Effective multimodal management of hepatocellular carcinoma. An update

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Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally, with 854,000 new cases and 810,000 deaths per year [1]. The incidence of hepatocellular carcinoma (HCC) increases progressively with age, reaching a peak at 70 years. HCC is usually developing in chronic liver disease patients, mainly due to chronic hepatitis B and C (HBV, HCV) infection, but also to non-alcoholic fatty liver disease (NAFLD). It is estimated that 500,000-900,000 new cases of HCC in the USA may develop as a consequence of the high prevalence of NAFLD [2]. HCC has a male preponderance, with a male to female ratio estimated to be 2–2.5:1. It represents about 90% of primary liver cancers. Chronic active HBV, HCV infection, high alcohol consumption, aflatoxin exposure, NAFLD, haemochromatosis and steatohepatitis represent the main risk factors. The incidence of HCC is increasing despite effective antiviral therapy for HBV, HCV, and HBV vaccination at birth [3].

Diagnosis of HCC is based on contrast enhanced imaging methods such as multiphase computed tomography (CT) and magnetic resonance imaging (MRI). MRI has higher sensitivity compared to CT for small lesions 1-2cm [1]. HCC may also be diagnosed by ultrasound or biopsy, while PET-CT contributes slightly to the diagnosis. Without therapy, survival is ranging between 6-8 months, whereas transarterial chemoembolization (TACE) achieves 20-25 months survival [4].

HCC is characterized by phenotypic and molecular heterogeneity. Biomarkers represent a non-invasive way to detect HCC at early stages and have the potential to estimate disease prognosis and recurrence. The specificity of αFP for HCC is close to 100% but the sensitivity falls below 45% [5]. For this reason, it is imperative to find other more sensitive biomarkers for the diagnosis and identification of recurrence. More specifically, autophagy's molecules, such as beclin-1, LC3-II and p62 seem to play a significant role in HCC [6]. Basal autophagy acts as a tumor suppressor by maintaining genomic stability in normal cells. However, once carcinogenesis is established, unbalanced autophagy will promote tumor growth. According to multicenter studies increased autophagy has been detected in advanced HCC and is closely related to low survival. Moreover, autophagy contributes to the chemoresistance of HCC cells [6]. Another serological and histochemical marker that is specific for HCC is glypican GPC3. Recent studies report higher levels of GPC3 expression in poorly differentiated HCC [7]. Other biomarkers involved in the development and progression of HCC is β-catenin, cell free DNA (cfDNA) and circular RNAs (such as cSMARCA5 and circZKSCAN1). The latter have been used in clinical trials as biomarkers for diagnosis, early recurrence detection and treatment of HCC [8].

Advances in the surgical management of hepatocellular carcinoma

Surgery (liver transplantation, resection and ablation) can offer potential cure and long-term survival. Liver transplantation is the ideal treatment for liver cirrhosis and HCC, but has several limitations, as it is mainly applied in patients which fulfil the Milano criteria (single

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tumor <5 cm, 3 tumors <3cm each, absence of vascular infiltration) [9].

Liver resection is the treatment of choice for large HCCs with preserved liver function. Among more comprehensive staging systems, six have been thoroughly tested, three European (the French classification, the Cancer of the Liver Italian Program [CLIP] classification and the Barcelona- Clínic Liver Cancer [BCLC]) and three Asian (the Chinese University Prognostic Index [CUPI] score, the Hong-Kong Liver Cancer [HKLC] staging system and the Japan Integrated Staging [JIS]. The Barcelona Clinic Liver Cancer (BCLC) is the most commonly accepted system for prognosis and study comparisons. It is an evolving system that links tumor stage with treatment. It entails prognostic variables related to tumor status, liver function and health performance status along with treatment-dependent variables obtained from randomized trials. It is an evolving system that correlates tumor stage with treatment strategy in a dynamic manner, enabling the incorporation of novel advances in the understanding of the prognosis and management of HCC [1]. Nevertheless, BCLC proposes only conservative treatments for the intermediate and advanced stage, excluding these patients from liver transplantation and resection [1]. The guidelines of TACE, as the only management option for the intermediate stage, according to BCLC algorithm, has been heavily criticized by the international hepatobiliary surgical community. An observational multicenter study showed that 36% of patients who underwent liver resection for HCC were classified as intermediate stage and a 5years overall survival of 57% was achieved [4].

