Abstract / Povzetek predavanja

Does surgical treatment of benign liver tumors affect the survival and quality of life of patients?

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BACKGROUND

The clinical management of benign liver tumors (BLT) is still subject to controversy, especially with respect to patient selection for surgery. The aim of this retrospective cohort study was to assess the outcomes of laparoscopic liver resection (LLR) for solid BLT.

METHODS

Between April 2008 and December 2024, a retrospective review of a prospectively maintained database of all consecutive patients who underwent LLR at a single tertiary referral center was performed. Study inclusion criteria was solid BLT and these LLR were then analyzed in details. The endpoints of the study were perioperative complications, relief of symptoms and quality of life (QoL).

RESULTS

A total of 277 consecutive patients underwent pure LLR, and 26/277 (9.4%) patients with solid BLT met the study inclusion criteria: 10 patients with hemangioma, 9 patients with focal nodular hyperplasia (FNH) and 7 patients with hepatocellular adenoma (HCA). Median blood loss was 80 (0-700) mL and transfusion were not required (0/26) in any of patients. Overall, 90-day postoperative morbidity (Clavien-Dindo grades from 1-5) occurred in 3/26 patients, with no major morbidity or mortality (Clavien-Dindo grades from 3a-5). The portion of symptomatic patients was 21/26, and among these 18/21 patients reported relief of symptoms and better QoL.

CONCLUSIONS

If patients with solid BLT require surgery, LLR can be carried out with low morbidity and without mortality. Patients with preoperative symptoms show a high rate of postoperative symptom relief.

INTRODUCTION

Benign liver tumors (BLT) such as hemangioma, focal nodular hyperplasia (FNH) and hepatocellular adenoma (HCA) are often found incidentally. In most of the cases, there is no indication for treatment of these benign lesions. However, when patient present with symptoms, such as abdominal pain, tenderness, nausea and tiredness, if malignant transformation is suspected or when the diagnosis remains uncertain, liver resection is sometimes performed (1).

Laparoscopic liver resection (LLR) may be considered a safe alternative to the traditional open hepatic

surgery and the number of these procedures has been increasing worldwide. Three consensus conferences acknowledged the benefits of this approach when experts applied it to selected patients and encouraged its dissemination (2-4). Minimally invasive liver resection is typically associated with faster functional recovery, shorter length of hospital stays and fewer complications, all of which are outcomes that could contribute to an improved quality of life (QoL) after surgery. Moreover, in this group of mostly young female patients, the favorable cosmetic outcomes of laparoscopy make it an appealing alternative to open surgery.

Actually, the majority of LLR in its pioneer era, were for benign diseases. At the time of the first international consensus in Louisville in year 2008, more than 50% of all LLS performed up until that time were for benign tumors. At that time, most of the surgeries (20%) were for liver cysts (not precisely liver resections) or for debatable indications, such as FNH or hemangiomas in 36% of the reported cases (5). Surprisingly, even a more recent survey in 2020 showed very similar results: 43% of the patients underwent laparoscopic surgery for benign liver diseases (6).

The aim of this retrospective, single center study is to provide an overview on indications for surgery, relief of symptoms, QoL and general surgical outcomes after LLR for solid BLT.

METHODS

A retrospective review of a prospectively maintained database of all consecutive patients who underwent LLR at a single tertiary referral center was performed. At this institution, LLR was first undertaken in April 2008 and data were collected until December 2024. Only pure LLR has been done; no hand-assisted or hybrid procedures were performed. Surgical techniques were applied as reported previously (7). Laparoscopic ultrasonography of the liver was mandatory.

Study inclusion criteria was solid BLT and these LLR were then analyzed in details. Study exclusion criteria were as follows: malignant tumors, cystic (parasitic and nonparasitic) lesions, Caroli disease, intrahepatic duct stones and liver trauma.

Patients' demographics, preoperative clinical parameters, operative details, histopathological data, and postoperative outcomes were reviewed from the database and analyzed. Symptoms were defined such as abdominal pain, tenderness, nausea and tiredness. Indications for operation in asymptomatic patients were defined as suspected malignant tumor or uncertain diagnosis. Diagnoses were based on the final pathology. The conversion was defined as the requirement for the laparotomy at any time of the procedure, except for the extraction of the resected specimen. Postoperative 90-day morbidity and mortality were graded according to the Clavien-Dindo classification and based on the most severe complication. All the events classified as grade 3a or higher were considered as major complications.

The primary endpoint of the study were intraoperative (IOC) and postoperative complications (POC). IOC was described as an objective marker of a complex operation and its key markers were blood loss over 775 mL, unintentional damage to the surrounding structures, and conversion to open approach. POC was defined as morbidity according to the Clavien-Dindo classification. Established indicators of a technical difficulty, such as operative time, blood transfusion requirements, the need for the hepatic pedicle clamping and its duration, length of postoperative hospital stay (LOS), and readmission, were used as surrogate endpoints.

