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Chapter 1

Introductory Chapter: Updates on the Management of Hepatocellular Carcinoma

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1. Introduction

Due to many factors, such as the frequent coexistence of chronic liver disease, the wide heterogeneity in HCC presentation, increased available therapeutic options with diverse responses to these therapies in addition to the variable biologic behavior of the tumor, it is crucial to manage HCC patients by multidisciplinary team [1–3].

2. Early stage HCC

Only 15–30% of patients present in early stage HCC and can receive curative treatments [4]. This is mainly due to liver cirrhosis associated with hepatocarcinoma, and the late presentation reported in most patients.

2.1. Resection

Surgical resection is the best treatment option for solitary tumors in patients without cirrhosis with postresection 5-year survival rates of 41–74% [5, 6]. A cirrhotic liver loses its regenerative potential and has less functional reserve [7, 8]. The best outcome after resection is achieved in cirrhotic patients with well-compensated Child-Pugh class-A cirrhosis, normal bilirubin, and no portal hypertension [20]. Poor prognosis is influenced by pathological findings, such as vascular invasion, presence of satellites, and poor differentiation. Anatomic resection margins of 2 cm are recommended as it provides better survival outcome than narrow resection mar-

gins <1 cm, provided that appropriate remnant liver volume is maintained [9]. The minimal critical remnant liver volume for resection is approximately 25% (15–40%) for noncirrhotic and 50% (25–90%) for cirrhotic livers. Preoperative portal vein embolization (PVE) is recommended when the estimated remnant liver volume unmet the minimal requirement.

Portal hypertension, hepatic venous pressure gradient (HVPG) ≥ 10 mmHg, was found to be the best predictor of postoperative liver decompensation and poor long-term outcomes in compensated cirrhotic patients undergoing hepatic resection [10]. Postresection tumor recurrences often have multifocal presentations and repeat resections are rarely ideal, instead, salvage liver transplantation, or other loco-regional therapies, with or without oral multi-kinase inhibitors are more suitable. Molecular biomarkers and gene signatures [11] can be used for better selection of patients for hepatic resection with low risk for late recurrence.

2.2. Liver transplantation (LTx)

LTx is a potentially curative treatment and the best treatment option for patients with decompensated cirrhosis, and it allows the removal of the primary tumor and treats hepatic insufficiency by removing cirrhotic tissue simultaneously [12]. In an attempt to identify the most appropriate transplant patients, the Milan criteria have emerged as main inclusion criteria for LTx. LTx is recommended for the patients with single lesion not larger than 5 cm, or up to three lesions with each less than or equal 3 cm. Restriction to Milan criteria is compatible with early BCLC stage and results in a 5-year overall survival rate of 75% with a risk of recurrence less than 15% in specialized liver transplantation centers. The perioperative mortality and 1-year mortality are expected to be approximately 3 and ≤10%, respectively [5]. Milan criteria was found to be an independent prognostic factor for outcome after liver transplantation with 5-year survival rate similar to non-HCC patients (65–78%) [13].

MELD score, initially proposed for prediction of early mortality in patients with cirrhosis, is the standard method to prioritize assignment of cirrhotic patients to the LTx waiting list. However, the MELD score is not able to predict the drop-out rate and mortality in the patient with HCC; therefore, a "MELD exception" has been developed to assign extra points to the HCC patients on the basis of the tumor burden leading to increased percentage of LTx (30–40%) performed for HCC [14, 15]. Several priority scores have been assigned to these patients. Early proposals assigned 24 and 29 points to single <2 cm and single 2–5 cm or three nodules each <3 cm, respectively. In the current era, no extra points and 22 points are assigned to those patients, respectively. Several studies have investigated the effect of expanding the Milan criteria, the University of California San Francisco (UCSF) proposed criteria for LTx for HCC (one tumor ≤6.5 cm or up to three nodules with the largest ≤4.5 cm, and the total tumor diameter ≤8 cm). These criteria have been prospectively and retrospectively validate with an overall survival comparable to those within Milan criteria [16]. Modest expansion of Milan criteria to "up-to-seven" criteria was proposed. This pathology-based proposal (HCCs having the number 7 as the sum of the size of the largest tumor and the number of tumors in patients without microvascular invasion) [17] has been externally validated in an independent series [18] but requires prospective validation studies using pretransplant radiolog.

