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Στη σύζυγό μου Ευγενία
και στην κόρη μας Μαριέττα.

POSTGRADUATE PROGRAM:
“MINIMALLY INVASIVE SURGERY
ROBOTIC SURGERY & TELESURGERY”

NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

MEDICAL SCHOOL

MASTER THESIS

THE USE OF ROBOTICS IN SURGERY OF BENIGN LIVER DISEASES:

A SYSTEMATIC REVIEW

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Περίληψη

Εισαγωγή/Σκοπός: Η χειρουργική θεραπεία των καλοηθών ηπατικών νόσων (Benign Liver Diseases, BLD) αποτελεί πεδίο αντιπαράθεσης, εξαιτίας του αυξημένου κινδύνου και του υψηλού ποσοστού επιπλοκών. Ωστόσο, η εισαγωγή της ελάχιστα επεμβατικής χειρουργικής (Minimally Invasive Surgery, MIS) έχει αυξήσει τον αριθμό των ασθενών με BLD που αντιμετωπίζονται χειρουργικά, με παρόμοια αποτελέσματα και λιγότερες επιπλοκές. Η τρέχουσα βιβλιογραφία υποστηρίζει την εφαρμογή της λαπαροσκοπικής (Laparoscopic Surgery, LS) και της ρομποτικής χειρουργικής (Robotic Surgery, RS) στη χειρουργική αντιμετώπιση ηπατικών κακοηθειών, όμως δεν υπάρχουν επαρκή δεδομένα σχετικά με την εφαρμογή της ρομποτικής χειρουργικής στις BLD. Στην παρούσα συστηματική ανασκόπηση, στοχεύσαμε στην αξιολόγηση της εφαρμογής της RS στη χειρουργική αντιμετώπιση των BLD.

Υλικό και Μέθοδος: Κατόπιν διεξοδικής έρευνας στις βάσεις δεδομένων Medline, Scopus και Cochrane , καταλήξαμε σε 12 μελέτες που πληρούσαν τις προϋποθέσεις εφαρμογής της RS σε BLD[1] : ο συνολικός αριθμός ασθενών ήταν 115.

Αποτελέσματα: Εν συντομία, η RS φαίνεται να είναι μια ασφαλής και εφικτή επιλογή για χειρουργική επέμβαση BLD. Σε σύγκριση με την ανοιχτή χειρουργική επέμβαση, η RS σχετίζεται με χαμηλότερη απώλεια αίματος, μικρότερη χρονική διάρκεια και μικρότερο ποσοστό επιπλοκών. Όσον αφορά τη LS, τα περι- και μετεγχειρητικά αποτελέσματα ήταν παρόμοια, αλλά η RS μπορεί να ξεπεράσει τους τεχνικούς περιορισμούς της LS. Ωστόσο, το κόστος της RS παραμένει ένα σημαντικό μειονέκτημα στην ευρεία εφαρμογή της.

Συμπέρασμα: Λαμβάνοντας υπόψη τα ευρήματά μας, η RS μπορεί να είναι μια ασφαλής και εφικτή επιλογή για χειρουργική αντιμετώπιση BLD, αλλά απαιτούνται περαιτέρω μελέτες για να δικαιολογήσουν την εισαγωγή της RS στη χειρουργική του ήπατος καθώς και να καθοριστεί το είδος των ασθενών που θα ωφεληθούν περισσότερο από αυτήν.

Λέξεις Κλειδιά:
Ρομποτική χειρουργική, καλοήθεις ηπατικές παθήσεις, χειρουργική επέμβαση ήπατος, αποτελέσματα

Abstract

Background. Surgical treatment of benign liver diseases (BLD) remains a field of conflict, due to increased risk and high complication rate. However, the introduction of minimally invasive surgery (MIS), has led to increased number of patients with BLD being treated surgically, with similar outcomes and fewer complications. Current data support the application of laparoscopic surgery (LS) and robotic surgery (RS) in surgical treatment of liver malignancies, but there are insufficient data concerning the application of robotic surgery in BLD. In the present systematic review, we aimed to evaluate the application of RS in BLD surgery.

Methods. After a thorough search of Medline, Scopus and Cochrane library 12 studies were considered eligible with a total number of 115 patients with BLD[1].

Discussion**.** In brief, RS appears to be a safe and feasible option for BLD surgery. When compared to open surgery, RS is associated with lower blood loss, shorter length of stay and fewer complication rate. Regarding LS, the peri- and post-operative outcomes were similar, but RS can overcome the technical limitations of LS. However, the cost of RS remains a major drawback in its widespread application.

Conclusions. Considering our findings, RS can be a safe and feasible option for BLD surgery, but further studies are needed to justify the introduction of RS in liver surgery and to define the type of patients that will benefit the most from it.

Key Words:
robotic surgery, benign liver diseases, liver surgery, outcomes

Ευχαριστίες

Η παρούσα διπλωματική εργασία εκπονήθηκε στα πλαίσια του Προγράμματος Μεταπτυχιακών Σπουδών (Π.Μ.Σ.) «Ελάχιστα Επεμβατική Χειρουργική, Ρομποτική Χειρουργική και Τηλεχειρουργική» του Τμήματος Ιατρικής του Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών. Με την ολοκλήρωση της συγκεκριμένης εργασίας, οφείλω να ευχαριστήσω τους διδάσκοντες του Προγράμματος καθώς και το προσωπικό του Εργαστηρίου Πειραματικής Χειρουργικής και Χειρουργικής Έρευνας «Ν.Σ. Χρηστέας» για τη δυνατότητα που μου δόθηκε να διευρύνω το επιστημονικό μου υπόβαθρο και να εξελίξω τις χειρουργικές μου δεξιότητες στην Ελάχιστα Επεμβατική Χειρουργική.

