

# Multimodal therapy for hepatocellular carcinoma: the role of surgery

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**Abstract. – OBJECTIVE:** Liver cancer is one of the widest spread malignancies in the world and its incidence is still on the rise. The surgical resection of liver cancer has become a widely performed procedure with considerably improved outcomes, low mortality rate, transfusions, and post-op bed stay.

**MATERIALS AND METHODS:** Our goal with this paper was to conduct a narrative review of the literature in regard to the surgical treatment of hepatocellular carcinoma (HCC).

**RESULTS:** There are various modalities of treatment for the HCC, e.g., hepatic resection, LT, or radiofrequency ablation (RFA) – the selection of a specific treatment regimen plays a decisive role in the survival rate of the patient and this, in turn, is guided by factors like size and distribution of lesion and the stage of malignancy. A more efficient patient selection for each treatment increases the survival rate of the patients in each subgroup.

**CONCLUSIONS:** Surgical procedures play a crucial role in treatment of hepatocellular carcinoma as part of a multimodal therapy.

*Key Words:*

Hepatocellular carcinoma, Surgical treatment, Multimodal treatment.

of cirrhosis and other chronic liver diseases. The treatment regimens have evolved a great deal too. The surgical resection of liver cancer has become a widely performed procedure with considerably improved outcomes, low mortality rate, transfusions, and post-op bed stay. In the past, this procedure used to be an intensive measure with quite a limited scope<sup>4</sup>. With the advancement of technology in the field of medicine and increased awareness of the factors that dictate the chances of success in such an operation, our assessment of the disease severity and extent has greatly improved<sup>5</sup>. Other such procedures, such as ablative approach and minimally invasive procedures have added to our paraphernalia that is to be employed to treat this disease<sup>6</sup>.

There are various modalities of treatment for the HCC, e.g., hepatic resection, LT, or radiofrequency ablation (RFA) – the selection of a specific treatment regimen plays a decisive role in the survival rate of the patient and this, in turn, is guided by factors like size and distribution of lesion and the stage of malignancy<sup>7</sup>. A more efficient patient selection for each treatment increases the survival rate of the patients in each subgroup<sup>8</sup>.

## Introduction

Liver cancer is one of the widest spread malignancies in the world and its incidence is still on the rise<sup>1</sup>. Primary hepatocellular carcinoma, which was previously termed uncommon is now encountered quite frequently, possibly because of increased incidence of hepatitis C infections<sup>2</sup>. Owing to the improvements in the employed treatment procedures, the mortality rate has been reduced to less than 10%, and the chances of about 5 years survival up to 30% to 50%<sup>3</sup>. Therefore, the treatment most often becomes quite complicated due to the simultaneous occurrence

## Materials and Methods

Our goal with this paper was to conduct a narrative review of the literature about surgical treatment of hepatocellular carcinoma and outline the latest principles of its multimodal treatment depending on the disease-stage.

### *Predictors of Surgery Outcome*

In a non-cirrhotic liver, HCC is not usually diagnosed until it becomes large and symptomatic. An intensive surgical approach can be employed to treat these cases where there is no other mor-

bidity of the liver occurring simultaneously. This is a safe approach, and a 5-years survival rate is up to 37%<sup>9</sup>. In the case of HCC, it has been difficult to find specific biomarkers that are needed for the assessment of the patient before surgery. A motley of other markers such as des- $\gamma$ -carboxy prothrombin, glypican-3, cytokeratin 19, Next-Generation Sequencing (NGS), proteomic analysis, circulating microRNAs, have been tested for the purpose but has yielded no satisfactory result<sup>10</sup>. Only AFP has been the most consistent diagnostic and prognostic tool that is evidenced based<sup>11,12</sup>. The monitoring of liver functioning has become another important diagnostic and predictive biomarker of the extent of the disease. Particularly, the stages of cirrhosis (Child-Pugh score) assessment and the treatment in the early phases of this disease create a longer “window of opportunity” in which the malignancy can be operated on and resected<sup>13</sup>. Moreover, other biomarkers of the immunologic nature are also used in the assessment of the patient before surgery. In certain cases, the resection is contraindicated as in conditions in which the functional capacity of the liver is severely impaired. These conditions include ascites, jaundice, Child-Pugh B and C, and liver atrophy. In these conditions, there is a great risk of decompensation and loss of functional capacity post-operatively. Other conditions that preclude surgical treatment are the presence of portal vein thrombosis, lymph node metastases, extra-hepatic localizations, and intra-hepatic diffuse disease<sup>14</sup>.

