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Diagnostic and Therapeutic Challenges of Intrahepatic Biliary Cystadenoma and Cystadenocarcinoma: A Report of 10 Cases and Review of the Literature

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The objective of this study was to present our experience with intrahepatic biliary cystadenomas and cystadenocarcinomas in 10 patients surgically managed in our department. Intrahepatic biliary cystadenomas and cystadenocarcinomas are rare cystic tumors that are often misdiagnosed preoperatively as simple cysts or hydatid cysts. They recur after incomplete resection and entail a risk of malignant transformation to cystadenocarcinoma. A retrospective review was conducted of patients with histologically confirmed intrahepatic biliary cystadenomas and cystadenocarcinomas between August 2004 and February 2013 who were surgically managed in our department. A total of 10 patients, 9 female and 1 male (mean age, 50 years), with cystic liver were reviewed. The size of the cysts ranged between 3.5 and 16 cm (mean, 10.6). Five patients had undergone previous interventions elsewhere and presented with recurrences. Liver resections included 6 hepatectomies, 2 bisegmentectomies, 1 extended right hepatectomy, and 1 enucleation due to the central position and the large size of the lesion. Pathology reports confirmed R0 resections in all cases. All patients were alive after a median follow-up of 6 years (range, 1–10 years), and no recurrence was detected. Intrahepatic biliary cystadenoma and cystadenocarcinoma should be considered in differential diagnosis in patients with liver cystic tumors. Because of the high recurrence rate and difficult accurate preoperative diagnosis, formal liver resection is

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mandatory. Enucleation with free margins is an option and is indicated where resection is impossible.

Key words: Liver cysts – Biliary cystadenoma – Biliary cystadenocarcinoma – Invasive biliary mucinous neoplasm – Liver resection

Intrahepatic biliary cystadenomas (IBCs) are rare biliary cystic tumors and account for approximately 5% of all hepatic cysts. These tumors are regularly benign with the potential for malignant transformation to intrahepatic biliary cystadenocarcinoma (IBCC).[1,2] Although almost 85% to 95% of those affected are women, with the mean age at presentation being 45 years, IBCC is more evenly distributed between males and females and typically presents a decade later.[3] Clinical presentation may vary, and most of the patients are asymptomatic or presenting with nonspecific symptoms as tumors are discovered incidentally during imaging studies, such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI). However, the radiologic features of these complex cystic lesions are nonspecific, whereas calcifications resembling hydatid cysts are depicted in 20%.[4–7] Being misdiagnosed as simple or hydatid cysts, especially in endemic regions, they are often undertreated with aspiration or incomplete resection, or they may be found on pathologic specimens after the unroofing or enucleation of presumed benign cysts. The consequence is recurrence or persistence of the cyst with an impending malignant transformation.[1,8]

With the extensive use of medical imaging the diagnosis is frequently made early in asymptomatic patients, and the prognosis after complete excision is excellent. Thus, IBC and IBCC should be suspected when a single or multilocular liver cystic lesion is diagnosed, and the lesion should always be considered for resection.

This study reviews our center's experience with patients who underwent surgery for intrahepatic cystic tumors. All patients were misdiagnosed during their clinical course and management, with final pathology reports revealing both IBC and IBCC.

Materials and Methods

After obtaining approval from our hospital ethics committee, the records of 10 patients with histologically confirmed IBCs or IBCCs that were surgically managed between August 2004 and February 2013 were retrospectively reviewed.

Mean age was 50 years (range, 41–77 years). A total of 9 patients were female and 1 male, whereas 5 patients included previous liver interventions in their medical history. Data were collected from hospital medical records, pathology reports, and operative case logs, and included patients' characteristics, clinical presentation, and results of imaging studies.

Transabdominal US, CT, and MRI in selected cases were the most commonly used imaging modalities for preoperative evaluation. Laboratory tests on admission included complete blood count, serum biochemistry, tumor and viral markers, and serologic test for hydatid disease. Preoperative percutaneous cyst fluid aspiration was not performed in any patient.

