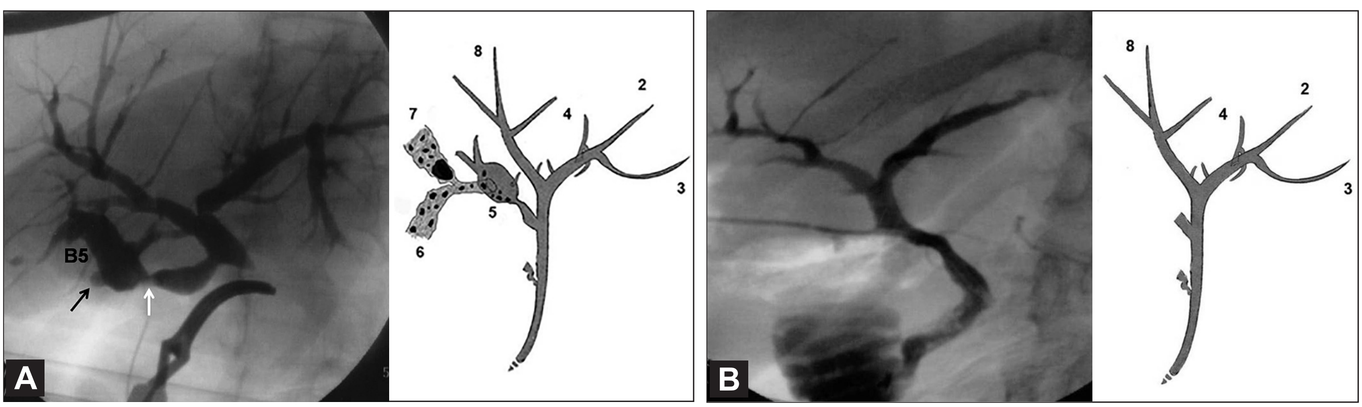


Figure 14. Primary intrahepatic lithiasis (PIL) involving hepatic segments 5,6 and 7, associated with biliary anomaly and treated by anatomic segmental hepatectomy. **A**) Intraoperative direct cholangiography through the stump of cystic duct before resection and schematic representation on the right side. Biliary branches from right posterior sector (black arrow) join the bile duct from segment 5 (B5). Bile duct from segment 5 is dilated proximally to a stricture (white arrow). Bile ducts from segments 5, 6, and 7 were filled with contrast only after choledochal clamping (Bulldog) and cholangiography under higher pressure, but were visible on intraoperative ultrasound (IOUS). **B**) Intraoperative direct cholangiography after resection of segments 5, 6, and 7 through the stump of the bile duct of segment 5. Schematic representation of the right side.

Perioperative **mortality** after hepatectomy for hepatolithiasis in recent Western studies is nil (**Table 3**). Studies with Eastern populations have also shown low postoperative mortality, despite involving more complex cases than those reported in Western studies (as represented, for example, by higher rates of bilateral intrahepatic lithiasis and cirrhosis).

Postoperative **morbidity** rates in Eastern and Western studies have ranged from 7.4% to 58.8% (**Tables 2 and 3**) and are mainly represented by septic complications. Diagnosis and surgical treatment of hepatolithiasis at an early stage are key factors in performing liver resections with low operative risk.[31] Preoperative recurrent cholangitis, due to the disease itself or related to preoperative endoscopic or percutaneous procedures, increases the risk of infectious complications. In fact, preoperative or intraoperative bile culture present positively in most cases, and multi-drug resistant bacteria colonization can occur after multiple endoscopic and/or percutaneous procedures or recurrent episodes of cholangitis. Therefore, preoperative direct cholangiography should be avoided and preferably limited to therapeutic percutaneous or endoscopic procedures (such as PTBD), or in case non-invasive methods (such as CT and/or MRI and/or MRC) do not provide enough information to properly define the best treatment approach. Likewise, sampling bile from intrahepatic ducts for microbiological studies is mandatory during surgical procedures; it is also recommended to irrigate the whole biliary tree with saline solution during surgery. Appropriate prophylactic antibiotics are given empirically and/or according to bacteriological studies.

When liver resection is being considered, operative planning should be decided according to the following issues: location of stones, biliary strictures, and/or dilations; number of involved liver segments; presence of extrahepatic stones; presence of choledochal cysts; presence of anatomical variation; presence of cirrhosis; and suspicion of malignancy. Furthermore, the need for other associated procedures should be accurately evaluated and planned.