Θα ήθελα να ευχαριστήσω ιδιαιτέρως το Διευθυντή του Π.Μ.Σ. Καθηγητή Νικόλαο Νικητέα, τον Αναπληρωτή Καθηγητή και επιβλέποντα της εργασίας κ. Δημήτριο Δημητρούλη, τον Επίκουρο Καθηγητή Γεράσιμο Τσουρούφλη και το Συντονιστή του Π.Μ.Σ. κ. Ελευθέριο Σπάρταλη για την καθοδήγησή τους στην αποπεράτωση της διπλωματικής μου εργασίας.

Επιπλέον, ευχαριστώ τη Γραμματεία του Π.Μ.Σ., και συγκεκριμένα τις κυρίες Λαμπρινή Κώνσταντου και Μαρία Παναγιωτακοπούλου για την υποστήριξή τους.

Ιδιαίτερες ευχαριστίες οφείλω στον κ Νικόλαο Μαμάκο για τη συμβολή του στο ερευνητικό και συγγραφικό μέρος της εργασίας αυτής. Από καρδιάς του εύχομαι καλή σταδιοδρομία καθώς στο εγγύς μέλλον θα δώσει τον Όρκο των Πτυχιούχων της Ιατρικής Σχολής.

Τέλος, ένα μεγάλο ευχαριστώ στην οικογένειά μου για τη στήριξη, τη βοήθεια και κυρίως για τη μακρόχρονη υπομονή τους.

Contents

Introduction

Benign liver diseases are common, and account up to 57% of liver lesions detected by ultrasound and might require surgical treatment [2]. The original approach of open liver surgery was associated with increased complications and mortality, which lead to the introduction of minimally invasive surgery (MIS) in liver surgery [3]. MIS is also associated with reduced blood loss and allows better sparring of liver parenchyma [4]. The first MIS technique applied in liver surgery was laparoscopic surgery (LS) in 1993 [5]. LS has shown to be effective in liver surgery with fewer complications and equal outcome compared to open surgery [6]. Despite its efficacy, LS in not widely used, due to limited experience of surgeons on this technique. In addition, there are several technical limitations that restrict the wide application of LS in BLD surgery, with difficulty in approaching posterosuperior segments being the most important [7]. In addition, amplification of hand tremor, 2-dimensional view, steep learning curve and reduced mobility are further limiting widespread use of LS in liver surgery [7]. Technological advances have led to the development or robotic surgery (RS), as a MIS technique, which can overcome the limitations of LS and was first applied in liver surgery in 2006 [8]. Robotic surgery provides 3-d view, 7 degrees of freedom compared to 3 of LS and movement in all axes, dexterity and precision of gestures [9]. In addition, there is no amplification of hand tremor, while it is associated with decreased fatigue and better comfort for the surgeon [9,10]. The major drawback for RS is the cost of the operation, the increased operative time and the limited centers with adequate experience on this type of surgery [11]. RS has been shown to be a safe and feasible approach in liver surgery compared to open surgery (OS) and has been associated with fewer complications, morbidity and shorter length of stay with similar outcomes [12].

Furthermore, accumulating data suggest non- inferiority of RS compared to LS in liver surgery [11]. Most published studies are focused on surgical management of malignant liver diseases and there are insufficient data about the effectiveness of RS on treating exclusively benign disease. Considering the above, we aimed to evaluate the application of RS in BLD surgery.

Methodology

Search method and data sources

The present systematic review was conducted following the guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) [13]. A study protocol was designed and strictly followed by all authors. A thorough research was conducted in Medline, Scopus and Cochrane Library from 1st of May to 30th of June 2020 to identify eligible studies. The following search terms were applied: ((robot) OR (robotic)) AND ((((((((((benign liver disease) OR (hemangioma)) OR (haemangioma)) OR (hepatic cyst)) OR (liver cyst)) OR (hydatid cyst)) OR (focal nodular hyperplasia)) OR (liver adenoma)) OR (hepatic adenoma)) OR (cystic echinococcosis)) OR (hepatolithiasis)). Two authors (Konstantinos Tsekouras, Nikolaos Mamakos) independently performed the literature screening. After choosing the eligible studies, we manually assessed their reference list in order to identify any relevant publication (snowball method).

Inclusion and exclusion criteria

Studies including patients undergoing robotic surgery or robotic assisted surgery for benign liver diseases were considered eligible. Benign liver diseases included: hemangiomas, adenomas, echinococcal cysts, intrahepatic biliary stones, focal nodular hyperplasia. Exclusion criteria were: 1) study published in other language than English, 2) studies reporting on minimally invasive surgery (laparoscopic and robotic surgery); with no separate results concerning robotic liver surgery for benign liver diseases, 3) liver transplantations, 4) reviews and meta-analyses, 5) editorials and letters to the editors, and 6) overlapping studies. As for the overlapping populations, only the most recent or most informative study from a single center was included in the present review.