Results

The size of the cysts ranged between 3.5 and 16 cm (mean, 10.6; Table 1). Liver function tests were within normal range in all patients. Hepatitis virus markers were negative in all patients. Serum carcinoembryonic antigen (CEA), carbohydrate antigen (CA 19-9), and alpha fetoprotein had been preoperatively assessed in all patients. CA 19-9 serum levels were mildly elevated in 3 patients with IBC and in 1 patient with IBCC. Two patients with IBC had slightly elevated CEA serum levels (Table 1). Alpha fetoprotein levels were normal in all cases.

Three patients were asymptomatic, and the liver cysts were incidentally discovered during imaging studies for other indications (Fig. 1). In 1 patient, a liver cystic tumor was diagnosed intraoperatively during a pancreatoduodenectomy for a pancreatic cystic tumor. The patient underwent liver resection concurrently, and pathology diagnosis was IBC with simultaneous pancreatic cystadenoma, both with ovarian stroma. One patient with positive indirect hemagglutination test for hydatid disease underwent radical surgery of the cyst, and pathology report additionally revealed IBC (Fig. 2).

Table 1 Patient characteristics and clinical features of 10 cases in this study

Patient no.	Age, y/gender	Symptom	CEA serum level (<5)[a], ng/mL	CA 19-9 serum level (0–37)[a], U/mL	Location/maximum size, cm	Operative procedure	Pathology	Follow-up, y
1	51/F[b]	Abdominal pain	5	25	Left/11	Hepatectomy	IBCC	9
2	55/F[b]	Asymptomatic	6	68	Right/7	Bisegmentectomy	IBC	10
3	77/F	Abdominal pain	2	35	Left/8	Hepatectomy	IBC	10
4	71/M	Asymptomatic	4	56	Left/9	Hepatectomy	IBC	8
5	49/F[b]	RUQ pain	7	34	Right/13	Hepatectomy	IBC	7
6	67/F	Abdominal pain	4	30	Left/9	Hepatectomy	IBC	5
7	71/F[b]	RUQ pain	2	40	Right/16	Extended hepatectomy	IBCC	5
8	68/F[b]	Asymptomatic, diagnosed i.o.	9	34	Right/3.5	Bisegmentectomy	IBC	4
9	70/F	Abdominal pain	5	30	Right/13.5	Hepatectomy	IBC	2
10	71/F	Epigastric pain	4	58	Both lobes/16	Enucleation	IBC	1

i.o., intraoperatively; RUQ, right upper quadrant.
[a]Number in parentheses indicates the normal level/range.
[b]History of previous surgery.

Five patients had undergone previous interventions elsewhere and presented to our clinic with recurrences. One patient had undergone unroofing and partial resection of a hydatid cyst 9 years before presenting at our clinic. The remaining 4 patients received a diagnosis of a simple cyst and had undergone a partial resection of the cystic wall laparoscopically. These patients underwent liver resection in our department, and pathology report revealed IBC in 3 patients and IBCC in 2 patients.

Regarding our perioperative data, 9 of 10 patients had liver resection of the involved segments. The mass was confined to the left lobe in 4 patients and to the right lobe in 5 patients. There were 6 hepatectomies, 2 bisegmentectomies, and 1 extended right hepatectomy. In 1 patient, enucleation of the cyst was carried out because of the central position and the large size of the lesion (bilobed; Fig. 3). There was no perioperative mortality and there were no major postoperative complications. One patient presented with an extrahepatic biloma on the 26th postoperative day, which was successfully treated by percutaneous drainage. Mean postoperative hospital stay was 12 days (range, 5–20 days). Final pathology reports revealed cystadenoma in 5 cases, cystadenoma with mesenchymal (ovarian) stroma in 3 cases, and cystadenocarcinoma in 2 cases (Figs. 4 and 5). Pathology reports confirmed R0 resections in all cases. Neither of the two patients with IBCC presented metastatic disease, and no adjuvant therapy was given. All patients were alive after a median follow-up of 6 years (range, 1–10 years), and no recurrence was detected.