In case of **unilateral disease** (up to 61% of cases), partial hepatectomy represents the treatment of choice that can radically resolve recurrent cholangitis and stone formation, and prevent the risk of cholangiocarcinoma. Again, the left liver is affected more commonly (58% to 86%) than the right liver.[14,16,31,42–45,64,65] Left hepatic resections

Table 2. Mortality and morbidity rates after liver resection for primary intrahepatic lithiasis (Eastern studies).

Author, year	Patients (n)	Mortality (%)	Morbidity (%)
Chen, 2004 [16]	103	2.0	28.0
Kim, 2006 [56]	128	0	25.7
Li, 2007 [64]	312	0.3	>19
Lee, 2007 [65]	123	1.6	33.3
Huang, 2008 [89]	245	0.4	16.3
Uenishi, 2009 [90]	86	3.5	-
Lee, 2009 [9]	64	0	42.2
Yang, 2010 [8]	136	2.2	46.3
Jiang, 2010 [63]	106	0	29

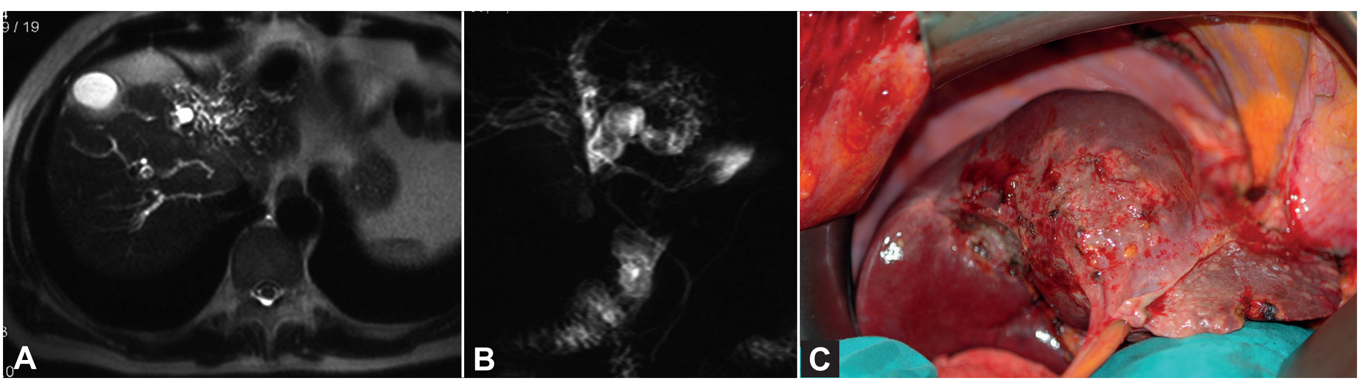


Figure 15. Unexpected cholangiocarcinoma found intraoperatively in a 66-year-old male with intrahepatic lithiasis. **A**) Preoperative magnetic resonance imaging. **B**) Preoperative magnetic resonance cholangiography. Left bile duct dilations and stones are apparent, as well as left lateral sector atrophy. No signs of possible cholangiocarcinoma are present. **C**) Intraoperative view, showing unresectable cholangiocarcinoma. Diagnosis confirmed by anatomopathological study of frozen sections.

are associated with lower morbidity rates than right hepatic resections for unilateral PIL, and represent the most frequent type of hepatectomy (**Figure 16**). The extension of left resections (i.e. left hepatectomy or left lateral sectionectomy) is controversial, but could be based on a precise evaluation of extension of the disease in order to reduce the risk of postoperative biliary fistula or stone recurrence. Sun et al.[66], in a retrospective analysis of 128 patients with left-sided PIL, showed that left hepatectomy was more effective than left lateral sectionectomy, with a significantly lower rate of residual stones (4% vs. 22%; P<0.01). Conversely, Lee et al. [5] showed that there were no significant differences in stone recurrence and complications between left hepatectomy and left lateral sectionectomy for treatment of left-sided PIL. Actually, accurate evaluation of the presence and precise location of bile duct strictures, as well the biliary anatomy (especially the site of junction of ducts from segment 4), should be used to define the extension of left liver resections. The involvement of biliary ducts of the caudate lobe should also be considered. Indeed, the caudate lobe can be affected in up to 21% of cases of PIL,[67] and in this case it should be resected in order to prevent postoperative biliary fistula and late stone recurrence (**Figure 16**).

Intraoperative cholangiography during hepatectomy should be performed when preoperative cholangiography is not complete, with the extension of resection not clearly

Table 3. Mortality and morbidity rates after liver resection for primary intrahepatic lithiasis (Western studies).

