Review Article

Hepatic adenoma: indications for minimally invasive resection

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Abstract: Hepatic adenoma (HA) is a rare benign disease. Only selected patients require a liver resection: all male patients; female patients with a progressively enlarging nodule or HA >5 cm or β-catenin mutated tumors (especially if β-catenin mutated HA exon 3); symptomatic patients. We performed a review of the literature to analyze the indications and the results of a laparoscopic resection in patients with HA. The number of minimally invasive resections performed for HA reported in the literature has progressively increased in the most recent years. Laparoscopic resection of HA is safe and feasible and carries the same advantages of minimally invasive liver surgery for other diseases. The minimally invasive approach is standard for HA requiring limited resection of antero-lateral segments or left lateral sectionectomy. Laparoscopic complex resections for HA have been reported, but they are still under evaluation and should be reserved to high-volume centers with adequate expertise. A three-step decisional process should be respected. The surgeon should evaluate: firstly, if the patient needs surgery; secondly, which resection is appropriate; thirdly, if a laparoscopic approach is suitable in his/her center. The possibility to perform a laparoscopic resection for HA should not widen indications or modify surgical strategy. Furthermore, the surgeon's awareness of his/her expertise and learning curve and that of the entire teams' capabilities is paramount to increase patient safety and optimize outcomes.

Keywords: Hepatic adenoma; hepatic benign tumor; indication to resection; laparoscopic liver resection; conversion and postoperative morbidity; review and guidelines

Received: 04 August 2019; Accepted: 23 August 2019; Published: 27 August 2019.
doi: 10.21037/ls.2019.08.03
View this article at: http://dx.doi.org/10.21037/ls.2019.08.03

Introduction

Hepatic adenoma (HA), also known as hepatocellular adenoma, is a benign tumor of the epithelial cells of the liver. Although it is benign, HA has a risk of malignant transformation as well as hemorrhagic complications (1). It is relatively uncommon with the incidence being 1/1,000,000 and it affects more women than men with a ratio of approximately 10:1. HA is usually hormonally-induced and therefore strongly associated with the use of oral contraceptive pills in female patients and anabolic steroids in males. Recent evidences have associated HA with obesity and metabolic syndrome (2,3).

During the last 15 years, laparoscopic liver surgery has had a wide diffusion thanks to the standardization of the technique and its reported benefits (4,5). As compared to open liver resection, laparoscopic liver surgery has been associated with lower blood loss, shorter hospital-stay, and faster postoperative recovery (4). To date, the laparoscopic approach is standard for small lesions (<5 cm) in the antero-lateral segments, while it is still under evaluation for major hepatectomies and resection of postero-superior segments

(6,7). Nevertheless, the scenario is rapidly evolving and HPB referral centers perform 15% to 30% of liver resections using a minimally invasive approach (8-10). This can reach 50–80% in some centers (8,11).

Patients with benign tumors of the liver are the ideal candidates for laparoscopic surgery for different reasons: firstly, they do not need a safety resection margin or any lymph-node dissection; secondly, benign diseases are often diagnosed in young people who are mainly concerned about cosmetic results. Nevertheless, not all the HA should be removed as only some of them are at risk for complications (hemorrhage/malignant transformation). The present review aims to analyze the indications and the results of a laparoscopic resection in patients with HA.

Methods

A systematic search of PubMed, Science Citation Index, and Embase databases was performed for articles published before May 2019 relevant to laparoscopic resection of hepatic adenoma. English language articles were selected using the keywords 'hepatic adenoma', 'hepatocellular adenoma', 'hepatic benign tumor', 'laparoscopic hepatectomy', 'laparoscopic liver surgery', and 'laparoscopic liver resection' to identify all reports that may pertain to the review issue. Manual cross-referencing was performed, and relevant references from selected papers were reviewed. Case reports were excluded.

Results

After the literature review, 7 manuscripts, specifically focused on HA and their minimally invasive resection, were identified (12-18). Additional data have been extracted from a review about HA management (19) or from papers about benign solid tumors and laparoscopic liver resection that also considered some HA (20-26).

Which adenoma should be resected?