### ***Neoadjuvant Therapy***

In other solid organ malignancies except for HCC, neoadjuvant therapy is employed to slow down and downstage an advanced tumor. This approach has improved chances of survival and outcome of the treatment in many patients. But in the case of HCC, the role of neoadjuvant therapy is yet to be established on better grounds<sup>15</sup>. This therapy works efficiently in some instances given the unique characteristics of the HCC but not the others. The aggressive nature of this tumor, coupled with underlying cirrhosis and delayed diagnosis are some of the factors that call for the preservation of normal liver function until the surgery is performed<sup>16</sup>.

Hepatectomy is a challenging modality of treatment in cases where there is cirrhosis along with HCC due to increased portal pressure and impaired coagulation system in such patients<sup>17</sup>. For hepatic resection, some of the individual

centers have reported a 5-year survival rate of 40%-50%<sup>3,18,19</sup>, and a 10-years survival rate of 8%-17%<sup>20-22</sup>. In early resection, a %70 survival rate and 60% 5-years recurrence rate were observed in one of the studies<sup>23</sup>.

With the advent of modern techniques that allow proper control of blood coagulation hemostasis, the surgical treatment of HCC is being promoted by most authorities. The two most important procedure types in this regard are laparoscopic hepatectomy (LH) and open surgery<sup>24</sup>. Both of these techniques have their pros and cons. Laparoscopic hepatectomy has an advantage in being minimally invasive and is more beneficial in the case of HCC with cirrhosis. Many studies have shown that patients who had concurrent cirrhosis with HCC and underwent LH for the treatment had experienced less blood loss, fewer complications post-operatively, and shorter stay in hospital as compared to those patients undergoing open resection<sup>25,26</sup>. Most of the above-mentioned studies were retrospective and limited to minor resections. Since then, some randomized clinical trials (RCT) and other case-matched studies focused on HCC associated with cirrhosis have also reported the favorable outcomes of LH<sup>27-29</sup>. The classification of minor and major resection is such that a hepatectomy of fewer than three sections is defined as minor and major resection is defined as removal of more than three sections<sup>30-32</sup>.

Open hepatectomy is a widely adopted curative treatment of HCC in the whole world. However, those patients who have a poor liver function, such as in cases of cirrhosis, will undergo OH with a large surgical incision, greater extent of resection, and relatively more blood loss. LH is now emerging on the horizon as a more promising alternative procedure for HCC patients with cirrhosis<sup>33</sup>.

### ***Other Techniques***

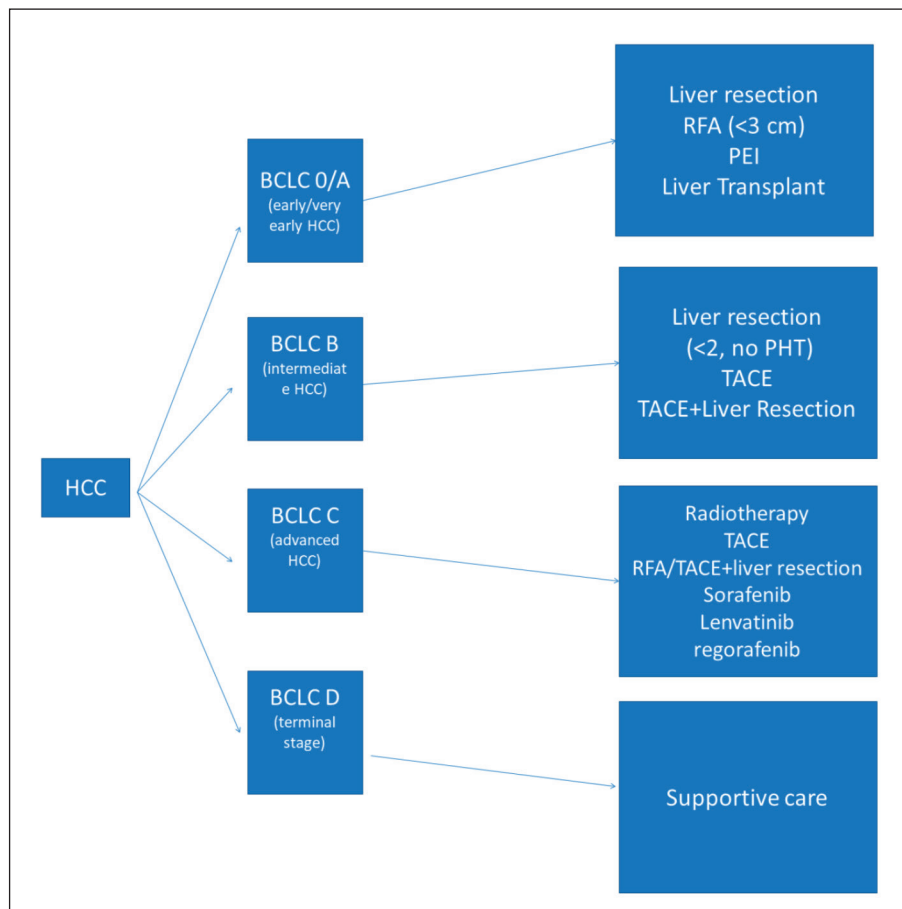
HCC is a malignancy that is heterogeneous in nature due to its etiology and its biologic and clinical behavior<sup>34</sup>. Barcelona Clinic Liver Cancer classification system divides HCC into five stages namely 0, A, B, C, and D based on the established diagnostic and prognostic criteria. For example, for patients with BCLC-B, the recommended treatment is transarterial chemoembolization (TACE)<sup>35</sup>. Owing to the improvements in surgical techniques and perioperative care in recent years, the morbidity and mortality associated with liver resection have been greatly reduced. In certain settings, this treat-