Author, year	Patients (n)	Mortality (%)	Morbidity (%)
Di Carlo, 2000 [42]	12	0	16.6
Kassahun, 2005 [73]	27	7.4	58.8*
Herman, 2006 [43]	27	0	7.4
Catena, 2006 [14]	17	0	29.4
Bockhorn, 2006 [44]	9	0	-
Vetrone, 2006 [60]	22	0	27.3**
Mabrut, 2007 [31]	27	0	44.4
Ulrich, 2008 [74]	33	0	37.5
Nuzzo, 2008 [10]	34	0	20
Clemente, 2010 [67]	47	0	24.5
Jarufe, 2012 [41]	52	0	30.8

* including liver transplantation. ** including hepaticojejunostomy

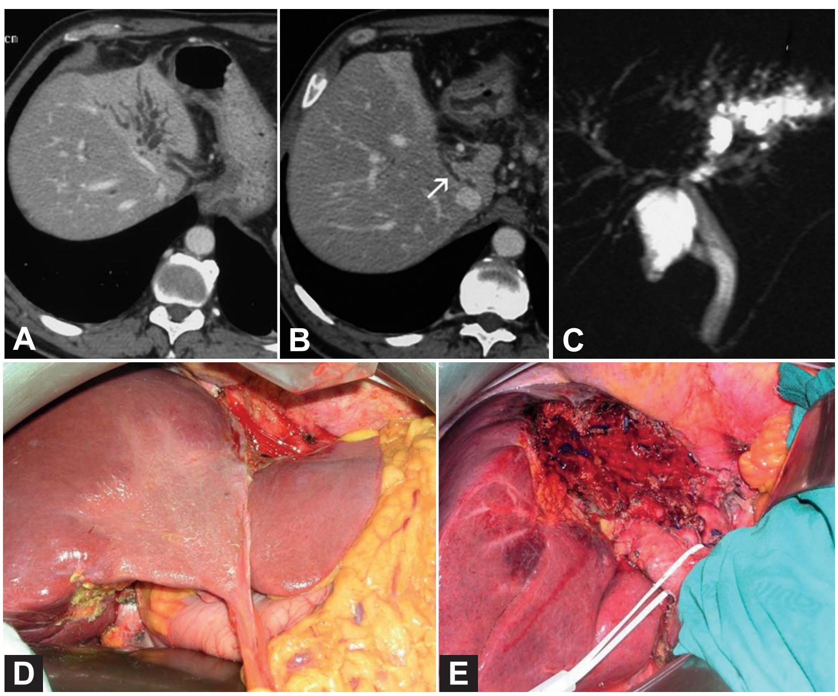


Figure 16. Left-sided primary intrahepatic lithiasis (PIL) associated with parenchymal atrophy treated by liver resection. **A**) Computed tomography (CT) revealing dilated left bile ducts associated with parenchymal atrophy. **B**) Dilated bile ducts from caudate lobe (arrow) are also identified on CT. **C**) Magnetic resonance cholangiography confirming unilateral involvement of PIL. **D**) Intraoperative view confirming parenchymal atrophy, especially of segment 4. **E**) Intraoperative aspect after left hepatectomy extended to the caudate lobe.

defined, and in case of imprecise delineation or doubt of the intrahepatic biliary anatomy (**Figure 15**). Also, intraoperative cholangioscopy is an important tool for further evaluation of extent of the disease (strictures and stones), lithotripsy (such as hydroelectrolitic or by laser) and removal of stones, and eventual biopsy of suspicious strictures. Intraoperative ultrasonography (IOUS) is extremely useful to visualize bile ducts filled with stones (including those not visualized on cholangiography) and to guide anatomical segmental hepatic resections (**Figures 17**). However, artifacts due to pneumobilia can complicate its use.

After liver resection, rates of stone clearance (83% to 100%), late stone recurrence (3.7% to 15.4%) and recurrent cholangitis (0% to 24%) are satisfactory (**Table 4**). The highest rate of stone clearance can be obtained with the addition of intraoperative and postoperative treatments (such as stone extraction by cholangioscopy, percutaneous or through a hepaticocutaneous jejunostomy or T-tube). Immediate and late results depend on extent and severity of disease, presence and site of biliary strictures, time interval between onset of symptoms and treatment, and duration of preoperative treatments. Anatomic segmental hepatectomy seems to be associated with better results than non-anatomic resection, resulting in lower rates of residual stones, bile leakage and recurrence.[63]

Recently laparoscopic liver resection for PIL have been reported with good results, suggesting that laparoscopic hepatectomy could be an effective therapeutic option for these patients, in particular, for those with left sided disease, which is the most frequent.[68–70] Recent series of laparoscopic left hepatic resections for PIL report a morbidity of 11% to 21%, rate of stone clearance of 100%, and no recurrence.[70,71] It is of note that laparoscopic liver resection for PIL should be performed by surgeons with experience in both open and laparoscopic hepatobiliary surgery. In fact, liver resections for PIL are frequently more technically demanding than those for tumors due to severe perihepatic adhesions, parenchyma fibrosis, deformed intrahepatic biliary anatomy, and atrophic changes.