HA is usually asymptomatic and is discovered incidentally on routine imaging such as ultrasonography in most patients (1). Patients with a diagnosis of HA should be accurately evaluated to exclude any sign of current malignant disease, namely hepatocellular carcinoma, and to elucidate the risk of later bleeding and of malignant transformation. Several classifications of HA have been proposed to accomplish this aim and, consequently, to identify patients that should undergo liver surgery. The latest one has been proposed by Nault *et al.* on the basis of an extended molecular analysis of more than 500 HA (27). Six different types of HA were identified: HNF1A inactivated HA, Inflammatory HA, β-catenin mutated HA exon 3, β-catenin mutated HA exon 7/8, sonic hedgehog HA and unclassified HA. β-catenin mutated HA exon 3 has been associated with a high risk of malignant transformation, while sonic hedgehog HA has been associated with a high risk of bleeding. How can this molecular classification be translated into clinical practice? HNF1A inactivated HA can be diagnosed by magnetic resonance imaging, while, in the remaining cases, a liver biopsy could identify mutations at risk for complications (3). However, this is not yet the standard and clinical data still drive current practice. First, the risk of malignant transformation is persistently high in all HA in male patients. Second, large HA size (>5 cm) is associated with an increased risk for both malignancy and bleeding. Accordingly, EASL proposed a very practical and easy-to-apply flowchart for HA management (1). Three main parameters determine treatment, i.e., sex, HA size, and β-catenin mutation. Liver resection is recommended in all male patients, irrespective of the HA size. In women, the first step is lifestyle change and re-evaluation after 6 months. If the HA increases in size or is stable and >5 cm, resection is indicated. If not (HA regression or stable and <5 cm), follow-up is adequate. Liver biopsy is not recommended, but if it is performed and identifies a β-catenin mutated HA, especially if exon 3 is mutated, surgery should be considered, independently of the HA size. Finally, liver resection is indicated in symptomatic patients or in patients with non-conclusive diagnosis of benign disease and suspicion of malignant tumor.

An additional clinical scenario should be considered, i.e., a liver adenomatosis (>10 HA). The term adenomatosis has now been replaced by "multiple HA". Management of such patients is complex: an adequate follow-up of all tumors can be difficult to perform and the resection of all HA can require complex procedures that carry significant risks or can even be impossible to perform. Some patients with multiple HA have been scheduled for transplantation. Present EASL guidelines recommend a more cautious stepwise approach: (I) resection of HA >5 cm, (II) resection of any lesion suspected of malignant transformation and (III) follow-up of the remaining lesions (1).

Which hepatic adenoma can be resected by laparoscopy?

The first laparoscopic left lateral sectionectomy, that was also the first anatomic hepatectomy performed by laparoscopy, has been reported in 1996 by Azagra *et al.* for a symptomatic HA (28). During the last decade, the proportion of HA undergoing laparoscopic resection has progressively increased (13-15,17,18), as the proportion of all liver tumors also increased (4). The most recent series reported a laparoscopic approach in about 40–50% of resections for HA (17,18). The large tumor size (>5 cm in most patients) probably limited a further diffusion. It is not possible to identify specific indications for minimally invasive liver surgery for HA because very few papers have focused on this topic. The available series mostly included patients with single tumors and HA having a median size that ranges from 50 to 85 mm. Most procedures were minor hepatectomies, even if some major liver resections have been reported in the more recent series. Interestingly, some authors highlighted the possibility of using a laparoscopic approach even in patients with so-called "hemorrhagic HA", i.e., HA having had a hemorrhagic complication in their history (18).

The indications of a minimally invasive approach for HA mainly rely on technical considerations. A laparoscopic approach is standard for limited resections of antero-lateral segments and left lateral sectionectomy, especially in the presence of small tumors (6,7). HA requiring such resections should be routinely considered for a laparoscopic resection, even if their size (usually >5 cm) could be a limitation. Limited resections of postero-superior segments (segments 7, 8 and 4 s) and segment 1 are more difficult to perform, as are major hepatectomies. However, high-volume centers reported feasibility and safety of such complex procedures with excellent outcomes (29-31).

The type of resection is not *per se* sufficient to predict the difficulty of laparoscopic liver surgery. Additional data should be considered, such as the tumor size and its proximity to major intrahepatic vessels (32). Those parameters together with the scheduled resection have been included in the Ban *et al.* score (32). The authors identified three different classes of laparoscopic liver resections that require progressively increasing surgical expertise. The most complex procedures are the less standardized ones and, if performed by non-adequately trained surgeons, are at risk for intraoperative problems, namely bleedings and postoperative severe complications. Halls *et al.* demonstrated that an emergency conversion of laparoscopic liver resection because of an unfavorable intraoperative event is associated with poor outcomes, even with non-negligible mortality risk (33). Every surgeon should be aware of his/her proper expertise and of the skills of the entire team (surgeons, anesthesiologists, and nurses). Adequate training in both laparoscopic and liver surgery is mandatory to approach any laparoscopic liver resection (7,34) and the learning curve should be completed before facing the most complex procedures (35). These rules must be respected even if HA is a benign disease mainly of young patients.