The secondary endpoint was to estimate the relief of symptoms and QoL.

RESULTS

A total of 277 consecutive patients underwent pure LLR and 209/277 (75.5%) patients with malignant tumors were excluded. Only 68/277 (24.5%) patients with benign liver lesions were enrolled in the study, and finally 26/277 (9.4%) patients with

solid BLT, accurately hemangioma (10 patients), FNH (9 patients) and HCA (7 patients) met the study inclusion criteria (Figure 1.). The distribution of women/men were 6/10 in the hemangioma, 6/9 in the FNH and 6/7 in the HCA group, respectively. The median age was 47 (41-71) years in the hemangioma, 42 (29-52) years in the FNH and 50 (38-82) years in the HCA group, respectively.

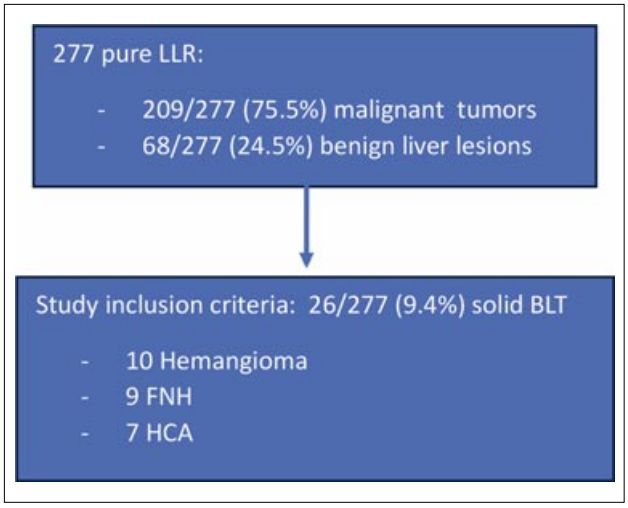

Figure 1. Study inclusion criteria and patient flow. LLR, laparoscopic liver resection; BLT, benign liver tumors; FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma.

Median tumor size was 6,8 (2.0 -18.5) cm, and the majority of BLT (24/26) were located in more accessible anterolateral segments. The majority of LLR (24/26) were minor hepatic resections and 14/26 were anatomical resections in contrast to 12/26 non-anatomical resections.

Median blood loss was 80 (0-700) mL and transfusion were not required (0/26) in any of the patients. Median operative time was 120 (20-240) minutes. Hepatic pedicle clamping was used in 6/26 patients. No IOC was detected with no conversion to open surgery.

Overall, 90-day postoperative morbidity (Clavien-Dindo grades from 1-5) occurred in 3/26 patients. Ninety-day major POC (Clavien-Dindo grades from 3a-5) has not occurred in any of patients. The median LOS was 3 (2-7) days and the readmission rate was 0/26.

The portion of symptomatic patients was 21/26, and among these 18/21 patients reported relief of symptoms and better QoL on follow up. In 5/26 asymptomatic patients the indication of operation was suspected primary liver carcinoma or uncertain diagnosis, but none of these patients' reported occurrence of symptoms on long-term follow up.

DISCUSSION

The present study was designed to investigate on general surgical outcomes, relief of symptoms, and QoL after LLR for solid BLT. The most important findings of this study demonstrated a benefit of minimally invasive surgery in symptomatic patients, which was achieved with no major morbidity or mortality. Besides QoL and relief of symptoms, operative outcomes are essential to determine the place of LLR in the treatment of BLT. In our experience with 26 minimally invasive liver resections for BLT, no patients received a blood transfusion, no conversion to open surgery was necessary and no major morbidity (Clavien-Dindo grades from 3a-5) or mortality were observed.

However, the benefit of resection of BLT remains debatable since there is a lack of randomized data regarding the outcome after surgery (8). The results of the present study clearly suggest a benefit of LLR in BLT, though the lack of comparative analyses with conservative treatment should be kept in mind as these patients are obviously subjected to the risks of an operation that are absent in the conservatively treated group. There is a consensus that the indications for the LLR of BLT, despite the procedure being feasible and safe, should not be expanded in the face of the adoption of a lesser invasive approach (9). The present study demonstrated, that the indications for liver resection had not been overexpanded in the era of minimally invasive liver surgery, since the majority of patients in this series (75.5%) underwent LLR for malignant tumors.