The optimal management of patients with **bilateral PIL** remains a very complex and challenging task, especially because of the difficulty inherent to obtaining complete stone clearance. Several treatment options have been proposed, including: i) bilateral limited liver resections (**Figure 10**); ii) partial hepatectomy of the most affected side, combined with contralateral stone extraction by intraoperative cholangioscopy or by other perioperative non-surgical procedure; iii) partial hepatectomy and hepaticojejunostomy (**Figure 18**) or hepaticocutaneous jejunostomy (**Figure 19**) or common bile duct exploration with T-tube insertion for further biliary access; and iv) liver transplantation.

Table 4. Early and long-term results after liver resection for primary intrahepatic lithiasis.

Author	Patients (n)	Final stone clearance (%)	Median follow-up (months)	Stone recurrence (%)	Cholangitis recurrence (%)	Good results (%)
Chen [16]	103	98.0	56.0	8.8	5.5	91.2
Kim [56]	128	99.0	25.6	4.2	8.3	89.6
Lee [65]	123	96.0	40.3	5.7	-	94.3
Uenishi [90]	86	95.0	75.0	10.1	24.0	76.0
Lee [9]	64	-	42.7	7.8	9.4	-
Di Carlo [42]	12	-	42*	8.3	8.3	83.3
Kassahun [73]	27	-	44.0	-	-	92.5
Herman [43]	27	-	41.2	3.7	7.4	83.3
Catena [14]	17	-	50*	6.2	6.2	87.5
Bockhorn [44]	9	-	31	-	-	100
Vetrone [60]	22	-	67*	-	0	100
Mabrut [31]	27	95	80	15.4	-	84.6
Ulrich [74]	33	-	86.5	-	12.5	87.5
Clemente [67]	47	-	58*	-	19.4	80.6
Jiang [63]	106	86	40.3	11.3	-	-
Yang [8]	136	83	50.7	29.3	25.7	-
Jarufe [41]	52	90.4	63.7	5.8	-	-

♯ Free of symptoms and no recurrent stones. * Mean follow-up.

When partial hepatectomy of the most involved side is planned, complete clearance of the contralateral bile ducts should be obtained. For this, the use of tools such as intraoperative cholangiography, ultrasonography, and cholangioscopy is useful. Recently, Yang et al.[8] compared bilateral hepatectomy (54 patients) with unilateral hepatectomy (82 patients), combined with stone extraction in the treatment of biliary strictures and bilateral hepatolithiasis. Operative mortality was 5.6% after bilateral and 0% after unilateral liver resections. Postoperative residual stones and stone recurrence rate were higher after unilateral hepatectomy. In addition, cholangiocarcinoma developed in 4.9% of patients after unilateral resections and in only 2% after bilateral resections. Therefore, bilateral resection seems more effective, but is possibly associated with higher mortality. These results confirm the complexity of the management of bilateral intrahepatic stones. Risks of extended resection, based on the evaluation of remnant liver, should be weighed against the efficacy of other perioperative techniques to obtain complete removal of