ment can be provided irrespective of the risk factors involved such as portal hypertension, impaired liver function, or any multifocal disease, and surgery seems a favorable approach with great potential towards a cure<sup>36-38</sup>. Several studies<sup>39,40</sup> have done a comparison of the outcomes of liver resection beyond the current guidelines. As some of the patients may get a lot of benefits from the surgical treatment with curative intent, there is no evidence that those who do not benefit from this treatment are left with any disadvantage. In one of the studies, outcomes of the patients who had undergone surgical resection as their first or second treatment after the initial diagnosis within two years span were compared with those patients who had been given a non-surgical treatment. The results showed that the overall survival rate was significantly better for patients who had adopted liver resection as a treatment for HCC<sup>41</sup>. Moreover, Yin et al<sup>42</sup> reported that liver resection had better overall outcomes in terms of the survival rate of the patient as compared to TACE for multiple HCC beyond Milan's

guidelines in a randomized trial. The overall 1-, 2-, 3-years survival rates for the resection and TACE were 76, 64, and 52 percent, and 52, 35, and 18 percent respectively. In a later meta-analysis that compared the survival rates between liver resection and TACE, patients who received the resection therapy showed better overall survival outcomes than those in the TACE group<sup>43</sup>.

Radiofrequency ablation (RFA) is a thermal treatment that uses local application of electric energy (high frequency alternating current) to obtain tumor necrosis. A needle electrode connected to a generator is inserted inside the malign tumor. Due to frictional heat caused by ions movement around the electrode, the local temperature will reach around 60°C. At these temperatures irreversible cellular necrosis occurs around the electrode.

Based on the Barcelona Clinic Liver Cancer staging system, RFA is applied for the treatment of patients having very early (Stage 0) and early stage (Stage A) HCC. Patients with Child-Pugh class A or B and three or fewer



**Figure 1.** Liver cancer treatment algorithm. BCLC, Barcelona Liver Cancer; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; RT, radiation therapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

HCC nodules less than 2 cm are indicated for RFA (Figure 1).

In HCC tumor having a diameter less than 2 cm, RFA can be safely used as an alternative to hepatic resections. There are published reports showing the superiority in terms of outcome of RFA compared with surgical resection in HCC measuring up to 2 cm<sup>44,45</sup>. The benefit is even higher for patients with tumors located in the central part of the liver<sup>46</sup>. RFA was also indicated for patients with 2-3 tumors under 3 cm and studies suggest that can be also used for the treatment of larger tumors. RFA showed similar long-term results compared with open surgery in patients with a solitary tumor less than 5 cm. In these patients the 1-year survival rate after RFA was 96% vs. 93% for open surgery. At 4 years the overall survival rate was 68% after RFA, and 64% following resection<sup>47</sup>.

One important trial showed a 1 and 5-year overall survival rates for the RFA group and the resection group of 87%, 55%, and 98%, 76%, respectively. At 5 years' interval the recurrence rate was 63% for the RFA group and 42% for the resection group<sup>48</sup>.

All the actual guidelines<sup>45,49-51</sup>, recommend RFA treatment only in very early/early stages of the BCLC staging system.

Microwave ablation (MA) utilizes high-frequency microwaves around a probe inserted into the malignant tissue<sup>52</sup>. The technique allows the use of multiple probes simultaneously. In comparison with RFA, it performs larger areas of necrosis in shorter time.

The available data have shown similar results of microwave ablation in early stages patients compared with RFA. Complete tumor necrosis was obtained in 87-98% of cases, the recurrence rate was 10-24% with a 5-years survival rate of 24-78%<sup>53</sup>.

Based on these results, microwave ablation has replaced RFA in several departments specialized in liver cancer treatment<sup>54</sup>.