Data extraction

The results yielded by the initial algorithm and the successive steps of the selection process are described in the Flowchart **(Figure 1**). From the 1227 records retrieved, 12 studies were finally deemed eligible adding to a total of 115 patients [14-25]. The majority of studies were from centers in Asia (7/11), followed by Europe (3/11) and the USA (2/11). All included studies were published from 2013 onwards; however, the first robotic resections in the series were performed as early as 2007.

Data extraction was performed by two independent authors (KT and NM) and cross-checked by a third author (ES). Any discrepancies were solved after team consensus. Variables of interest included: general study characteristics (eg, author, year of publication, country of enrollment, journal of publication, study design, number of patients), patient demographics (eg, age, gender, cirrhosis, ASA score, previous abdominal surgery), number of benign lesions, lesion size, lesion pathology, perioperative outcomes (eg, operative time, blood loss, conversion rates, length of stay, number of patients with complications, number of complications, type of complications according to Clavien- Dindo classification, mortality).

Definitions and analysis

The types of liver resections were defined following to the Brisbane 2000 classification [26]. In most studies, minor resection was defined as resection of less than three hepatic segments, whereas major resection was defined as resection of three or more contiguous Couinaud segments. When information about specific liver segments resection were available, were included in the tables of the present paper (**Supplementary Table**). Data concerning age, BMI, operative time, blood loss, length of stay, are presented as mean and standard deviation or median and intraquartile range, based on the presentation followed by the original authors. The variables of interest for each study are presented as mean value whenever possible and the median of the means was calculated for each variable for the total number of studies. As for continuous outcomes, we applied the method proposed by Hozo et al. when data was presented as medians with a range, in order to estimate the respective means and standard deviations [27]. Categorical variables were extracted as numbers and proportions. Complications are presented namely and following Clavien-Dindo classification.

Regarding complications (**Table 3**) the absolute numbers (*n*) and the relevant percentages (%) pertaining to each category have been calculated from the studies providing information on these variables. Data concerning Clavien-Dindo classification were available in 5 studies (**Table 3**) and the total number of patients in these studies equals to fifty-three (n=53). The study of Hu et al [17], was excluded from **Table 3** and complication analysis, due to lack of sufficient data. In addition, in two studies [19,23], data were provided only in cases of severe complications. Detailed recording of complication rate was available in a total number of 97 patients.

Results

Patient characteristics, lesion type and location (Tables 1, Supplementary)

After a meticulous search of Medline, Scopus and Cochrane Library as described above, twelve (n=12) studies met the inclusion criteria with a total number of one hundred fifteen (n=115) patients.

All of the patients included had benign liver disease. Patient age ranged from 15 to 83 years with mean age of 51.7. Male to female ratio was 0.51. Median BMI was 25.68kg/m^2 kg/m^2 (**Table 1**) Data regarding previous surgery were available only in one study [20], where nine patients had previous surgeries, seven of which had one and two of which had two. Furthermore, information regarding presence of cirrhosis were available in only 3 studies [15,17,20], whereas only 2 patients, originating from the study of Shu et al., had cirrhosis (not depicted in tables). The most common indication for robotic liver surgery was hepatolithiasis in a total of forty-six patients, followed by haemangioma in a total of twenty-three patients. Robotic surgery for hepatic cysts was performed in twenty patients and twenty-one patients were treated for hepatic echinococcal cysts. The lesion size ranged from 15mm to 185mm (**Supplementary Table**). Type of procedures performed in each study, is demonstrated in detail in **Table**

1 and the affected liver segments are given in **Supplementary Table**.

Perioperative Outcomes (Tables 2, 3)

Median operative time was 226 min (range, 51-660 min) and median blood loss was 223 ml (range, 10-700 ml). Among the included patients (n=115) undergoing RS, only one patient required conversion to open surgery (rate <1%) due to severe adhesions around the hepatic hilum [20]. Median length of stay was 5.5 days (range 1-28 days). The type of complications according to Clavien-Dindo classification was provided in five studies with a total number of patients equal to fifty-three (n=53) [14,19,20,22,23], (**Table 3**) Grade I/II complications were observed in sixteen patients whereas grade III/IV were observed in seven patients (**Table 3**). Grade V complications were not observed in any patient. The most frequent complication observed was bile leak in a total of five patients followed by intra-abdominal fluid collection in a total of four patients. Raw surface effusion, pulmonary infection and pleural effusion were observed in a total of three patients each. We must note, that the vast majority of complications were observed in a single study [20] (**Table 3**). There were no cases of perioperative mortality in the total population. One patient died of progressive colorectal cancer [20], which co-existed with benign liver pathology, for which the patient underwent RS. Data concerning the cost were available only in two studies [20,22].In the study of Kim et al., the mean total cost for patients with benign disease was 8017$ (no confidence intervals were provided in the study), whereas the study of Shu et al. the mean total cost was 15239.14$ (±4498.92$).