Discussion

Cystadenomas are believed to arise from the biliary epithelium, with approximately 85% of them being located in the intrahepatic portions of the biliary tree.[9–12] IBC was first reported in 1892 by Keen, whereas Willis[13] described the first case of intrahepatic biliary cystadenocarcinoma in 1943. Wheeler and Edmondson[14] later described mesenchymal cystadenomas with an "ovarian-like" stroma that occur exclusively in women. As a result, hepatobiliary cystadenoma was classified based on the presence or absence of mesenchymal stroma. Those without mesenchymal but with hyaline stroma arise in both men and women and exhibit an extremely aggressive clinical course.[15] Regrettably, ovarian-type stroma can sometimes be discontinuous and require considerable sampling for identification.[15,16] These lesions were redefined and classified by the

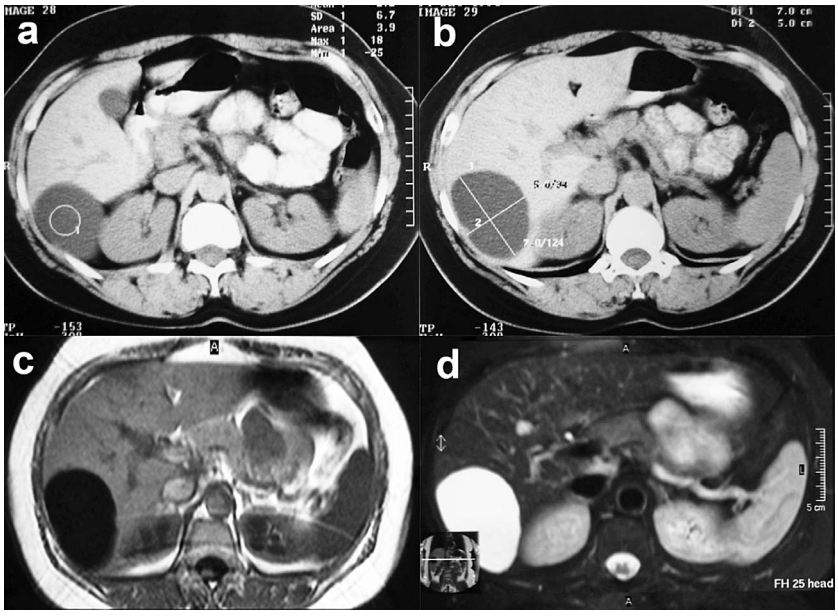

Fig. 1 Imaging study of an asymptomatic patient exhibiting a unilocular thin-walled lesion 7 cm in diameter without discernible upstream bile duct dilatation. There are no internal diaphragms, papillary projections, or solid component. Radiology report described a solitary cystic lesion compatible with simple hepatic cyst. Signal density and intensity are analogous to those expected for a simple hepatic cyst. The lesion proved to be IBC. (a and b) Consecutive 10-mm axial nonenhanced CT slices. (c) Axial nonenhanced T1W MRI. (d) Axial T2W fat-suppressed MRI.

World Health Organization in 2010.[17] They are now referred as mucinous cystic neoplasms, "a cyst forming epithelial neoplasm with no communication with the bile ducts, composed of cuboidal to columnar, variably mucin-producing epithelium, associated with ovarian-type subepithelial stroma." Accordingly, they are subdivided into 3 noninvasive types characterized by low, medium, and high intraepithelial dysplasia, and an invasive type. Because of the current 2010 World Health Organization classification and the requirement for the presence of ovarian-type stroma, the neoplasms without ovarian stroma are now classified as intraductal papillary mucinous neoplasms biliary type with marked cystic changes.[9,17,18] They are characterized by mucin production and prominent intraductal papillary proliferation and occur equally in both sexes, with a mean age of 58 years.[3]

Cystadenoma has a potential for malignant transformation into a cystadenocarcinoma, the invasive type of this lesion, because more than 90% of cystadenocarcinoma samples also have areas of cystadenoma.[19,20] A malignant transformation rate of up to 30% has been reported, and biliary cystadenocarcinoma accounts for 0.41% of malignant hepatic epithelial tumors.[2,13,21–24] Patients are mainly asymptomatic, and once the tumor invades the porta hepatis or compresses the extrahepatic bile duct, obstructive jaundice may be the presenting feature. Painful intracystic hemorrhage, rupture and fever from secondary infection, ascites, retrohepatic vena cava obstruction, and thrombosis have also been reported.[1,25] In addition to simple cysts, the differential diagnosis includes hydatid cysts, liver abscesses, cystic degeneration of a liver neoplasm, Caroli disease, liver abscess, intraductal papillary mucinous neoplasm biliary type, posttraumatic cysts, hemangiomas, microhamartomas, peliosis hepatis, and polycystic liver disease.[8,10,26,27] Moreover, every patient presenting with recurrence of a