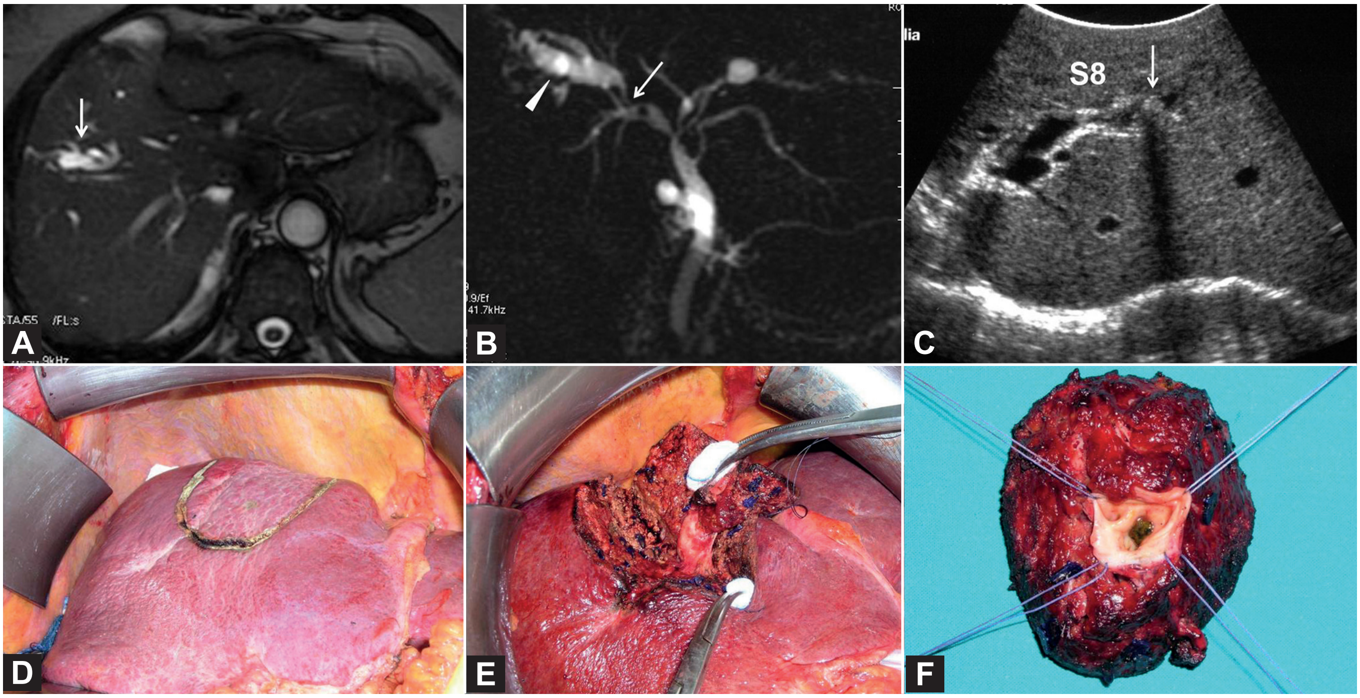


Figure 17. Primary intrahepatic lithiasis of segment 8 treated by anatomical hepatic resection. **A**) Magnetic resonance imaging: dilated bile duct of segment 8 (arrow). **B**) Magnetic resonance cholangiography: Stricture of bile duct of segment 8 with proximal dilatation (arrow head). **C**) Intraoperative ultrasound (IOUS): stone (arrow) in dilated bile duct near the stenosis. **D**) Intraoperative view: demarcation of limits of resection guided by IOUS. **E**) Intraoperative view during parenchymal transection; dilated bile duct of segment 8 is evident at the deeper plane of section. **F**) Surgical specimen after anatomical segmental resection; stones are seen in dilated bile ducts.

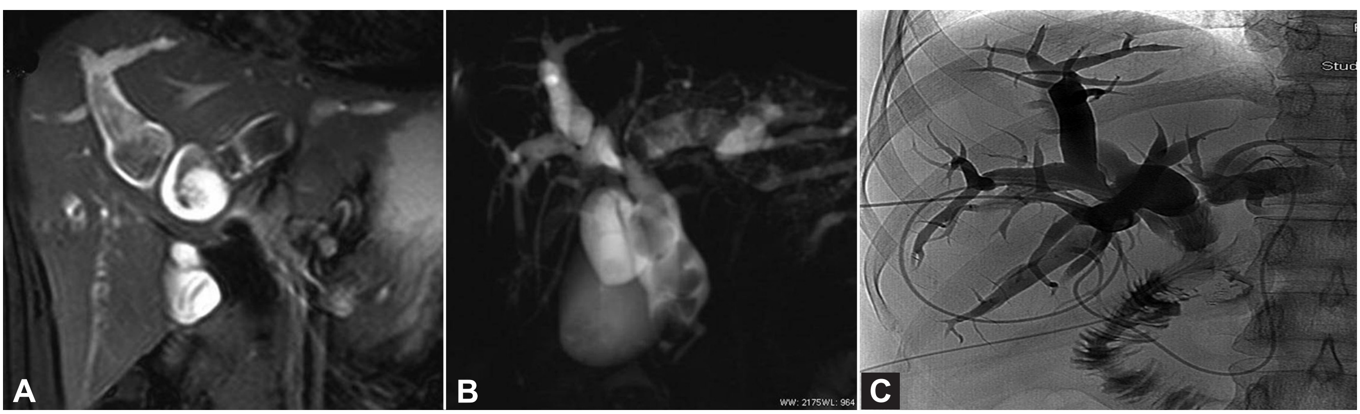


Figure 18. Diffuse bilateral primary intrahepatic lithiasis in a 36-year-old female. **A**) Magnetic resonance cholangiography (MRC) showing multiple bilateral intrahepatic stones. **B**) A choledochal cyst filled with stones is also seen on MRC. **C**) Intraoperative direct cholangiography after left lateral sectionectomy, contralateral cholangiocopic extraction of stones, resection of choledochal cyst, and hepaticojejunostomy (arrow).

the stones.