Comparison of perioperative variables in the RS, LS, and OS Groups (Table 4)

In **Table 4**, we provide a direct comparison between the perioperative outcomes among the RS, the LS and the OS group, based on the available data from each study. In a total number of four studies, direct comparison between the different surgical techniques was available [15,17]. In the study of Kim et al., two groups of patients undergoing RS or LS were included, whereas Shu et al. compared a robotic assisted laparoscopic group with an open surgery group. Similarly, Lee et al. included two groups of patients undergoing RS or OS for left lateral sectionectomy, while Hu et al. conducted a three-part comparison between RS, LS and OS in terms of perioperative outcomes. In the study of Hu et al., the OS group had significant lower OR time than the RS group and the LS group (190.2 ± 51.8vs 256.3 ± 57.7 and 268.4 ± 93.6min, P<0.05, respectively). No significant differences were observed between the RS and LS OR time. When the setup time in the RS group was excluded from total OR time calculation, the operative time of the RS group was significantly shorter than that of the LS group (216.3 ± 57.7 vs 268.4 ± 93.6 min, P<0.05, respectively) [17]. In contrast, there were no significant differences regarding OR time between LS and RS in the study of Kim et al. (P=0.203). Similarly, Shu et al. and Lee et al. did not observe a significant difference in OR time between RS and OS (376.69 ± 129.05 vs 319.15 ± 127.58min, P= 0.065 and 214 vs 220min, P=0.906 respectively).

The average blood loss in RS was significantly lower compared to OS in all included studies with available data (315.38 ± 237.81 vs 542.88 ± 518.70 ml , 319.5 ± 206.0 vs 628.0 ± 231.0 ml, 50 vs 200 ml, P<0.05 for all of them) In contrast, there was no significant difference in blood loss between LS and RS in any of the two studies. In addition, only Shu et al. reported a lower transfusion rate compared to OS [RLS (15.4%) vs OS (46.2%), P=0.008]. Similarly, the length of stay was shorter in the RS group vs the OS group (5.5 ±2.1 vs 7.2 ± 2.3 days, and 13.54 ± 6.54 vs 17.81 ± 7.49 days, 5.5 vs 8 days, P<0.05 for all of them.). As for the recurrence rate of lesion, and specially hepatolithiasis, no significant differences were observed among the included studies (not depicted in tables). The length of stay did not differ significantly between the RS and the LS group. RS was associated with a shorter time to oral intake compared to OS (3.50 ± 1.30 vs 5.88 ± 4.00 d, P=0.004) [20],(2.2 ±1.1 vs 1.9 ± 0.9 vs 3.1 ± 1.1 d, P=0.002) [17] , whereas this difference was not significant compared to LS. The cost of RS was higher than that of OS (15239.14 ± 4498.92 vs 12172.51 ± 5371.68 $, P=0.014) [20], but no significant difference was noted between RS and LS (8017 vs 7437 $, P=0.826), by Kim et al. Finally, no significant differences between the groups in terms of open surgery conversion rate, complications and mortality were observed, in any of the four studies included in **Table 4**.

Discussion

Robotic surgery has emerged as a novel and safe approach for liver surgery [28]. Currently, RS is mostly applied in malignant diseases, such as hepatocellular carcinoma and colorectal liver metastases, while accumulating data suggest its utilization in hepatobiliary surgery [29]. Data concerning the application of RS in BLD surgery are limited and, to the best of our knowledge, the current review is the first one to summarize the published evidence about utilization of RS exclusively in BLD.

Surgical intervention for BLD remains a field of conflict, particularly due to the increased risk and complications accompanying this type of surgery [30]. Surgical treatment is preferred for symptomatic benign liver lesions and the gold standard is OS or LS, based on the type and location of lesion [31]. MIS, including RS and LS, has been applied in BLD surgery, with similar outcomes, fewer complications and shorter length of stay [17,20,22]. Robotic liver surgery highlights the advantages of minimally invasive techniques over open surgery and current literature supports the use of MIS in hepatobiliary surgery, mainly for malignant diseases [32].

When compared to OS, RS is associated with reduced intraoperative blood loss, shorter length of stay and reduced time to oral intake (**Table 4**). These parameters are associated with less postoperative morbidity and a quicker return to the daily activities of the patients [32], which are major characteristics in favor of RS. In terms of peri- and post-operative mortality, the outcomes are similar, which can be attributed to the small number of patients and advances in OS techniques, preventing serious complications, as suggested before, when comparing LS to OS [34]. Interestingly, despite the fact that the mean operating time appears to be increased in RS compared to OS several authors concluded that this difference was not significant in terms of complications and postoperative course of the patient [12]. In addition, most studies find that there is increased operating time associated with RS since the robot set- up time was included in the calculation of total time (**Table 2**). Particularly, Kim et al. showed that, when the robot set up time is excluded from the calculation of total operative time, the net operative time does not differ significantly between RS and OS. Similarly, Lee et al. did not observe a significant difference in operation time between RS and OS (Table 4). This can be of great importance when compared to open surgery, since, despite the same duration, robotic surgery minimizes the risks accompanying open surgery. Nevertheless this exclusion might be misguiding, since the set up time is an integral part of the operation and is still taking up theatre slot time. Finally, RS provides improved precision in dissection of liver parenchyma, which reduces the need for multiple usage of the Pringle's maneuver thus lowers the overall ischemic time of the liver parenchyma [35].