Hepatic hemangioma is the most common benign mesenchymal tumor with an estimated prevalence

of 0.5% to 20%, and it is usually found incidentally during radiological imaging for upper gastrointestinal organs. Most hemangiomas are small in size and asymptomatic, never shows malignant transformation and they are especially prevalent in women. However, giant hemangiomas (diameter > 5 cm) sporadically rupture, cause Kasabach-Merrit syndrome, or cause abdominal complaints. In these extremely rare circumstances, resection of larger hemangiomas is warranted (10).

In our experience, the median size of resected hemangiomas in 10 patients was 8.5 (2-12.5) cm, and the main indications were abdominal pain (seven patients) and misdiagnosis of suspected malignancy (three patients). Of note, in the whole study group, three patients did not report relief of symptoms and all of them had giant hemangiomas in the right side of the liver.

FNH is the second most common BLT, generally diagnosed incidentally during an abdominal imaging, usually affects women between 30 and 50 years of age, and its incidence is not influenced by the use of oral contraceptives. It is characterized by the presence of a well delineated hypervascular mass with fibrous septa and a central stellate nonenhancing scar. FNH represents a hyperplastic response to an arteriovenous malformation, being more common in young women, although up to 10% of cases may be in men. FNH never shows malignant transformation and is extremely rarely complicated by bleeding or rupture. However, large FNH tumors may be difficult to distinguish from HCA in imaging studies. If the diagnosis remains uncertain after biopsy, or severe complications are present, surgery for these tumors is sometimes justified (11).

In our experience, we resected 9 FNHs, with 4 misdiagnosed as HCA and 1 as hepatocellular carcinoma (5 misdiagnoses). The remaining 4 patients underwent LLR due to a large left lateral section tumor leading to gastric compression symptoms.

In patients diagnosed with HCA, surgery is generally accepted as treatment of choice, for lesions larger than 5 cm, because they may bleed and rupture in approximately 25% of the patients, or may evolve into hepatocellular carcinoma in 5% of the patients. The estimated incidence of HCA is one per one million inhabitants, rising to 30–40 per million in long-term oral contraceptive users. The association with glycogen storage diseases, the use of anabolic steroids, obesity, and metabolic syndromes is also well-established. HCA is typically occurring in young women of childbearing age and promoted by oral contraception. HCA is most often asymptomatic and is frequently found incidentally during radiological imaging for unrelated causes (12).

Malignant transformation and hemorrhage are the main complications of HCA. Based on the genetic and phenotypic characteristics different molecular subtypes have been described: HNF1A-inactivated HCA, inflammatory HCA, β-catenin-mutated HCA exon 3, β-catenin-mutated HCA exon 37 or 8, sonic hedgehog HCA and unclassified HCA. Malignant transformation of HCA is more frequent in males and in β-catenin mutated HCA exon 3. Tumor size and sonic hedgehog HCA are risk factors in tumor bleeding (13).

The new classification with several LCA subtypes shows the complexity and heterogeneity of the disease. However, from a practical point of view, it is not useful since a complex molecular process to identify all subtypes is necessary. Moreover, the whole adenoma specimen is needed for precise evaluation. For these reasons, this classification is not yet fully applicable in daily practice.

The new knowledge of the molecular profile and its impact on clinical behavior led to changes in the diagnosis and treatment of this challenging disease. In daily practice, the diagnosis of HCA subtypes is based on MRI findings whose capacity to distinguish different HCA subtypes (especially steatotic and inflammatory HCA) is well-established. In cases of doubt, a percutaneous biopsy can be

performed. Currently, resection should be recommended for all adenomas affecting men and for nonsteatotic adenomas larger than 5 cm, after 6–12 months of oral contraceptive interruption and weight loss, in women (14).

In our experience, 7 patients with HCA of median size 5.0 (3-7.5) cm underwent elective minor LLR. The open approach was employed for the resection of larger and ruptured tumors, but these patients were not included in this study.

The present study is associated with certain limitations. The first involves its cohort size. Although the study included 277 patients, the number was relatively low when the patients were divided into subgroups, and especially reflected by the low number and rate (9.4%) of LLRs in the solid BLT group. The limited number of patients who underwent surgery for benign lesions provides clear evidence that, despite the study spanning a substantial period of 16 years, the range of indications for LLR has not been expanded solely on the basis of its minimally invasive nature. However, the small sample size precludes robust statistical analysis. Second, open resections for solid BLT were not included. Third, the lack of a control group receiving conservative treatment.

In conclusion, LLS for solid BLT is feasible and safe and can relieve symptoms in the majority of symptomatic, selected patients. Each BLT has a specific and restrictive indication for resection. These indications are usually due to the presence of symptoms that impact the QoL or the risk of complications, such as malignant degeneration or rupture and bleeding. Before considering the surgical indication, a multidisciplinary case discussion is recommended not only to confirm the diagnostic hypothesis or the eventual need for a biopsy but also to establish the best therapeutic approach.

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