Does a laparoscopic approach modify indications?

Many patients with HA do not need a liver resection and should be scheduled for a simple follow-up by annual imaging (1). However, lifelong follow-up is quite demanding, especially considering that HA is often diagnosed in young people, who may have low compliance to follow-up protocols in the long term. The laparoscopic approach achieved excellent safety and outcome, including cosmetic outcomes, with a very quick return to normal life (4). Those results led some authors to propose an upfront resection of all easy-to-remove HA to prevent costs and discomfort of follow-up, and to prevent any future risk (36). In the literature, it is evident that surgeons adopted widened indications to resection in patients with benign tumors suitable for laparoscopic surgery. Benign tumors are a rare indication to surgery in HPB centers, but they represent a consistent part of laparoscopic hepatectomies. Ciria *et al.* reviewed approximately 9,000 laparoscopic liver resections published before July 2014: more than one-third of procedures were performed for benign tumors (4). In the I Go MILS (Italian Group of Minimally Invasive Liver Surgery) prospective registry, 1,678 minimally invasive liver resections have been performed between 2014 and 2017 of which 22% were for benign tumors (8). Toro *et al.* reviewed all the manuscripts reporting resections of benign liver tumors between 1971 and 2010. Even if the whole number of resections for HA (open and laparoscopic) progressively decreased, the number of laparoscopic resections constantly increased (25). These data most likely reflect an inappropriate widening of surgical indications justified by the minimally invasive

approach.

The first consensus conference about laparoscopic liver surgery held in Lousville in 2009 immediately addressed this point (34). The scientific committee had to answer the following question: "Should indications for resection of asymptomatic benign hepatic lesions be widened?". The experts clearly stated that the possibility to perform a laparoscopic resection should not modify the indications to resect a benign tumor. Hypothetical benefits from HA resection do not outweigh the actual surgical risks when we are out of standard indications.

Results of minimally invasive surgery for hepatocellular adenoma

Very few analyses specifically considered laparoscopic resection of HA. Little additional data can be extrapolated from large series of laparoscopic liver resection of benign tumors that included some HA, but rarely reported specific data. *Table 1* summarizes the largest available series. About 600 laparoscopic liver resections for HA have been analyzed, the two largest series collecting two-third of patients through multicenter analyses and only 7 series reporting more than 10 patients. Conversion rates range from 0 to 18%. Operative time was short and blood loss was low in all series.

Mortality was nil. Severe morbidity ranges from 0 to 12%, the highest values being observed in patients with hemorrhagic HA (18). The largest series consistently reported an overall morbidity rate of 22–24% and a severe morbidity rate of 5%. Transfusion rates were nil in most series, and 4% in the multicenter series by Landi *et al.* (17). The hospital stay was short (median 5 days).

Five studies compared the outcome of open and laparoscopic resections for HA (13-15,17,18). All were retrospective analyses. Only one study used a propensity score analysis to match open and laparoscopic patients (17). In the analysis of Biezel *et al.*, the laparoscopic group had shorter operative time (100 *vs.* 170 min in the open group) and shorter hospital stay (5 *vs.* 7 days) (13). Cho *et al.* reported the following advantages in the laparoscopic group: shorter hospital stay (3 *vs.* 7 days in the open group), lower blood loss (69 *vs.* 305 mL), and lower RBC units transfused (0 *vs.* 2.5) (14). de'Angelis *et al.* did not show any significant difference between groups, except for a lower rate of pedicle clamping in the laparoscopic group (28% *vs.* 58% in the open group) (15). The study by Laurent *et al.* distinguished hemorrhagic and non-hemorrhagic HA (18). In both types of HA, the laparoscopic group had lower bleeding (hemorrhagic HA: transfusion rate 0 *vs.* 16% in the open group; non-hemorrhagic HA: blood loss 130 *vs.* 310 mL, respectively) and shorter hospital stay (5 *vs.* 8 days; 4 *vs.* 7 days, respectively). In non-hemorrhagic HA, the laparoscopic group had lower overall and severe postoperative morbidity rates (23% *vs.* 47% in the open group; and 4% *vs.* 11%, respectively), while, in hemorrhagic HA, the two groups had similar complications rate. Finally, Landi *et al.*, who adopted a propensity score matching, reported similar operative time, overall morbidity rate, and severe morbidity rate in laparoscopic and open group, but observed lower blood loss (93 *vs.* 196 mL), lower transfusion rate (8 *vs.* 24 RBC units transfused), and shorter hospital stay (5 *vs.* 7 days) in the laparoscopic group (17).