When comparing RS vs LS, most variables of interest appear not to differ significantly, while no- inferiority of RS was reported in previous published studies [36]. Mean blood loss, operative time, complication rate and length of stay was similar in the studies of Kim et al. and Hu et al., as depicted in **Table 4**. In contrast, a recent meta-analysis by Montalti et al., showed that LS is associated with reduced blood loss and operation time compared to RS, but there were no available data concerning exclusively BLD [37]. However, a growing amount of evidence suggest there are several advantages of RS vs LS in liver surgery. Most importantly, RS provides a 3-D view of the operating field, in contrast to the 2-dimensional view of LS. In addition, the mechanics of the instruments used in RS, allow greater degrees of freedom in movement [10,38]. The combined effect of greater range of motion and better visualization is RS settings, enables better and more delicate performance in the so-called difficult segments of the liver compared with LS, which is required for the cautious dissection of complex anatomical structures and in the presence of cirrhosis [7] . Furthermore, RS limits hand tremor, which is amplified by laparoscopic instruments and diminishes fatigue related complications due surgeon's better posture [39]. As for the operation time, net operation time appears to be lower compared to LS, when the set-up is excluded [17]. Of note, the learning curve of complex robotic-assisted liver resections appears to be shorter compared with laparoscopic resections which further supports its role in technically demanding cases that require increased dexterity [40,41]. Recently, Kandil et al suggested that a robotic approach to single-port access appears technically feasible and safe for BLD surgery, which can be an additional advantage of RS vs LS in BLD surgery [16].Nevertheless, this remains a challenging procedure, requiring both hepatobiliary and laparoscopic experience.

We must note that, most of the available data show no superiority in safety and feasibility of the robotic approach over laparoscopic, however the results originated from single centers and may be biased due to the learning curve of the robotic system, since some studies depicted the initial experience of each individual center.

In general, the major drawback of RS in liver surgery is the increased cost, compared to other techniques [9,42]. However, there insufficient data about the cost of RS in BLD surgery. In our review, only two studies provided data concerning the cost of RS and LS in BLD and a direct comparison between them. Shu et al. reported an increased total mean cost of RS compared to OS, while Kim et al. did not observe any significant difference between the mean cost of RS and LS. However, the discrepancy observed in the study of Shu et al. can be partially attributed to the small number of patients included and the significantly prolonged stay of one patient, affecting the mean total cost. In addition, Lee et al. reported a cost of RS equal to 3200$, compared to 1350$ of OS, but no direct comparison between them was performed [15]. Current literature for RS in liver pathology suggests an increased cost, which can be explained by the start-up costs of the robotic surgical system, the cost of disposable high-value supplies and maintenance expenses [43]. Interestingly, some authors propose that the increased cost of robotic surgery can be partially but not totally counterbalanced by the reduced postoperative hospital stay as well as the lower risk of major complications that might require further medical attention [43]. Further cost-effectiveness studies are needed to determine the efficacy of RS in BLD surgery.

Another factor limiting the widespread utilization of RS in liver surgery is the demand of highly experienced surgeons, with few centers having the necessary experience worldwide. However, considering the lower learning curve of RS compared to LS, several authors suggest that surgery of benign liver lesions is a good start up point for hepatobiliary trainees in robotic surgery due to fewer intraoperative challenges in contrast to malignant lesions data [44]. The use of dual console robotic system and virtual reality training consoles could help in the training of hepatobiliary surgeons to perform robotic liver surgery [1].

Several limitations should be addressed, regarding the present paper. All included studies were single center, retrospective, with a small number of patients included, which might have affected recording of perioperative outcomes; in particular, complications and conversion rates may be underestimated due to selection and publication biases. In addition, it should be noted that there are several different indications for surgery in the current review some of which require radically different operations thus affecting the comparison of the variables among the studies included. Not all studies had available data concerning the variables of interest, especially detailed recording of post-operative complications according to Clavien-Dindo classification. The cost of RS in BLD was available in only two studies with limited number of patients.

In conclusion, RS appears to be a safe and feasible alternative to open and laparoscopic surgery for benign liver pathology. However, due to the limited amount of available evidence, further large, multicenter, randomized prospective trials are needed to evaluate the exact role of RS in the treatment of patients with benign liver diseases.

Authors Contributions

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Disclosures

The authors declare that they have no conflict of interest.

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Appendix

Figure 1. Flow Diagram.