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2.3. Local ablative therapy

Tumor ablation techniques induce their therapeutic effect by destroying tumor cells, either directly by exposing tumor cells to chemical substances (ethanol or acetic acid) or physically by modifying the temperature (heating or cooling).

2.4. Percutaneous ethanol injection (PEI)

PEI has been considered the most appropriate technique utilized for many years owing to its impacts on the natural history of HCC as shown in several studies. The major limitation of PEI is the high incidence of local recurrence (33–43%). PEI is indicated for the treatment of nodular-type HCC up to 5 cm and achieves complete necrosis in 50–90% of tumors 2–5 cm.

2.5. Radiofrequency ablation (RFA)

In the last decade, RFA appears to be superior to all other local ablative therapies and is now the first-line technique for ablation [19]. RFA is considered the standard of care for patients with very early and early stage tumors not suitable for or refusing surgery. Patients with Child-Pugh class A and tumor size of less than or equal 3 cm in diameter undergoing percutaneous ablation had the best prognosis [20]. RFA depends on energy production, via utilization of elevated frequency alternated currents, through an electrode inserted directly into the tumor that induces coagulative necrosis of the tumor with safety margins of the apparently healthy tissue around the lesion. RFA is less invasive, less expensive with lower complication rates and shorter hospital stay than surgical resection (**Figure 1**). However, RFA is size-dependent. RFA can produce a necrotic area of about 4 cm so it should be considered the first option for the treatment of small HCC measuring up to 3 cm. With development of technology, the use of

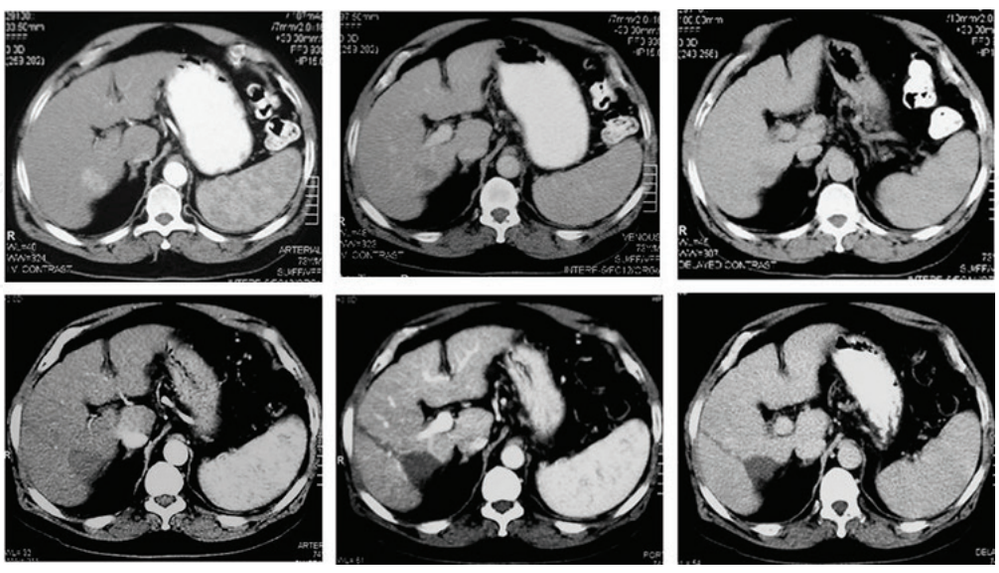

Figure 1. Above, left to right: Triphasic CT scan revealed enhancing right lobe focal lesion (segment VII) showing washout in the portovenous phase and in the delayed phase. Below, left to right: Post-RFA triphasic CT scan obtained 1 month later revealed complete necrosis with no residual enhancing tumor.

expandable tipped or cool-tip electrodes will achieve ablation of areas 5 cm or more in diameter effectively. Bipolar RF electrodes can create a larger (up to 8.4 cm) ablation in a short time [21].