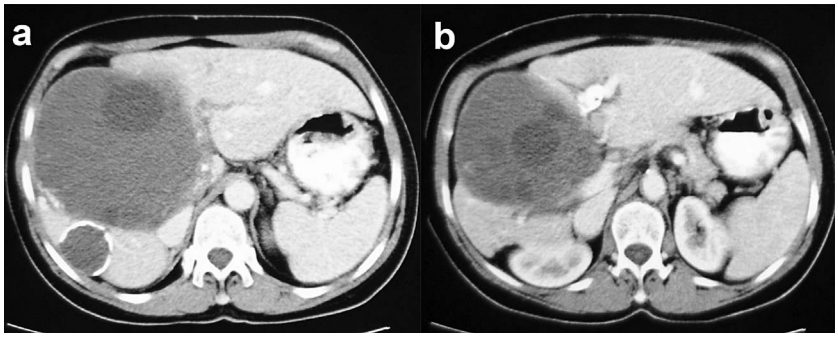

Fig. 2 Imaging study depicting 2 complex cystic liver masses with curvilinear wall calcification (more prominent in the smaller lesion) compatible with echinococcal (hydatid) cysts. In contact with the wall of the larger echinococcal cyst, pathology revealed a small biliary cystadenoma, which is not visible even retrospectively in contrast-enhanced CT. (a and b) Axial contrast-enhanced CT slices.

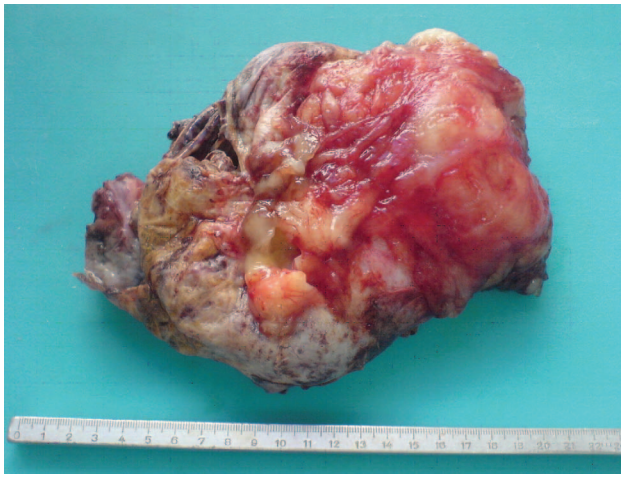

Fig. 3 Gross view of a large multicystic tumor of the liver, measuring 16 × 15 × 6 cm.

liver cyst should be suspected of having a cystadenoma.

So far, no laboratory findings have been specifically assigned to IBC in the literature as the role of serum tumor markers, and cyst fluid analysis remains debatable. Serum tumor markers, such as CA 19-9, may be occasionally elevated in both IBC and IBCC, but the CEA and the alpha fetoprotein levels are usually in the normal range, as in our study (Table 1). Elevated CA 19-9 serum levels could be helpful in the differential diagnosis of simple hepatic cystic lesions, but not between cystadenoma and cystadenocarcinoma, or other cancers originating from the biliary tract.[28] CA 19-9 levels are

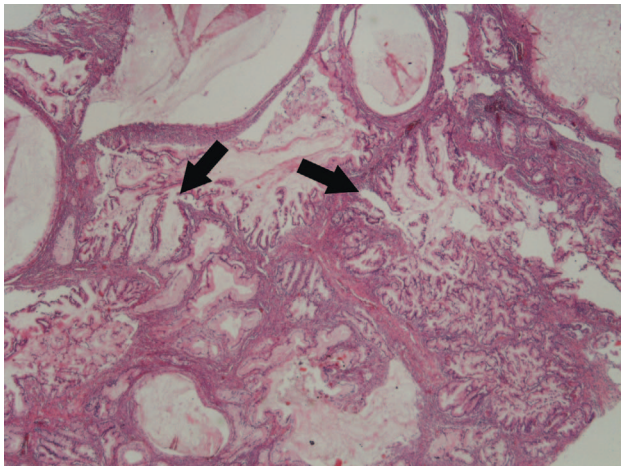

Fig. 4 Hematoxylin-eosin (×25) stained histologic section of the hepatobiliary neoplasm showing complex papillary structures (arrows) in mucus-filled cystic spaces, separated by thin stroma.