A recent systematic review has shown that liver resection may broaden its indications as it can be applied in intermediate and advanced stages of the disease (multinodular HCCs, HCCs with limited macrovascular invasion) with satisfactory long-term survival [10]. Recently the Pan-Asian adapted ESMO clinical practice guidelines have included liver resection as a reliable option for multinodular HCC and for advanced stage HCC with intrahepatic macrovascular invasion without extra-hepatic metastases [11]. Patients with HCC and pre-existing liver disease often present the problem of small future liver remnant (FLR). The gold standard for patients with HCC and inadequate FLR is portal vein embolization (PVE) [12]. Recently a new technique named radiological simultaneous portohepatic vein embolization (RASPE) has been developed which aims to rapidly increase the FLR in order to perform major hepatectomy. During RASPE the right hepatic vein (HV) and the right portal vein are embolized simultaneously [13]. Recent studies showed that RASPE is safe and induces faster and greater FLR, with better functional capacity, in comparison to PVE [13]. The increase in regeneration rate versus PVE could be due to the following reasons: embolization of the hepatic vein could reduce portal inflow and minimize porto-portal collaterals. Furthermore, RASPE can increase liver injury by reducing the flow in the hepatic artery through the hepatic arterial buffer response.

RASPE has the potential to overcome the disadvantages of PVE and ALPPS, since it increases FLR rapidly, is safe and has low post-operative mortality. However, until nowadays most studies are conducted on patients with metastatic liver lesions without pre-existent liver disease [14]. Therefore, new trials should be carried out with HCC, as the regeneration process differs significantly.

Minimally invasive liver resection (MILR) gains more and more ground on a global scale. MILR includes laparoscopic liver resection (LLR) and robotic liver resection (RLR). For patients with resectable HCC, LLR has many advantages over the open approach. The main advantages are lower incidence of ascites and postoperative liver failure, as the abdominal trauma is smaller and the surgical stress significantly less [15]. According to a recent systematic review LLR for HCC is feasible and offers improved short-term outcomes in respect to complication rate, blood loss, and duration of hospital stay, as well as comparable long-term outcomes to those of the open approach [16]. Several studies have shown the feasibility of LLR for HCC in cirrhotic patients and reported reduced complications rates and shortened hospital stay [17]. As regards to the size and location of the mass, they do not represent contraindications for LLR in specialized centers [17]. However, LLR remains a technically demanding procedure that requires advanced laparoscopic technology and an experienced surgical team.

Moreover, the introduction of robotic surgery might bridge the gap of conventional laparoscopy. The most significant clinical benefit of the robotic system over conventional laparoscopy is presumably the performance of minor resections in difficult located liver lesions. Also, the endo-wristed instruments make the robotic system appropriate for parenchymal-sparing resection, and parenchymal preservation [18]. It seems that robotic liver resection maintains the benefits of minimally invasive surgery, but its superiority over laparoscopy has

not been proved yet [18]. On the other hand, robotic surgery has much higher cost in comparison with LLR.

Liver transplantation (LT) is the ideal therapy since it may cure both cirrhosis and HCC. Until nowadays, LT has been offered to patients with HCC within the Milan criteria and preserved liver function. However, there is a lack of potential donors for deceased donor liver transplantation (DDLT). Latest data indicate that many patients with HCC have low probability of receiving DDLT before tumor progression [19]. Therefore, Living Donor Liver Transplantation (LDLT) is emerging as an additional therapeutic option, since it has remarkable advantages: (1) The transplantation can be performed on an elective basis before serious decompensation of the recipient or tumor growth, (2) waiting time can be short minimizing the risk of dropout, (3) grafts are in excellent condition and (4) LDLT provides immunological benefits. Due to the technical complexity of the LD allograft, LD recipients have higher complication rates, including bleeding, hepatic artery thrombosis, biliary complications and late biliary strictures. Another complication often associated with LDLT is small for size syndrome (including coagulopathy, cholestasis, encephalopathy and ascites), which can increase mortality. Studies from Asian centers demonstrate that with the incorporation of biological markers in the selection criteria, in order to eliminate biologically aggressive HCCs, LDLT may contribute to better survival rates for HCC patients [20].

In conclusion, significant advances have taken place in the surgical management of hepatocellular carcinoma, over the last 10 years, such as liver resections in the advanced stages of the disease, complex interventional radiology techniques for the management of the small liver remnant, broad application of minimal invasive surgery and living related liver transplantation. All these, along with the conservative management (TACE, targeted therapies, immunotherapy) can offer long term survival with good quality of life and can transform an aggressive disease to chronic disease. It should be emphasized that the management of HCC should be done in specialized hepatobiliary centers with harmonic collaboration of different specialities, the cases should be discussed in the multidisciplinary tumor boards and an individualized approach should be followed.

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