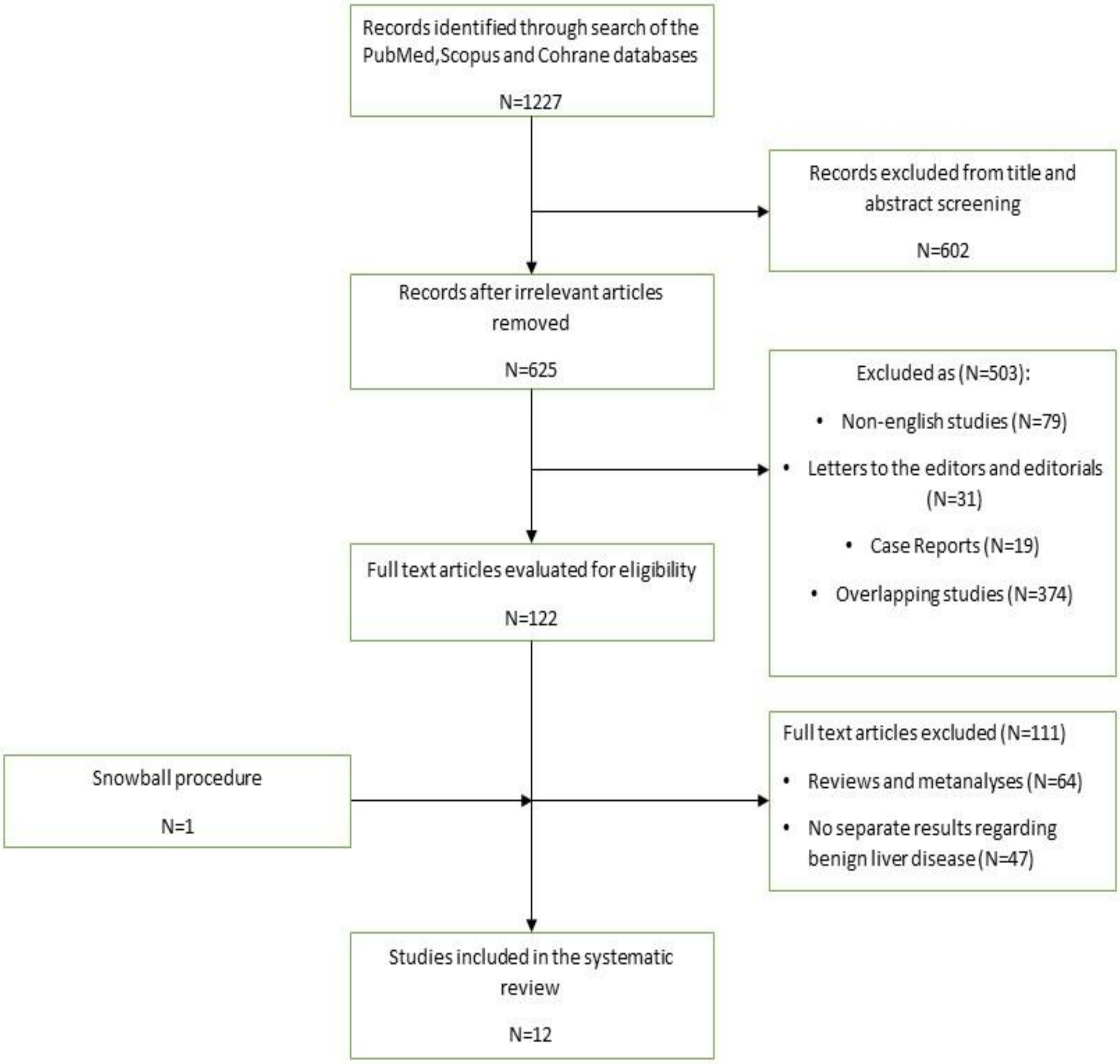

Figure 1. Flowchart depicting search methodology and included studies selection.

Table 1. Baseline characteristics of included studies.

Author	Country	Type of study-years of enrollment	Bening liver disease/ total patients enrolled	Males	BMI (kg/m²)	Mean Age (years)	Type of procedure	Pathology
Magistri et al., 2019	Italy	Retrospective study	15/15	8	23.05 (21-29)	51(24-76)	Right hepatectomy 1 (6.25%) Left lateral sectionectomy 2 (12.5%) Segmentectomy 5 (1 caudetoctomy) (31.25%) Wedge resection 3 (18.75%) Cyst-Pericystectomy 5 (31.25%)	CE 16 (100%)
Tsirlis et al., 2019	UK	Retrospective study January 2016-January 2018	17/17	2	NA	64(42-83)	Robotic fenestration Deroofing cysts 17(100%) Cholecystectomy 5(29,4%)	Hepatic cyst (100%)
Shu et al., 2019	China	Retrospective study Propensity score matcing analysis RLS:OS 1:2	26/26	9	NA	53(20-70)	RLS Left lateral hepatectomy 3 (11.5%) Left hemihepatectomy 16 (61.5%)	Hepatolithiasis 26 (100%)

		October 2010-August 2017					Right hemihepatectomy 4 (15.4%)Segmentectomy 2 (7.7%) Hilar bile duct plasty and reconstruction alone 1 (3.8%) Combined with bile duct reconstruction 6 (23.1%) Combined with CBD exploration 12 (46.2%)	
Kandil et al., 2013	USA	Retrospective study February2011-August 2011	3/7	2	1. 26.4 2. 36.5 3. 28.1	1. 21 2. 45 3. 64	1.Left lateral sectionectomy (33,3%) 2.Left lobe resection (33,3%) 3.Single port:Left lateral segmentectomy (33,3%)	Hepatic adenoma 1 (33.3%) Focal nodular Hyperplasia 1 (33.3%) Adenoma 1 (33.3%)
Lee et al., 2019	South Korea	Retrospective study June 2016-April 2018	2/13	1	24.6 ± 4.2 (SD)	1. 69 2. 69	Left hepatectomy 2 (100%)	Biliary cyst 1 (50%) Hepatolithiasis 1 (50%)
Giulianotti et al., 2019	USA	Retrospective study July 2015-November 2018	3/3	3	1. 24.87 2. 27.36 3. 25.49	1. 42 2. 45 3. 61	Robotic enucleation of angioma 3 (100%) Cholecystectomy 1 (33,3%)	Haemangioma 3 (100%)