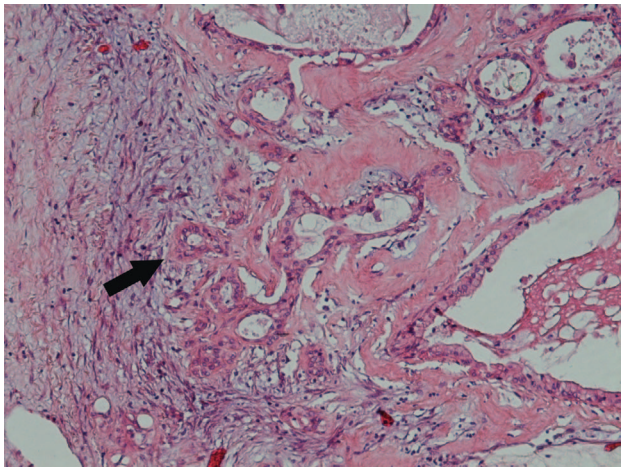

Fig. 5 Hematoxylin-eosin (×120) stained histologic section of the hepatobiliary cystadenocarcinoma showing capsular infiltration by neoplasmatic glands (arrow).

supposed to be a diagnostic and a predictive postoperative tool, particularly of IBC with mesenchymal stroma, because they return to normal levels after complete resection.[10] Even though some centers incorporate cyst fluid CA 19-9 and CEA measurements into their management algorithm, definite diagnostic criteria have not been established because both normal and dramatically increased CA 19-9 and CEA levels may also be detected in patients with simple cysts.[29,30] CA 19-9 and CEA are expressed by normal biliary epithelial cells in bile ducts and gallbladder epithelium. Thus, CA 19-9 and CEA levels cannot accurately differentiate hepatic simple cysts from IBC, and moreover cannot be related to malignant potential. In addition, aspiration cytology does not provide adequate information, and a negative result will give a false sense of security.[13,31,32] In a recent study, Fuks *et al*[33] investigated Tumor-associated glycoprotein 72 (TAG-72) in liver cysts. This study showed that cystic fluid concentration of TAG-72, but not that of CA 19-9 or CEA, can differentiate hepatic simple cysts from IBC, IBCC, or intraductal papillary mucinous neoplasms of the bile duct. The authors conclude that TAG-72 level in cyst fluid is a promising tool for the differential diagnosis of hepatic simple cysts and cystic liver lesions that require complete excision. Until now, both preoperative aspiration cytology and needle biopsy of papillary projections or mural nodules are not generally recommended (separately or together) because of the risk of disseminating tumor cells in case of malignancy and the subsequent develop-

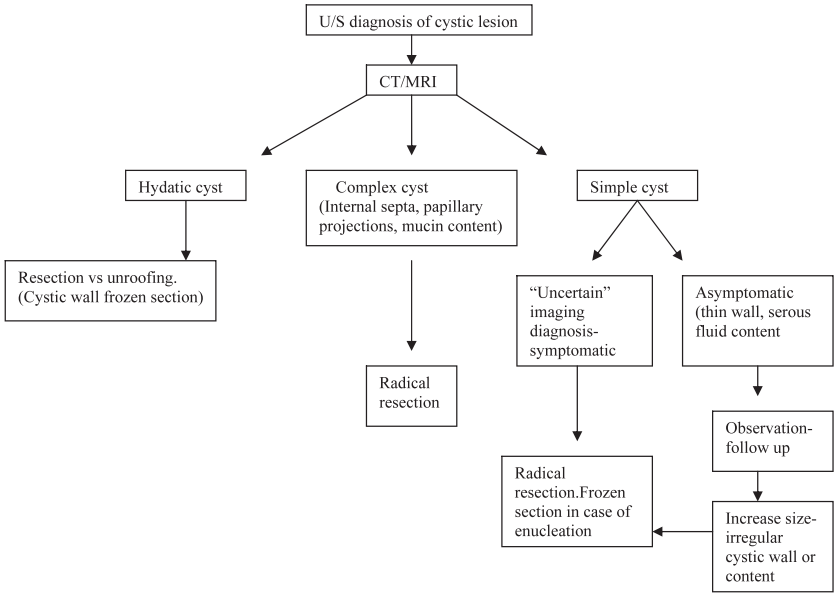

Fig. 6 Algorithm for surgical management of liver cystic tumor.