Some final considerations

HA is a rare benign disease. Only selected patients require a liver resection: male patients; female patients with progressively enlarging nodule or HA >5 cm or a β-catenin mutated tumor (especially if β-catenin mutated HA exon 3); symptomatic patients. The number of minimally invasive resections performed for HA reported in the literature has progressively increased in the most recent years. Laparoscopic resection of HA is safe and feasible and carries the same advantages of minimally invasive liver surgery for other diseases. The minimally invasive approach is standard for HA requiring limited resections of antero-lateral segments or left lateral sectionectomy. Laparoscopic complex resections for HA have been reported, but they are still under evaluation and should be reserved for high-volume centers with adequate expertise. A three-step decisional process should be respected. The surgeon should evaluate: firstly, if the patient needs surgery; secondly, which resection is appropriate; thirdly, if a laparoscopic approach is suitable in his/her center. The possibility of performing a laparoscopic resection for HA should not widen indications or modify surgical strategy. Furthermore, the surgeon's awareness of his/her expertise and learning curve and that of the entire teams' capabilities is paramount to increase patient safety and optimize outcomes.

Table 1 Data from the largest available series of laparoscopic resection of HA

First author	Year	#	Tumor size, mm*	Major hepatectomy	Conversion	Operative time, min*	Blood loss, mL*	Blood transfusion	Mortality	Overall morbidity	Severe morbidity±	Hospital stay, days*
Katkhouda (24)	1999	9	NA	0	1 [11%]	NA	NA	NA	0	0	0	NA
Descottes (22)	2003	17	NA	0	1 [6%]	NA	NA	1 [6%]	0	2 [12%]	0	NA
Ardito (21)	2007	7	NA	NA	1 [14%]	NA	NA	NA	0	NA	NA	NA
Cho (14)	2008	9 (4 hand-assisted)	NA	1 [11%]	0	NA	69 [0–150]	0	0	0	0	3 [1–7]
Troisi (26)	2008	11	NA	NA	2 [18%]	NA	NA	NA	NA	NA	NA	NA
Abu Hilal (12)	2011	15	85 [25–180]	NA	0	270 [135–360]	500 [100–2,000]	1 [7%]	0	1 [7%]	1 [7%]	4 [1–18]
Herman (16)	2012	31	75 [30–140]	3 [10%]	0	NA	NA	0	0	1 [3%]	1 [3%]	3.8 [1–15]
de'Angelis (15)	2014	36	50.5 [25–130]	9 [25%]	3 [8%]	165 [90–390]	200 [50–1,600]	0	0	3 [8%]	3 [8%]	7.5 [3–26]
Bieze (13)	2014	5	84 [60–110]	0	0	100 [69–144]	NA	NA	0	3 [60%]	0	5 [2–7]
Laurent (18)	2016	26 Hemorrhagic	NA	NA	NA	NA	NA	0	0	10 [38%]	3 [12%]	5 [2–10]
		182 Non–hemorrhagic	NA	13 [7%]	NA	132 [83–510]	130 [50–560]	NA	0	41 [23%]	7 [4%]	4 [2–6]
Landi (17)	2017	208	60 [40–82]	20 [10%]	13[6%]	149 [113–230]	93 [50–271]	8 [RBC units]	0	50 [24%]	10 [5%]	5 [4–7]

*Values are expressed as median [range] except for Herman *et al.* that reported mean [range] and Landi *et al.* who reported median [interquartile range]; ± Grade ≥3 complications according to the Clavien-Dindo classification; NA, not available; RBC, red blood cells.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Francesco Ardito) for the series "The Role of Minimally Invasive Liver Surgery to Treat Hepatic Benign Disease" published in *Laparoscopic Surgery*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ls.2019.08.03). The series "The Role of Minimally Invasive Liver Surgery to Treat Hepatic Benign Disease" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/ls.2019.08.03
Cite this article as: Viganò L, Elamin A, Costa G. Hepatic adenoma: indications for minimally invasive resection. Laparosc Surg 2019;3:38.