2.6. Microwave ablation

Microwave ablation (MWA) is an emerging form of thermal ablation, alternative to RFA, evaluated for the treatment of HCC using electromagnetic waves with frequencies greater than 900 kHz [22]. MWA utilizes active ablation heating, enables continuous and uniform ablation, permitting generation of higher temperatures and larger ablation zones, thus leading to higher rates of tumor necrosis. Another advantage of MWA over RFA is that treatment outcome overcomes the "heat-sink" effect of vessels proximal to the tumor which can lead to incomplete ablation.

3. Intermediate stage HCC

3.1. Transarterial therapies

Transarterial therapies include TACE, transarterial embolization (TAE), transarterial bland embolization, transarterial chemotherapy, and transarterial radioembolization [23, 24]. TACE is currently considered the standard of care for patients with large multifocal lesions with compensated liver function, without evidence of vascular invasion or extra hepatic spread; however, TACE is recommended in Japan for HCC patients with vascular invasion if radiological portal invasion (Vp) is Vp1 or Vp2; distal to, or in the second-order branches of, the portal vein [25]. Success of TACE is controlled by the maximum and sustained retention of the chemical agent used (**Figure 2**). Lipiodol has been widely used in TACE protocols due to the great hunger of HCC to lipiodol. However, there is no data validated the effect of lipiodol in achieving slow release of the chemotherapeutic agents leading to sustained concentration of chemotherapeutic agents in tumor. Moreover, this can be achieved by the use of embolic microspheres which have the ability to sequester chemotherapeutic agents and release them in a controlled manner over a 1-week period and a subsequent increase of the local concentration of the drug with minimal systemic toxicity. Occurrence of complications after TACE may be related to more extensive disease; requiring nonselective embolization, and poor liver reserve. Selection of patients is mandatory to prevent post-TACE-induced liver failure. For example, patients with total bilirubin >3 mg/dL were excluded from TACE in several studies. MELD score can be used to select best candidates for TACE [26].

3.2. TACE with drug-eluting beads

Special particles of various sizes (from 100 to 1000 μm) can be used with the characteristic not only of embolizing the tumor but also of releasing substances overtime (up to 30 days) that determine antiblastic necrosis. Embolic microspheres have the ability to actively sequester chemotherapeutic agents as doxorubicin hydrochloride from solution and release them in a controlled fashion over a 1-week period. The use of embolic microspheres has been shown to substantially diminish the amount of the chemotherapeutic agent that reaches the systemic circulation, increase the local concentration of the drug, and the antitumor efficacy with negligible systemic toxicity. Tolerance to conventional TACE has improved by the use of drug-eluting beads that obstruct arterial vessels and slowly release chemotherapy [27].

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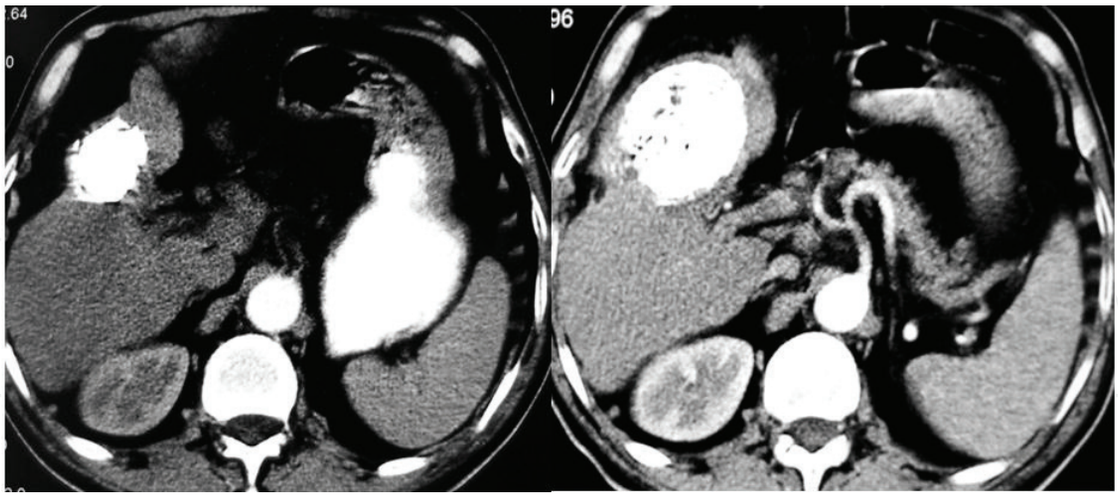

Figure 2. Left: Triphasic CT scan revealed enhancing right lobe focal lesion in the arterial phase. Right: Post TACE triphasic CT scan obtained 1 month showed complete cure.

