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Minimally Invasive Surgery for Hepatocellular Carcinoma; Latest Advances

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Abstract

Surgical resection is the gold standard for hepatocellular carcinoma management for early stages of the disease. With advances in technology and techniques, minimally invasive surgery provides a great number of advantages for these patients during their surgery and for their post-operative care. The selection of patients following a multi-disciplinary approach is of paramount importance. Adding to this, the developments in laparoscopic instruments and training, as well as the promising advantages of robotic surgery along with other forms of technology, increase the pool of patients that can undergo operation safely and with good results worldwide. We review results from great centres worldwide and delineate the accurate multi-disciplinary approach for this.

Keywords: laparoscopic, robotic, minimally invasive surgery, hepatocellular carcinoma

1. Introduction

Liver cancer is the 5th most common cancer and the second most frequent cause of cancer-related death globally, with 854,000 new diagnoses and 810,000 deaths per year [1, 2]. Hepatocellular carcinoma (HCC) accounts for approximately 90% of liver cancers and is generally associated with an unfavorable prognosis, with a 5-year overall survival (OS) of 10–15%, mostly due to a delay in establishing an early diagnosis. In case HCC is diagnosed at an earlier stage, the 5-year OS improves and may reach 70%, amid the possibility of curative treatments, such as liver resection (LR), liver transplantation (LT) and ablation [3, 4].

2. Minimally invasive surgery for HCC

2.1 Staging systems and treatment allocation

Once diagnosed, prognostication is pivotal in the management of HCC. Disease staging and classification is intended to assess prognosis and determine treatment candidacy. In patients with HCC, the co-existence of two life-threatening conditions, i.e., cancer and cirrhosis, needs to be tackled with, and further complicates

prognostic assessment [5, 6]. The 2018 European Association for the Study of the Liver (EASL) clinical practice guidelines endorsed the Barcelona Clinic Liver Cancer (BCLC) classification [7], as did the recent American Association for the Study of Liver Diseases (AASLD) guidance [3]. According to the BCLC classification system, patients are classified into five stages (0, A, B, C and D) according to pre-established prognostic variables. These variables comprise tumor characteristics (size, number, vascular invasion, lymph node involvement, distant metastases), liver function (bilirubin, portal hypertension, liver function preservation) and patient's health status (ECOG).

2.2 Liver resection

Determining eligibility for LR involves assessment of the tumor burden; assessment of liver function; the extent of hepatectomy and the expected volume of the future liver remnant; and the presence of portal hypertension and other co-morbidities. Liver function is objectively estimated by the Child-Pugh score and patients with Child-Pugh B or C are deemed at a high risk of liver failure following LR, even after a minor resection. More recently, the model for end-stage liver disease (MELD) score was integrated into the EASL guidelines for treatment allocation [7, 8]. The absence of cirrhosis allows for larger and more complex resections, and is associated with viable postoperative mortality and morbidity, even after major hepatic resection, with a 5-year OS of 50% [9–13]. Conversely, clinically significant portal hypertension (CSPH), defined as HVPG >10 mmHg, is a well-established predictor of liver decompensation and death after LR [14–18].

Surgery represents the backbone of HCC treatment, resulting in the best outcomes in appropriately-selected candidates. LR and LT represent the first-line treatment in individuals with early-stage tumors on an intention-to-cure perspective. In particular, the latest EASL guidance recommends LR in cases of a resectable solitary nodule without macrovascular invasion and extrahepatic spread, regardless of size [7, 19]. The AASLD guidelines advocate LR in patients with Child-Pugh A compensated cirrhosis and resectable HCC, i.e., solitary tumor <5 cm with or without vascular invasion, or multifocal tumor <5 cm [3]. Finally, the Asian Pacific Association for the Study of the Liver (APASL) recommends that all tumors without extrahepatic spread may be considered for LR, regardless of vascular invasion, number and size of lesions [4].

