

Innovative surgical approaches for hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, with an increasing diffusion in Europe and the United States. The management of such a cancer is continuously progressing and the objective of this paper is to evaluate innovation in the surgical treatment of HCC. In this review, we will analyze the modern concept of preoperative management, the role of laparoscopic and robotic surgery, the intraoperative use of three dimensional models and augmented reality, as well as the potential application of fluorescence.

Key words: Hepatocellular carcinoma; Liver resection; Hepatectomy; New perspectives; Innovative surgical approaches

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, with at least 1 million new cases each year^[1]. Even if liver transplantation remains the ideal treatment, hepatic resection remains the only curative treatment for HCC. Considering the early experience of liver resection for HCC in the 1980s, results were discouraging, with a mortality rate in the range of 10% and a considerable morbidity. Improvements in patient selection, early diagnosis, preoperative and postoperative management, surgical technique and development of new technologies have allowed to obtain a lower mortality and morbidity, achieving 0% in certain high-volume centers. The development of laparoscopic and robotic surgery, associated with the application of new technologies in patient care and progress in the medical treatment of HCC, represent a modern era challenge to optimize the management of HCC with the objective of improving overall and disease-free survival. The aim of this article is to describe all innovations in the surgical treatment of HCC.

ADVANCES IN THE ASSESSMENT AND PLANNING OF SURGICAL TREATMENT

The onset of HCC in a normal liver is an extremely rare situation. It is associated with the presence of pathological liver, and cirrhosis in most cases (80%). The presence of a pathological liver requires a comprehensive study of liver function and patient condition, in order to prevent any postoperative liver failure which occurs in approximately 8% of patients after major hepatic resections^[2]. The preoperative planning of a surgical procedure has improved the safety of liver resection in cirrhotic patients. The introduction of the concept of

future remnant liver (FRL)^[3] as a predictor of liver failure has contributed to the development of the concept of liver volumetry. In case of pathological liver, FRL was usually set at 50% of functional liver to prevent any postoperative liver failure^[3]. The necessity to calculate liver volumetry has increased the diffusion of three-dimensional (3D) surgical planning software^[4], with the double function of simulating surgery and calculating liver volumes. Even if conventional 2D images [magnetic resonance imaging (MRI) or computed tomography (CT)-scanning] reveal all the required information concerning tumors, major vessels and the biliary tract, surgeons could come across difficulties in perceiving the relationships of these structures before surgery, and during surgical planning. This platform allows to explore hepatic veins and portal triads from the hepatic pedicle up to segmental branches, allowing to evaluate spatial relationships with the tumor. This software allows to identify the vascular territory supplied by isolated vessels, allowing to simulate anatomical segmentectomy and easy planning of major and minor hepatectomies^[5]. Many software tools are now available to create a 3D model, offering a visualized model of patient organs and pathologies.

PORTAL VEIN EMBOLIZATION AND STEM CELLS APPLICATION

As previously mentioned, any hepatic resection must guarantee volume of FRL to prevent postoperative liver failure. In case of cirrhotic liver, the most common scenario in the presence of HCC, namely a portion of 40% to 50% of FRL, should be guaranteed so that liver function should not be affected. In case of insufficient FRL, portal vein embolization was suggested by Makuuchi *et al*^[6] in 1990, in order to stimulate liver hypertrophy before surgery. This hypertrophy usually requires 4 to 6 wk, but in some cases, more time could be necessary, especially in case of pathological parenchyma. However, during this period, the tumor could continue its progression, and the patient could well become inoperable. One possibility to reduce this risk is to obtain a quicker hypertrophy, reducing the time between portal vein embolization and hepatectomy. Several studies have suggested that stem cells could have an important role in the process of tissue regeneration^[7]. In case of acute or chronic liver suffering, stem cells can be stimulated from bone marrow. Among them, a subpopulation of cells (CD133⁺) have been recognized as potentially involved in liver regeneration after portal embolization, with encouraging results in some case series, demonstrating an augmented capacity of liver parenchyma regeneration^[7-11].