Hu et al., 2020	China	Retrospective study April 2011-April 2017	19/19	2	NA	49.2 ± 10.6 (SD)	Hemihepatectomy 19 (100%)	Haemangioma (100%)
Nota et al., 2015	The Netherlands	Technical Report	2/2	0	NA	1. 32 2. 51	Robot-assisted laparoscopic cyst fenestration 2(100%)	Hepatic cyst 1 (50%) Polycystic liver disease 1 (50%)
Lee et al., 2016	China	September 2010-April 2015	15/15	3	NA	56.5 (35-79)	Left lateral sectionectomy 10 (66.7 %) Left hepatectomy 3 (20.0 %) Right hepatectomy 2 (13.3 %)	Hepatolithiasis 15 (100%)
Kim et al., 2016	South Korea	Retrospective study May 2007-July 2013	4/12	1	NA	62.3 ± 6.6 (SD)	Left lateral sectionectomy 4(100%)	Hepatolithiasis 4 (80%) *Hepatic cyst 1 (20%)
Zhao et al., 2020	China	Retrospective study September 2019-December 2019	5/5	5	25.68 (21.22-30.10)	38.6 ±12.4 (24-56)	Caudate lobectomy 2(40%) Hepatectomy of segment VII 1(20%) Pericystectomy of segment VIII 1(20%)	CE 4 (80%) AE 1 (20%)

							Right hemihepatectomy 1(20%)	
Goja et al., 2017	India	Case series (Initial experience) February2015-January2016	4/10	3	NA	1. 15 2. 44 3. 55 4. 59	Deroofing cysts 2(50%) Partial cystectomy 2(50%) Left hepatectomy 2(50%)	Polycystic liver disease 2 (50%) Hemangioma 1 (25%) CE 1 (25%)

Table 1. Baseline characteristics of included studies. **Abbreviations: RLS=** robotic assisted laparoscopic surgery, **CBD=** Common Bile Duct, **CE=** cystic echinococcosis**, AE=** alveolar echinococcosis. **Notes:** As for the studies of Hu et al. and Tsirlis et al., number of patients concerning the pathology section were not mentioned, because several patients had multiple lesions.
*Direct information were not provided for this patient and was excluded from the analyses.

Supplementary Table. Baseline lesion size, ASA score, and affected liver segments.

Author	Lesion size mm	ASA score	Location of lesion Liver segments/Lobes
Magistri et al., 2019	NA	I:5 II:8 III:2	NA
Shu et al., 2013	NA	NA	III 1 (3.8%) II + III 3 (11.5%) II + III + IV 13 (50.0%) II + III + VI + VII 2 (7.7%) V + VI + VII + VIII 3 (11.5%) VI + VII 1 (3.8%) Left lobe + hilum 1 (3.8%) Left lobe + caudate lobe 2 (7.7%)
Lee et al., 2016	46	NA	NA
Kim et al., 2016	NA	NA	NA
Kandil et al., 2013	1. 80 2. 60 3. 15	NA	NA
Nota et al., 2015	Up to 100 (PLD)	NA	4B 1 (solitary hepatic cyst)
Giulianotti et al., 2019	1. 82 2. 39 3. 91	I:1 II:2	II 1 (33.3%) III 1 (33.3%) IV-V 1 (33.3%)
Hu et al., 2020	>100	NA	Right 15 Left 4
Tsirlis et al., 2019	142 (63-240)	NA	IV 2 (12%) VII 1 (6%) II+III 2 (12%) V+VI 2 (12%) VI+VII 1 (6%) VII+VIII 2 (12%) II+III+IV 2 (12%) IV+V+VIII 1 (6%) IVA+VII+VIII 2 (12%) IV+V+VI+VII+VIII 2 (12%)
Lee et al., 2016	NA	II (I-III) (median)	NA
Zhao et al., 2020	70.8 (51-80)	I:2 II:2 III:1	I 2 (40%) VII 1 (20%) VIII 1 (20%) VII+VIII 1 (20%)
Goja et al.,2017	1.120 (hemangioma) 2.NA 3.NA	NA	IV 1 (25%) VII 1 (25%) Left lobe 2 (50%) Right lobe 1 (25%)

Supplementary table. Baseline lesion size, ASA score, and affected liver segments**.** **Abbreviations**: ASA=American Society of Anesthesiologists**, NA=** not available. **Notes**: Hu et al. do not mention number of affected sections because several patients had multiple lesions and the location refers to the location of the largest liver hemangioma for patients with multiple lesions.

Table 2. Peri- and post-operative outcomes of the included studies.