Liver transplantation should be considered in patients with bilateral PIL complicated with liver fibrosis or cirrhosis.[31,44,72–75] Liver transplantation for PIL is rarely reported and represents only 0.2% of the total liver transplants reported in the European Liver Transplant Registry (ELTR).[31]

In summary, early and late outcomes after hepatectomy for PIL are usually favorable.[16] Depite the high rates of postoperative complications (20% to 44%), mortality rates are typically low (0% to 3.8%), and the rate of stone clearance is high (83% to 100%). Also, the long-term results of liver resection for PIL are encouraging and include low rates of stone and/or cholangitis recurrence. Despite the real incidence of cholangiocarcinoma after liver resection for PIL not being clear, some researchers suggest a lower risk of malignancy after hepatectomy than following other treatments. Therefore, liver resection represents the treatment of choice for hepatolithiasis located in one segment or lobe, associated with biliary stenosis or atrophy. Hepatectomy should also be considered the best treatment for bilateral hepatolithiasis when all affected segments can be safely resected and/or if cholangiocarcinoma is suspected.

ROLE OF HEPATICOJEJUNOSTOMY.

Historically, biliary-enteric anastomosis (choledochoduodenostomy and Roux-en-Y hepaticojejunostomy) was one of the most common procedures performed for PIL in order to facilitate postoperative spontaneous discharge of intrahepatic stones into the jejunum. More recently, the role of hepaticojenunostomy (HJ) in the treatment of PIL has been deeply reconsidered.[76,77] In fact, according to the results reported in recent papers, hepaticojejunostomy is not effective for drainage of residual and recurrent stones and increases the long-term risk of cholangitis. Li et al.[76] reported on a retrospective study of 314 patients who underwent HJ for PIL without biliary stricture or cystic dilation, and concluded that the results of HJ were not satisfactory due to the high rates of residual stones and postoperative cholangitis. Indeed, in patients with biliary-enteric anastomosis, reflux of intestinal contents into the bile duct may occur and cause cholangitis. In another retrospective study, Herman et al.[77] reported a higher rate of late complications when HJ was associated with liver resection.

Furthermore, HJ eliminates the continuity of the common bile duct and precludes further endoscopic procedures for removal of recurrent stones. For this reason, in patients with a high risk of recurrence, such as those with complex bilateral lithiasis, techniques that allow an easy access (percutaneous/endoscopic) to intrahepatic bile ducts have been proposed, including hepaticocutaneous jejunostomy;[78–80] hepatoduodenal anastomosis with an interposed jejunal loop;[42] and latero-lateral anastomosis between the jejunal loop of the HJ and duodenum.[81] However, in a large long-term study, Tocchi et al.[82] found that the biliary tract may have a tendency to develop malignancy following biliary-enteric bypass procedures for benign biliary disease (choledocholithiasis, sphincter of Oddi stenosis and postoperative benign stricture). This indicates that bile duct cancer may be a long-term complication of biliary-enteric anastomosis, probably due to the chronic inflammation of the bile duct. For all of these reasons, HJ is not recommended as a routine treatment for PIL. However, the concomitant presence of choledochal cysts or of extrahepatic bile duct strictures can indicate a need for biliary-enteric anastomosis (**Figure 18**).

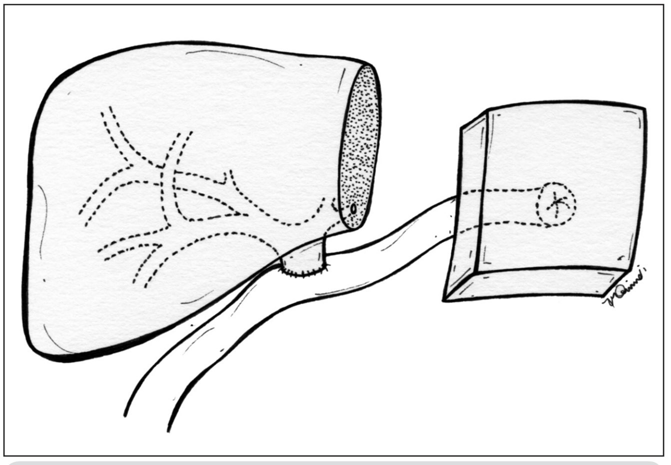


Figure 19. Schematic representation of hepatic resection of left lateral sector associated with hepaticocutaneous jejunostomy (Roux-en-Y) to provide postoperative access for cholangioscopy and residual stone extraction.