3D PRINT OF LIVER MODELS

Based on the data acquired by CT-scan which provide 2D information on geometrical measurements of tumors,

portal vein, hepatic vein and liver parenchyma, a 3D software edited model has been elaborated. 3D printing is a procedure which creates a solid 3D object based on a previous digital model. It is obtained *via* a 3D printer, which lays down thin layers of material in order to form a perfect 3D replica of the computer model. Initially developed to plan living donor liver transplantation^[12], an application is currently being found for it in liver surgery^[13]. The main objective for the development of this physical liver model is to overcome the limitation of conventional 3D models and 2D images such as the absence of reliable liver surface markers, the difficult appreciation of depth, and difficulties in identifying liver segmentation as well as the relationships between vascular and biliary structures. Another advantage is the possibility to use the 3D-printed model during liver surgery, packing the prototype into a sterilized nylon bag^[14], which allows to adjust the model to the surgical situation and the surgical field in order to obtain a better understanding.

REAL-TIME IMAGE FUSION FOR RADIOFREQUENCY ABLATION

Radiofrequency is currently considered an important support for the surgical treatment of HCC or in some cases it is considered an alternative to surgical resection^[15]. This treatment is highly operator-dependent, especially for targeting, monitoring and controlling, as well as in cases of very small lesions in a pathological parenchyma. The development of a real-time image fusion system is based on the fusion of real-time sonograms with images previously obtained on CT-scan or MR^[15-23]. To obtain this image fusion, a probe is equipped with a magnetic sensor, which generates a magnetic field interfaced with previously stored images. This fusion could lead to the detection of small HCCs, with an extremely high tumor-targeting success rate of 90% to 100%^[21-23]. Such encouraging results could improve the performance of RFA treatment for nodules, which could not be revealed by means of sonography. The development of this tool associated with a needle tracking system could be used to assess the efficiency of RFA, hence allowing for a 3D evaluation of the treated zone.

LAPAROSCOPIC SURGERY FOR HCC

Hepatic surgery still represents one of the most challenging and technical procedures requiring considerable experience. Despite such difficulties, some pioneers in laparoscopic surgery described the first laparoscopic liver resection in 1993^[24]. Initially considered a standard procedure for patients with a single and subcapsular lesion of less than 5 cm, located in the left liver or in the anterior sectors of the right liver, it currently represents a valid alternative to open surgery for major hepatectomies, as it is considered a safe and feasible

procedure for the treatment of malignant lesions^[25]. Even if the diffusion of this minimally invasive approach has rapidly gained consensus, laparoscopic resection of pathological livers was considered contraindicated due to the quality of parenchyma and condition of patients. A continuous progression of surgical devices over the last decades has improved the diffusion and safety of these complex procedures. The development of an ultrasonic scalpel (Ultracision™, Ethicon Endosurgery, Cincinnati, OH, United States) allows for a bloodless dissection of liver parenchyma. The ultrasonic dissector (Dissectron, Satelec, Mérignac, France) allows to divide and identify pedicles before being divided and clipped. Large vascular elements were divided after being secured with Hem-o-lok™ clips. Hemostasis and biliostasis of small elements were performed using saline-assisted bipolar electrocautery. Automatic vascular staplers allow for a safer and quick division and suture of large vascular structures, thereby reducing technical difficulties of manual suturing of large vessels. A crucial role during laparoscopic hepatic resection is the one played by ultrasonography, as it is used to localize hepatic veins and portal pedicles, allowing for a continuous control during parenchymal transection to check for safety margins. All these improvements, associated with the enhanced postoperative management of patients and augmented surgical skills have allowed the development of laparoscopic liver resection on cirrhosis, becoming a gold standard for treatment of HCC^[26]. Despite a strong association with augmented mortality and morbidity as compared to hepatic resection on non-pathological livers, liver resection guarantees several advantages, especially in the postoperative period^[27-30], reducing blood loss, postoperative pain, abdominal wall infection, length of stay, and facilitating the surgical operation in case of future liver transplantation^[31,32] due to a reduction of adhesions. As for non-pathological livers, and this is also true for HCC on cirrhosis, major hepatectomies, even associated with vascular resection^[33], are feasible with similar morbidity and mortality rates^[34].

ROBOTIC SURGERY FOR HCC

The development and diffusion of the da Vinci™ robotic surgical system (Intuitive Surgical, Inc., Sunnyvale, CA, United States) have introduced a novel approach in general surgery with an enormous potentiality of integration. The system is made up of a patient-site with four robotic operating arms and a surgeon-site equipped with a stereoscopic 3D camera. Using the robot, this system allows to replicate human hand movements with precise downscaling. As laparoscopy had reached a standardization in hepatobiliary surgery, difficult procedures could benefit from the integrated function of robotic surgery. The aim of robotic surgery is to improve clinical outcome. The two main limitations of laparoscopic surgery (visual and ergonomic limitations) have been totally overcome by the robotic system, allowing to perform advanced procedures with safety.