Author	Operative time (min)	Blood loss (ml)	Blood Transfusion	Conversion rate	LoS Days	Perioperative mortality	Complications
Magistri et al., 2019	210 (95-550)	100 (50-550)	NA	0(0%)	4(3-13)	0(0%)	4 (26%)
Tsirlis et al., 2019	174(97-335)	16 cases <50 1 case 200	NA	0(0%)	2.5(1-10)	0(0%)	2(12%)
Shu et al., 2019	376.69 ± 129.05 (SD)	315.38 ± 237.81 (SD)	4 (15.4%)	1 (3.8%)	13.54 ± 6.54 (SD)	0*(0%)	12(46.2%)
Kandil et al., 2013	1. 90 2. 79 3. 51	1. 200 2. 200 3. 15	0 (0%)	0(0%)	1. 1 2. 2 3. 5	0(0%)	Delirium and tremors were noted in patient #3
Lee et al., 2019	1. 195 2. 220	NA	0 (0%)	0(0%)	1. 7 2. 14	0(0%)	Fluid collection in patient #2
Giulianotti et al., 2019	1. 146 2. 121 3. 193	1. 100 2. 50 3. 600	1 (33.3%)	0(0%)	1. 3 2. 4 3. 5	0(0%)	Pulmonary embolism in patient #3
Hu et al., 2020	256.3 ± 57.7 (SD)	319.5 ± 206.0 (SD)	5 (26.3%)	NA	5.5 ± 2.1 (SD)	0(0%)	1 (5.3%)
Nota et al., 2015	1. 90 2. 115	1. 10 2. 20	NA	NA	1. 1 2. 3	0(0%)	0
Lee et al., 2016	313.9(137–620)	236(10–700)	2 (13.3 %)	0(0%)	9.7(4–22)	0(0%)	4 (26.7 %)
Kim et al., 2016	455.8 ± 144.2 (SD)	250 (123–462) Median(IQR)	NA	0(0%)	7 (7–7.5) Median(IQR)	0(0%)	1*
Zhao et al., 2020	242 (175-300)	210 (50-600)	1(20%)	0(0%)	10.8 (5-19)	0(0%)	5(100%)
Goja et al.,2017	527.5 (370-660)	NA	1(25%)	0(0%)	11.3(4-28)	0(0%)	1(25%)

Table 2. Peri- and post-operative outcomes of the included studies. In operative time, docking time is included. **Abbreviations: LoS=** Length of stay, **SD=** Standard Deviation.
*Direct information was not provided for this patient and was excluded from the analyses.

Table 3. Clavien-Dindo classification and specific types of complications of the included studies.

Complications

Clavien-Dindo classification,% (N=23/53)	
I/II	16 (30%)
III/IV	7 (13%)
V	0 (0%)
Type of complication (N=28/97)	
Bile leak	5
Intra-abdominal fluid collection	4
Raw surface effusion	3
Pulmonary infection	3
Pleural effusion	3
Haematoma	2
Incision infection	2
Abdominal infection	1
Pulmonary embolism	1
Small bowel perforation	1
Delirium	1
Stress cardiomyopathy	1
Thrombotic thrombocytopenic purpura	1

Table 3. Clavien-Dindo classification and specific types of complications of the included studies. **Notes:** For Clavien-Dindo classification we retrieved data from the studies Kim et al., Lee et al., Shu et al., Magistri et al., and Zhao et al. (Total number of patients: n=53). Data for types of complication were retrieved from all studies, except the study of Hu et al (Total number of patients: n=97).

Table 4. Summary of peri- and post-operative outcomes between OS, LS and RS.

Author	Kim et al., 2016			Hu et al., 2020				Shu et al., 2019			Lee et al., 2016		
Type of operation (number of patients)	RS (n=4)	LS (n=5)	P-value	RS (n=19)	LS (n=13)	OS (n=25)	P-value	RLS (*n* = 26)	OS (*n* = 52)	P-value	RS (n=10)	OS (n=27)	P-value
OR time (mean,SD) min	455.8 ± 144.2	330.6 ± 123.5	0.203	256.3 ± 57.7	268.4 ± 93.6	190.2 ± 51.8	0.001	376.69 ± 129.05	319.15 ± 127.58	0.065	214 (137–280)	220 (115–405)	0.906
Blood loss (mean,SD) ml	250 (123–462) Median(IQR)	350 (150–500)	0.762	319.5 ± 206.0	476.9 ± 210.8	628.0 ± 231.0	0.000	315.38 ± 237.81	542.88 ± 518.70	0.037	50 (10–500)	200 (40–684)	0.001
Blood transfusion rate	NA	NA	-	5 (26.3%)	4 (30.8%)	8 (32.0%)	0.916	4 (15.4%)	24 (46.2%)	0.008	0 (0.0 %)	1 (3.7 %)	0.999
LOS(mean,SD) days	7 (7–7.5) Median(IQR)	6 (6–7)	0.317	5.5 ± 2.1	4.7 ± 1.7	7.2 ± 2.3	0.002	13.54 ± 6.54	17.81 ± 7.49	0.016	5.5 (4–7)	8 (5–22)	0.001
Time to oral intake(mean,SD) days	NA	NA	-	2.2 ± 1.1	1.9 ± 0.9	3.1 ± 1.1	0.002	3.50 ± 1.30	5.88 ± 4.00	0.004	NA	NA	NA
Conversion to open surgery	0 (0%)	0 (0%)	1.000	NA	NA	-	-	1 (3.8%)	-	-	0 (0.0 %)	-	-
Complications	0 (0%)	1 (20%)	1.000	1 (5.3%)	1 (7.7%)	1 (4.0%)	0.890	12 (46.2%)	33 (63.5%)	0.196	0 (0.0 %)	9 (33.3 %)	0.079
Mortality	0 (0%)	0 (0%)	1.000	0 (0%)	0 (0%)	0 (0%)	1.000	0 (0%)	2 (3.8%)	NA	0 (0.0 %)	0 (0.0 %)	1.000
Cost($) (mean, SD)	8017	7437	0.826	NA	NA	NA	-	15239.14 ± 4498.92	12172.51 ± 5371.68	0.014	3200	1350	NA

Table 4. Summary of peri-and post-operative outcomes between OS, LS and RS. **Abbreviations: RS=** robotic surgery**, LS=** laparoscopic surgery, **OS=** open surgery, **OR time:** operation room time, **LS=** length of stay, **SD=** standard deviation, **NA=** not available