NON-SURGICAL APPROACH FOR PIL

Percutaneous and/or endoscopic procedures for hepatolithiasis are useful with patients at high surgical risk and those that refuse surgery. Also, patients that have previously undergone biliary surgery and/or those with diffuse hepatolithiasis can benefit from non-surgical methods. Moreover, initial approach to treat acute cholangitis is use of antibiotics, associated or not with biliary drainage, mainly percutaneous.

Both percutaneous and endoscopic procedures on the treatment of PIL have been widely described in the literature. They are effective for the clearance of bile ducts, but the choice between one of the two accesses depends on location of stones and strictures, presence of associated common bile duct stones, and local expertise.

The role of **endoscopic procedures** in the treatment of hepatolithiasis seems to be more limited than that of percutaneous ones. The treatment of PIL via the transpapillary route may be difficult in many circumstances, particularly in case of tightening strictures, peripheral stone impaction, or acute ductal angulation.[2,6] Okugawa et al.[83] followed, for an average of 93 months, 36 consecutive patients who underwent peroral cholangioscopic lithotomy for PIL. Complete stone removal rate was 64% and stone recurrence rate was 21.7%. Two patients in this study (5.5%) developed intrahepatic cholangiocarcinoma during follow-up. In patients with associated extrahepatic bile duct stones and that will undergo liver resection, ERC can be performed preoperatively to extract stones from the extrahepatic bile ducts. Furthermore, endoscopic approach is the first choice for common bile duct recurrent stones in patients with previous hepatectomy for PIL (**Figure 20**).

Percutaneous approach in the treatment of PIL, by PTBD and PTCS, has been supported since 1981 by Nimura et al.[84] and represents the most effective non-surgical treatment for hepatolithiasis.[85] The possibility of performing selective cannulation of multiple segmental bile ducts has been clearly shown to obtain precise intrahepatic biliary anatomy and complete removal of stones. The size of extractable stones was initially the limiting factor of this approach, but the development and refinement of electrohydraulic and laser lithotripsy has overcome this limitation. Percutaneous transhepatic cholangioscopic lithotomy (PTCSL) is the mainstay for the treatment of recurrent intrahepatic stones.[51]

The presence of **intrahepatic biliary strictures** represents the most debated issue in non-surgical treatment, because it is usually associated with failure in stone clearance and with intrahepatic stone recurrence. Biliary strictures were classified on the basis of feasibility of choledochoscopic removal of stones as: i) no stricture (grade 0); ii) ductal diameter of the strictured site >5 mm (grade 1, mild); iii) ductal diameter of the strictured site between 2 and 5 mm (grade 2, moderate); and iv) ductal diameter of the strictured site <2 mm (grade 3, severe).[86] Biliary strictures can be treated by dilation with balloons, stent placement, or biliary catheter (exchanging the catheter for a bigger one, step by step). Even after dilation and/or stenting of the biliary strictures, the rate of incomplete clearance in patients with intrahepatic duct strictures is higher than in those without strictures. Indeed, Lee et al.[50] performed a follow-up study with 92 patients that underwent percutaneous treatment for PIL and reported a rate of complete stone clearance rate of 58% in patients with bile duct stricture, versus 100% in those without strictures ($P<0.001$). Moreover, rate of stone recurrence in patients with severe strictures was 100%. Similar results were observed by Cheung et al.[87]

Another major concern with non-surgical approaches is the risk of misdiagnosis and inadequate treatment of an eventual associated **cholangiocarcinoma**. Severe biliary stricture should be carefully examined by PTC, and a biopsy is mandatory to exclude a possible association with cholangiocarcinoma. Despite the real incidence of cholangiocarcinoma after non-surgical therapies for PIL beingunclear, it is not negligible in either Eastern or Western countries.[8,10,31,42,53] Cheon et al.[39] reported an incidence of cholangiocarcinoma of 4.9% after non-surgical therapy, reaching 9% if residual stones remain after initial treatment. In a retrospective comparative study, Jan et al.[58] followed up with 427 patients for 4 to 10 years after surgical treatment (n = 380) or PTC treatment (n = 47), and patients who underwent hepatectomy had a significantly lower incidence of cholangiocarcinoma. It has also been reported that resection of cholangiocarcinoma with associated intrahepatic stones has a significantly poorer prognosis than cholangiocarcinoma alone, probably related to delayed diagnosis, lower diagnostic rate, and less radical resection.[54,88] Therefore, in all patients treated for PIL, after surgical or non-surgical treatments, regular follow-up with US and MRI is recommended for early detection of cholangiocarcinoma.