Precise dissections could be achieved, due to the possibility of using articulated systems with seven degrees of freedom and advanced 3D views. Major limitations of robotic surgery include operating costs and lack of haptic feedback. Once this limitation is overcome, the diffusion will be faster, and more cases will be described in the literature. Currently, regarding HCC, few case series^[35-39] are available and about 500 cases are described in the literature for liver malignant conditions. No benefits have been described as compared to laparoscopic surgery in terms of morbidity, mortality, and oncological results^[35,38]. This is probably due to the shortage of series and of patients and will require further studies.

ROBOTIC AND DEVELOPMENT OF AUGMENTED REALITY

The advent of robotic surgery has allowed the integration of the da Vinci™ robotic surgical system using virtual reality. During the surgical procedure, the 3D model reconstruction could be superimposed with real-time model mobilization, with the possibility to selectively view biliary structures, portal veins, the arterial system, hepatic veins, and lesions. This fusion is defined as augmented reality. This technique, initially described by Pessaux *et al.*^[40], use different skin landmarks associated with intra-abdominal landmarks to obtain a computer-assisted fusion of the 3D model with a real-time stereoscopic image of the operative field obtained *via* the 3D robotic camera. The superimposed image was used as a guide for the surgeon who, with the possibility to increase and decrease the transparency of the virtual model, could easily identify vascular structures as well as the correct localization of the lesion in order to obtain oncological resection margins. This modern era principle has found an application in other fields of surgery^[40-44], with an extremely interesting application of the lesion initially detected on CT-scan or MRI but impossible to detect preoperatively with ultrasound, called missing lesions^[45]. This superimposition of 3D model reconstruction of the first bi-dimensional imaging in which the lesion was available allows the robotic image to guide resection of the liver segment in which the lesion is supposed to be located, hence allowing to achieve satisfying oncological margins.

MINIMALLY INVASIVE APPLICATION OF FLUORESCENCE

Indocyanine green (ICG) is a non-toxic, non-radioactive and highly safe fluorophore with the capacity to appear green when excited by light in the near infrared spectrum. Historically used to predict liver failure^[46], its elimination from blood depends on hepatic blood flow. Cellular uptake and biliary excretion are measured using the ICG-plasma disappearance rate (ICG-PDR). In case of augmented values of ICG-PDR^[46,47], major

hepatectomies could be contraindicated to prevent postoperative liver failure. Considering the integration of a fluorescence camera in the robotic da Vinci™ system and laparoscopic camera, fluorescence could be integrated in operative strategies during hepatectomies. Arteries and veins are the first structures to be visualized after venous injection of ICG (5-60 s), and this could allow for an easier recognition of anatomical variations and identification of structures in the hepatic hilum. After vascular capitation, approximately 45 to 60 min after injection, ICG accumulates in the liver and is secreted in the bile. This application could be valuable to prevent complications during difficult cholecystectomies^[48], as it could allow to identify bile duct and cystic duct. In the future, it could well reduce the interest in using a perioperative cholangiogram, thereby reducing the exposure of patients to radiation.

Concerning the identification of liver neoplastic tissue, hemodynamic, metabolic and biliary excretion of ICG allow for the identification of tumoral parenchyma^[49]. Poorly differentiated HCCs are characterized by a low capitation of the lesion with a fluorescent rim, due to a perilesional alteration of biliary excretion^[50]. Well-differentiated HCCs have an intense fluorescent pattern^[50]. This finding, as demonstrated for colorectal cancer liver metastasis, could allow to detect undetected lesions with previous conventional preoperative imaging^[51], with a potentially significant impact on disease-free survival^[52].

CONCLUSION

HCC still represent a challenge for the surgeon of the next era. Considering the rapid evolution and quick technological progress applied to surgery, additional solutions will be put forward to achieve lower morbidity and mortality rates, guaranteeing a more precise resection, which will offer better oncological results. This progress, associated with progress in diagnosis^[53], advances in medical treatment, and an improvement of radiology and oncology will ensure a better future for our patients.

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