3.3. Radioembolization

Selective internal radiation therapy (SIRT) has been emerged as a therapeutic option for intermediate-stage HCC. SIRT aims to selectively target radiation to liver tumors while limiting the dose to normal liver parenchyma, thus preventing ischemia to the liver tissue, SIRT exerts its effect through deposition of yttrium-90 ((90)Y) microspheres into the hepatic artery that feed the tumor in a 3:1 to 20:1 ratio compared with a normal liver, so that tumor nodules are treated irrespective of their number, size, or location [28].

4. Advanced stage HCC

4.1. Systemic therapy

Systemic therapy with hormonal agents such as octreotide and tamoxifen or with biological agents as interferon therapy [29], and thalidomide showed poor results.

Systemic chemotherapy showed contradictory results. HCC is one of the most chemo-resistant tumors; in addition, chemotherapy is poorly tolerated by patients with liver cirrhosis because of major side effects. Hence, no systemic chemotherapy was recommended for patients with advanced tumors. Cytotoxic agents such as 5-fluorouracil, cisplatin, doxorubicin, gemcitabine, capecitabin, and epirubicin or combined regimens showed a low response rate (<10%) with only marginal improvements in overall survival [30]. Cisplatin, interferon, doxorubicin, and fluorouracil (PIAF) used in combination showed promising activity in a phase II study but not in phase III. Moreover, patients treated with the PIAF regimen experienced significantly higher rate of myelotoxicity compared with doxorubicin.

4.2. Molecular targeted therapy

Hepatocarcinogenesis is associated with epigenetic and genetic alterations that eventually lead to an alteration in the molecular pathways resulting in uncontrolled growth of the hepatocytes [31].

4.2.1. Sorafenib

Multiple cellular kinases are involved in the development and progression of the HCC through induction of angiogenesis and cellular proliferation. Overexpression of surface tyrosine kinases or mutational activation of *Ras* oncogene leads to Ras/MAPK pathway activation, an important step in HCC proliferation and angiogenesis. Sorafenib is an orally administered multikinase inhibitor drug, inhibits vascular endothelial growth factor receptor (VEGFR)- (VEGFR-) 1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR), Ras/MAPK pathway, involving Raf-1 (C-Raf) and B-Raf (wild and mutant types), FMS-like tyrosine kinase-3 (Flt), and c-kit with antiproliferative and antiangiogenic activity [32, 33]. The European guidelines recommended sorafenib for unresectable, advanced, Child–Pugh class A or B HCC with PS 0–2 and vascular invasion or distant metastasis [5]. According to the Japanese guidelines, sorafenib is recommended for unresectable, advanced, Child–Pugh class A HCC with vascular invasion or distant metastasis, as well as for patients intolerant to TACE or in whom the procedure of TACE is technically difficult [34]. Sorafenib was generally well tolerated with mild toxicity, predominantly including diarrhea, fatigue, weight loss, rash, or superficial skin desquamation and hand-foot skin reaction, hair loss, anorexia, nausea, and abdominal pain.

4.2.2. Molecular targeted agents other than sorafenib

Since the survival benefit achieved with sorafenib (compared to placebo) was minimal, search for alternative therapies was mandatory. Other targeted agents in phase III trials revealed nonsuperior results of antiangiogenic tyrosine kinase inhibitors (TKI) sunitinib, linifanib, brivanib, or the combination of sorafenib with erlotinib [35] for sorafenib-naive advanced HCC patients compared to sorafenib and none have exceeded the benefits of sorafenib, in addition, brivanib [36], ramucirumab [37], and everolimus [38] have been tested as second line, in patients who were refractory or intolerant to first-line treatment with sorafenib, with no significant improvement in overall survival, although TTP was significantly longer in the brivanib arm than with placebo. A decision-making process is required to tailor first-line medical treatment with sorafenib in the advanced stage. This should include nutritional, functional, and comorbidity status of the patient.

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