2.3 A laparoscopic approach

The advent of laparoscopic techniques transformed the treatment landscape of HCC. In spite of the relative paucity of prospective randomized studies, the laparoscopic approach appears to convey similar oncological outcomes with respect to conventional surgery [20]. Laparoscopic LR allows the preservation of the abdominal wall, minimizes peritoneal trauma, and is associated with fewer complications in comparison with open surgery, including both overall and liver-related complications, as also shown in a recent meta-analysis including 6,812 patients. Additionally, no differences in operative time, blood loss, intraoperative complications, hospital stay, and morbidity were found in laparoscopic LR for cirrhotics in comparison with non-cirrhotics [21–28]. Several studies demonstrated that minimally-invasive surgical techniques in patients with cirrhosis are associated with reduced risk of post-operative hepatic decompensation and liver failure [29–31]. Interestingly, this technique also appears safe in the elderly, even for a major hepatectomy, and is associated with improved outcomes [32–36]. One should bear in mind though that laparoscopic hepatectomy should be carried out in specialist centres and following

appropriate training and education of all team members involved. The importance of this factor is highlighted as the keys to successful LR include technical mastering of laparoscopic hepatic portal occlusion which can be more challenging than in laparotomy, and the lack of operational feel and need for rapid reactive mode as well as accurate hemostasis.

In light of the above, EASL 2018 clinical practice guidelines recommend laparoscopic LR for HCC resection in expert centres and for selected surgical candidates [7]. Similarly, the AASLD also recognizes the advantages of laparoscopic techniques in selected scenarios [3]. EASL recommends [7] that tumor size and location should determine optimal surgical approach. In particular, laparoscopic-robotic LR for HCC may be considered for tumors located in superficial peripheral positions of the liver; and is associated with optimal survival outcomes, low complication rate and reduced inpatient time. Minimally-invasive LR can be an effective option in very early (≤ 2 cm) and early HCC. Ablation represents still the treatment modality of choice for this disease stage, owing to the higher cost-effectiveness [16] and to milder liver function impact. However, several studies report that patients treated with minimally-invasive LR for such tumors, mainly located in superficial or antero-lateral positions, suffer less adverse outcomes and shorter hospitalization, in comparison with conventional open techniques, while achieving competitive oncologic results with respect to ablation [37–40].

Limited resections conducted via laparoscopic LR may also be considered for curative resection in selected patients with HCC with a borderline liver profile (i.e., Child Pugh B7, moderate portal hypertension and/or bilirubin around 2 mg/dl), especially in specialized centres [7]. A study reported that patients with Child-Pugh A and Child-Pugh B/C cirrhosis who underwent laparoscopic LR had a similar perioperative course [26]. Laparoscopic LR has also been explored as an option for patients with CSPH. A recent study by Lim *et al* assessed the short-term outcomes in patients with and without CSPH [41]. Although broadening eligibility criteria for minimally-invasive techniques would increase the rate LR, morbidity and hospital stay would be a significant concern for patients with CSPH. In light of the above, LT remains the gold standard in cases of HCC and advanced liver disease. Nevertheless, the laparoscopic approach may be beneficial prior to LT for HCC, with significantly reduced de-listing and death after LT when prior LR was performed laparoscopically [42]. Whether laparoscopic LR should also be considered in patients with HCC and CSPH not eligible for LT, will need to be addressed with further studies. Lastly, the safety and feasibility of laparoscopic major hepatectomy has been reported after sequential transarterial chemoembolization (TACE), which is classically associated with increased surgical difficulty [43]. Additionally, laparoscopic LR can be applied in living donor liver transplantation (LDLT) in centres with extensive experience in both laparoscopic LR and open LDLT.

2.4 Robotic liver surgery

Similar to laparoscopic LR, robotic LR is also emerging as an interesting minimally-invasive surgical technique, demonstrating a relative safe profile and allowing for an easier access to hepatic segments not amenable to laparoscopic approach, such as posterior sectionectomies and resection of tumors located in superior segments 4a and 8 [44]. The development of minimally invasive surgical techniques for liver tumors is in general limited by the characteristics of the liver itself, such as its texture, abundant blood supply, an increased number of structural variations of blood vessels and bile ducts.