ment of peritoneal carcinomatosis, pseudomyxoma, or pleural dissemination.[1,10,34,35]

Therefore, preoperative diagnosis of IBC relies heavily on radiologic interpretation, usually by the use of US, CT, and/or MRI. Imaging studies usually reveal a solitary complex cystic mass with internal septa, mural or septal nodules, and papillary projections, which may enhance after intravenous contrast administration. Lesions occasionally show mural or septal calcifications that depict well in CT. In MRI, signal intensity of cystic locules varies depending on blood and mucin content.[36] An extensive solid component and prominent mural nodularity favor malignant tumor; however, benign and malignant lesions cannot be distinguished reliably on the grounds of imaging features. In cases of atypical lesions (unilocular or without solid enhancing nodules), differentiation between cystic neoplasm and simple hepatic cyst may become challenging. In such cases, findings thought to be highly suggestive of cystic neoplasms on cross-sectional imaging are upstream bile duct dilatation and perilesional transient hepatic attenuation differences on contrast-enhanced studies. Because of their viscous proteinaceous fluid, cystic neoplasms exhibit a stronger mass effect compared with simple hepatic cysts containing serous fluid. Both of the above-mentioned imaging findings are believed to be caused by the mass effect and compression of bile ducts and portal branches, respectively.[37] Nevertheless, a preoperative assumption that the lesion is benign based on US, CT, or MRI findings is not safe and therefore not recommended because the preoperative radiologic diagnostic accuracy may be as low as 30% and can frequently lead to misdiagnosis.[6,26,38,39]

Hence, accurate preoperative diagnosis is extremely challenging and is often questionable and confusing. The most important concern in our patients was that they were all misdiagnosed preoperatively as having simple liver cysts or hydatid cysts. If the diagnostic wariness of a hepatic cystadenoma is high, then an appropriate surgical resection has to follow.[1,21,34] Furthermore, simple hepatic cysts can change into IBC and even IBCC with time.[40] Thus, based on imaging techniques a diagnostic algorithm is proposed for evaluation of an incidental hepatic cystic lesion (Fig. 6).

Although formal liver resection of the cystic tumors with clear margins is proposed, a major issue of importance is enucleation of very large centrally placed cysts and/or when blood vessels or bile ducts are invaded. Partial resection is not recommended, and thus every effort should be made for enucleation of the cyst as long as the condition of the patient allows him or her to tolerate the surgery.[28] Frozen section examination of enucleated tumors must be performed because resection of the adjacent parenchyma may follow in cases with positive results. After negative margin resection the prognosis is excellent. Lesser procedures are associated with recurrence rates as high as 90%.[14,41,42] Romagnoli *et al*[43] presented a case of biliary cystadenoma where both enucleation and hepatec-

tomy were not feasible. The authors proceeded with liver transplantation on the 42nd postoperative day after partial resection of the cyst and a complicated postoperative course, considering the low risk of disease recurrence. However, although this was a particular case, because of the ongoing shortage of liver donors, liver transplantation should be saved for selected cases with complete hepatic involvement and poor hepatic reserve where hepatectomy implies high risks.[10,21,43]

As cystic liver neoplasms are diagnosed more frequently, the diagnosis of IBC and IBCC should be considered in any multilocular-multiseptated cystic lesion of the liver, particularly in a middle-aged woman. The challenge is to distinguish these lesions from simple or hydatid cysts, especially in endemic regions, because presenting symptoms, laboratory values, and diagnostic imaging features are unreliable and frequently lead to delayed or incorrect diagnosis and unnecessary procedures. Partial resection is inappropriate, invasive examinations should be avoided, and percutaneous fine-needle aspiration cytology should not be recommended. The recommended treatment of choice is formal liver resection. Enucleation with free margins is an option and is indicated where resection is impossible because of the size and the anatomic location of the tumor and functional liver reserve.

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