Percutaneous ethanol or acetic acid ablation (PEI) is a technique with historical value and it was used long before the development of the RFA treatment. It was relatively cheap and easy to perform. The method was abandoned since it raised concerns in regard with the extent of necrosis following the procedure. In a retrospective study on 73,136 patients, Chang et al<sup>55</sup> showed that RFA was associated with a better prognosis than PEI/PAI in patients with early HCC especially in liver cirrhosis. According to the published data, the authors limit the technique in selected cases only. Patients with low-grade cancers, advanced tumor

stage and those without viral infection may benefit from PEI.

Cryoablation (CA) may obtain tumor necrosis in patients with advanced, non-resectable HCC. The technique uses an intratumorally metal probe for tumor freezing and necrosis<sup>56</sup>. It is relatively simple, has a low complications rate and is costless. Some authors recommend the technique in patients with tumors adjacent to large vascular pedicles in which RFA is not recommended due to possible vascular injuries. Several benefits have been attributed to CA in comparison with RFA such as low rate of complications, visual assessment of necrosis extent and increased immunological response<sup>57</sup>.

Serious concerns in regard with the postoperative complications following RFA have been raised. Colonic wall necrosis, diaphragmatic lesions, lung atelectasis and massive bleeding were all cited<sup>58</sup>. Several studies have shown that the overall incidence of these complications is lower after cryoablation<sup>59,60</sup>. Song et al<sup>61</sup> showed that for subdiaphragmatic tumors, the lung injury rate following RFA was around 25%. Other authors showed that common RFA complications such as bleeding, liver abscesses, biliary and gastrointestinal perforations were significantly lower following CA<sup>59</sup>. Therefore, we believe that CA is a safe therapy for HCC and should be performed especially in liver cancer located near major structures such as colon, stomach, diaphragm and cava vein.

### ***Treatment of HCC in Early-Stage Disease***

Liver resection is the treatment of choice in patients with normal liver tests with no hypertension in the portal system and small lesions (<2 cm)-BCLC 0-very early stage. (Figure 1).

In patients with early HCC BCLC-A -single nodule or 3 nodules <3 cm, at the current time two options are available. Liver resection is preferred in patients with low grade cirrhosis while liver transplantation is preferred in patients with more advanced cirrhosis<sup>62-65</sup>.

Several authors also recommend the use of PEI and RFA in this stage of the disease. However, extensive analysis performed by several authors has shown the superiority of liver resection techniques in terms of survival compared with PEI or RFA<sup>48</sup>.

### ***Intermediate-Stage Disease***

TACE is the treatment of choice in patients with multicentric HCC (BCLC stage B)



without major vascular invasion, lymph nodes metastasis or distant metastases<sup>66</sup>. Despite this recommendation, several authors suggest that liver resection may be also used in this stage<sup>67</sup>. Zhong et al<sup>68</sup> showed better oncologic outcome, on 393 patients with stage B disease. The 3 years survival was 59% in patients with surgery compared with 29% following TACE<sup>68</sup>. A study conducted by Ho et al<sup>38</sup> on 1,065 patients with stage B liver carcinoma showed a 5-year survival rate of 36.6% following liver resection and of only 11% following TACE. A more recent approach in stage B cancers was represented by preoperatively TACE followed by liver resection. The results were promising. In a prospective report including 168 patients with stage B liver cancer with lesions larger than 5 cm, the 5-year survival was 50.5%<sup>69</sup>. The rationale behind the combined procedure is the downstaging of the tumor followed by surgery. At the current time this approach is adopted by many specialized hospitals for the treatment of stage B hepatocarcinoma.

### **Advanced-Stage Disease**

HCC with a major vascular invasion, lymph nodes metastasis, distant metastases or patients severely ill is classified as BCLC C. The patients with stage C have low life expectancy. The first line treatment in these cases may include multikinase inhibitors who displayed some positive results in clinical trials such as REFLECT trial (lenvatinib)<sup>70</sup>. Several therapeutic options may be attempted such as systemic sorafenib therapy, radiotherapy, TACE and proton beam irradiation.

Some Asian authors suggest that surgical resection in stage C carcinoma, although palliative may prolong patient's life compared to systemic therapy. (27 months vs. 12 months)<sup>71</sup>. Other authors suggest that combination RFA/TACE+resection may provide a better outcome in bilobar HCC with normal liver tests<sup>72</sup>.

Regarding the novelties of this report, we show here that liver surgery is feasible and safe in advanced stages. The surgical resection in such cases must be performed by experienced surgeons.

### **Conclusions**

Surgical therapy is the only therapy with curative intent for patients with HCC. Multimodal therapy may provide acceptable medium to long term patient survival. Patients with good hepatic

function and significant functional remnant parenchyma are perfect candidates for resection.

### **Conflict of Interest**

The Author declares that he has no conflict of interests.

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