A recent literature review including 10 studies on robotic liver resection for HCC (with a total of 302 patients) reported disease-free (DFS) and OS at 2 years

of 72–84% and 94–98%, respectively [44]. It has also been proposed that a robotic approach may also improve the access to the abdomen in cases of recurrent disease with potential requirement of LT, expanding the opportunities of both down-staging and bridging strategies [45]. The broad use of the robotic approach, however, is limited due to several factors, most importantly the cost of the robotic surgical devices compared to laparoscopic equipment. Several analyses on costs of robotic surgery have been reported, with controversial findings regarding the balance between costs and benefits [46–51]. With regard to instrumentation, the lack of an efficient robotic transection device such as the Ultasonographic Aspirator (UA) is the most important limitation of robotic liver surgery. Another limitation would be the spatial distance between the operating and robotic platform and its considerable size, making undocking and gaining access to the patient particularly challenging in emergency scenarios [52, 53]. Lastly, a non-negligible obstacle of robotic surgery is the operative time, that is in the majority longer in comparison with other surgical approaches. In view of the above, robotic LR needs to be better evaluated before being integrated into routine clinical practice and therapeutic algorithms. On the other hand, however, robotic LR can overcome certain traditional laparoscopic liver resection limitations like the inflexible fixation of the operating instruments as well as visual result [54]. The Robotic System appears superior in regard to these limitations and there are constant developments in the field as per instruments applied crucial to LR. At present, the Da Vinci Robotic surgical assistant system is in use in several centres for both benign and malignant liver diseases with similar indications applied as per the laparoscopic LR, and in certain cases demonstrating a more advantageous nature [55].

2.5 Cost of minimally invasive surgery

The results so far comparing robotic to laparoscopic and open LR are conflicting as per the cost effect to the institution hosting them. A single institution retrospective study from the University of Washington compared cost data for 71 robotic LR to 88 open procedures and reported that although there were higher perioperative costs for the robotic procedures, the postoperative costs and subsequent direct hospital costs were lower when compared with open procedures, attributing this possibly to a 2-day shorter hospital stay on average after robotic procedures [56]. On the other hand other studies have demonstrated a higher cost for robotic LR when compared to both laparoscopic and open procedures although in some the trend of less hospital stay was in favor of the robotic procedures [57–59].

2.6 Emerging technologies

Recent advances in liver surgery from a technological aspect include near-infrared fluorescent (NIF) imaging applied intra-operatively. NIF imaging has been set in use in several laparoscopic and robotic camera systems enabling the identification of various dyes, such as indocyanine green, injected preoperatively. Indocyanine green is a green dye that is preferentially metabolized by hepatocytes and excreted in the biliary tree and it lights up the biliary tree. Its use has been utilized for robotic and laparoscopic assisted cholecystectomy. It has also been more recently applied for a more accurate parenchymal dissection following vascular control by identifying perfused from poorly perfused hepatic parenchyma [60].

Future advances of robotic liver surgery include the application of preoperative planning with virtual reality (VR) models and real-time augmented reality (AR) intra- operative endoscopic overlays to assist with surgical navigation on *da Vinci*® surgical systems. Computer-based three-dimensional (3D) reconstructions of

liver tumors have been shown to benefit the accuracy of tumor localization and precision of operative planning for liver surgery [61, 62]. Intraoperative Ultrasound is routinely used for real-time identification of liver tumors both in open and minimally invasive LR. However, with AR being developed to overlay accurate 3D reconstruction data onto the operative field itself, it can potentially eliminate the need to divert the attention from the operative field and to translate the 2D images into a 3D construct.

3. Conclusions

With the constant evolution of technology, it would be without a doubt that surgery techniques in terms of access and instrument implementation would evolve as well. Laparoscopic liver surgery appears to have gained considerable ground especially in centres where liver surgery and laparoscopic expertise co-exist. The robotic approach is still quite variable between institutions, as well as between countries and continents. Thus one can only anticipate for advances in minimally invasive surgery to continue as long as there are specialized liver centres aiming to increase patient volume undergoing surgery and decrease hospital stay, complications rates and in general offer the best possible liver service.

Conflict of interest

“The authors declare no conflict of interest.”

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