Residual and recurrent stones are the most troublesome problems after non-surgical treatment for hepatolithiasis. Cheon et al.[39] evaluated immediate and long-term results of more than 200 patients who underwent treatment by surgical therapy, PTCS, or peroral cholangioscopy. The rates of complete stone clearance were 83.3%, 63.9%, and 57.1%, respectively. In multivariate analysis, non-surgical treatment and intrahepatic bile duct strictures significantly increased the risk of residual stones after treatment. However, following complete stone clearance, similar rates of intrahepatic stone recurrence and/or cholangitis occurred after hepatectomy with postoperative cholangioscopy, after PTC with lithotripsy,

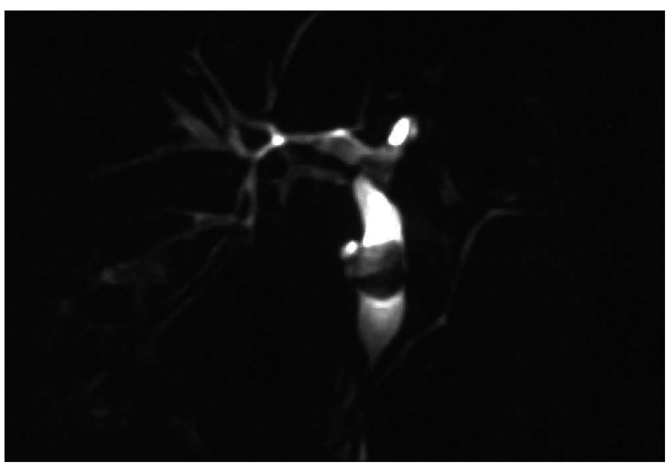


Figure 20. Magnetic resonance cholangiography showing recurrent common bile duct stone two years after a left hepatectomy extended to caudate lobe for primary intrahepatic lithiasis. The stone was removed by endoscopic retrograde cholangiography access.

and after peroral cholangioscopy (18%, 21%, and 25%, respectively).

Extracorporeal shock wave lithotripsy is particularly useful for cholesterol stones, and the use of holmium (Ho) YAG laser for calcium bilirubinate hepatolithiasis has been described with favorable results.[59]

Endoscopic and/or percutaneous approaches should be considered mainly in patients with a poor performance status and in patients with postoperative residual or recurrent hepatolithiasis after surgery.

FINAL CONSIDERATIONS

In summary, the best treatment for primary intrahepatic lithiasis is hepatic resection of the affected segments. Well-defined indications for hepatectomy are unilateral stones associated with strictures and parenchymal atrophy, or suspicion of malignancy. However, localized bilateral disease also seems to be adequately managed by liver resections. Approaching diffuse bilateral disease is challenging, and must be individualized with acceptable therapeutic options, including a combination of the following procedures: hepatic resection of the most affected side, perioperative stone extraction by cholangioscopy, hepaticojejunostomy, hepaticocutaneous jejunostomy, common bile duct T-tube insertion, stricture dilation with balloon or stent or surgical strictureplasty, or even liver transplantation. Regular follow-up is advisable regardless of the approach (surgical or non-surgical) in an attempt to detect an eventual cholangiocarcinoma at an early stage.

SUGGESTED READING

Yang, T. *et al.* Hepatectomy for bilateral primary hepatolithiasis: a cohort study. *Ann. Surg.* **251**, 84–90 (2010).

This large retrospective cohort study compares results of bilateral and unilateral hepatectomy for the treatment of bilateral primary intrahepatic lithiasis and biliary strictures. Long-term results were favorable for bilateral hepatectomy.

Chen, D.-W., Tung-Ping Poon, R., Liu, C.-L., Fan, S.-T. & Wong, J. Immediate and long-term outcomes of hepatectomy for hepatolithiasis. *Surgery* **135**, 386–393 (2004).

A large study including 103 patients with hepatolithiasis who underwent liver resection. Details of early and long-term outcomes are reported and discussed. The presence of cholangiocarcinoma is found as the main factor compromising survival.

Cheon, Y. K., Cho, Y. D., Moon, J. H., Lee, J. S. & Shim, C. S. Evaluation of long-term results and recurrent factors after operative and nonoperative treatment for hepatolithiasis. *Surgery* **146**, 843–853 (2009).

This large retrospective study including 311 patients compares long-term results of surgical, percutaneous, or peroral treatment for hepatolithiasis. Results are favorable to surgical treatment (hepatectomy).

Jarufe, N. *et al.* Anatomic hepatectomy as a definitive treatment for hepatolithiasis: a cohort study. *HPB (Oxford).* **14**, 604–610 (2012).

One of the largest western studies of liver resection for hepatolithiasis (52 patients).

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