Putting It All Together

Practical Guidelines and Considerations for Physicians

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1. INTRODUCTION

In the previous chapters, there was a systematic description of hepatocellular carcinoma (HCC) as a disease, its causes, clinical presentations, its various diagnostic tools, and treatment options that are available. This chapter offers some practical guidelines for the physician seeing a patient for the first time and some considerations of common management choices (Fig. 1).

2. SCREENING FOR HEPATOCELLULAR CARCINOMA

Much has been written on the subject of screening for HCC, including the usefulness of α-fetoprotein (AFP) as a marker and the best, simplest, and cheapest radiological method of treatment. There have been several papers showing that the cost–benefit of screening has not been proven, as judged by the cost for screening large populations that are known to be at risk compared with the small numbers of tumors that are detected at a treatable stage, as well as the false-positive outcomes. Without prejudice to the outcome of this ongoing debate, a patient in the United States who has chronic hepatitis B virus (HBV), chronic hepatitis C virus (HCV), or is known to be cirrhotic from any cause is at risk for subsequent development of HCC. Thus, cirrhosis is a premalignant condition. Considering that we know the cause of so few cancers of adult humans, it seems to us that the physician has an obligation to follow-up on patients with these diseases who are known to be at risk, in the hope of early diagnosis and, therefore, finding the HCC at a treatable stage. Therefore, it is our practice to perform twice-yearly computed tomography (CT) scans and AFP measurements, although the latter are elevated in only 50% of HCCs and there is no clear linearity between tumor size and AFP measurement. Given that the published figures for development of HCC in a patient with cirrhosis are between 2 and 5% per annum, it may be expected that routine annual or semiannual screening of patients with cirrhosis is likely to detect a reasonable number of HCCs at a treatable stage. All this needs to be weighed against the cost of managing patients at an advanced stage at diagnosis.

3. THE ROLE OF BIOPSY

Fine-needle aspiration biopsy is well-established, routine, and can detect cancer. It normally cannot supply the architecture for a confident diagnosis of
**HCC Identified**

<table>
<thead>
<tr>
<th>Resection candidate</th>
<th>Transplant candidate</th>
<th>Not a surgical resect</th>
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<tbody>
<tr>
<td><strong>Resection</strong></td>
<td><strong>Transplant evaluation</strong></td>
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<tr>
<td>Noncirrhotic</td>
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<td>Not a transplant Candidate</td>
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<tr>
<td>Child’s A</td>
<td>3 lesions ≤ 3 cm</td>
<td>Co-morbid factors</td>
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<tr>
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<td>Child’s A/B/C</td>
<td>≥ 4 lesions</td>
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<tr>
<td>No metastasis</td>
<td>No gross vascular invasion</td>
<td>Gross vascular invasi</td>
</tr>
<tr>
<td></td>
<td>No metastasis</td>
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<tr>
<td><strong>PEI or Lap.</strong></td>
<td><strong>Clinical Trials</strong></td>
<td><strong>TACE/90Yttrium/</strong></td>
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<tr>
<td>RFA</td>
<td>Single lesion</td>
<td><strong>New agents</strong></td>
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<td>&lt; 5 cm</td>
<td>Multi-focal</td>
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<td></td>
<td>Child’s A/B</td>
<td>&gt; 5 cm</td>
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<td>UNOS List (Cadaver)</td>
<td>Child’s A/B/C</td>
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<tr>
<td>transplant</td>
<td>MELD score (? &gt; 3 mo)</td>
<td>Bilirubin &lt; 1.5</td>
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**Fig. 1.** Treatment Decision Algorithm.
HCC. Usually, only core-needle biopsy can do that. Recent practice in some areas, particularly in Europe, has been to avoid biopsy when there is presence of cirrhosis, a vascular liver lesion, and a rising AFP level. It is our practice to always perform a biopsy before treatment, whenever practical. We believe that this is important for two reasons. First, it gives us complete confidence that we have the correct diagnosis and the correct tumor histological type. Second, as we enter the age of molecular proteomics and molecular diagnostics, there are an increasing number of tests that allow us prognostic group stratifications that require tissue for either special stains, in situ hybridization, or gene expression. It has been argued that percutaneous needle biopsy is associated with a risk of spread by needle tracking. Although this has been reported, in our experience of the last 1300 needle biopsies for confirmation for the presence of HCC, we have seen this only in seven cases, and all of them have been in the track of the needle, typically the chest wall, and thus easily treated. As with everything in medicine, there is a risk-and-reward calculation that must be made. We believe that the benefit or reward of obtaining a correct tissue diagnosis and tissue for prognostication hugely outweighs the very low risk of needle tracking, an even rarer risk of tumor bleed, or other rarer complications associated with the presence of ascites.

4. WHAT IF THE FIRST BIOPSY COMES BACK NEGATIVE FOR CANCER OR IS INCONCLUSIVE?

There are several choices in this situation. They include a repeat biopsy, laparoscopic biopsy, or repeat CT scan and then biopsy in 3–4 months, especially if any one of the tumors appears to be growing. Sometimes there can be multiple nodules smaller than 1 cm and two or more biopsies have been negative. This can be a difficult situation, and repeat CT scan follow-up clearly is indicated in this situation.

5. METASTATIC DISEASE INVOLVING THE LUNGS, BONES, OR BRAIN

A symptomatic approach is required for all cancers, including brain radiation for brain metastases and spinal radiation for lytic or blastic metastases, that put any spinal vertebra or the pelvis at risk. The literature does not support any chemotherapeutic agent or combination of agents as being effective in this situation. We try to enroll all our patients in phase II or I studies for extrahepatic metastases. However, we often find patients whose disease is almost entirely confined to the liver, other than some periportal lymphadenopathy. In this situation, we focus on the 99% of the disease that is in the liver and we simply watch the lymph node disease. Quite often, this never seems to change. If the tumor does enlarge, however, it normally can be treated with external beam ionizing radiation.
6. WHAT IS THE BEST TREATMENT FOR ONE TO TWO HEPATIC LESIONS, EACH 3 CM OR SMALLER?

The choices here depend on the location of the tumor, specifically, its proximity to major vessels or bile ducts, but usually the treatment methods are PEI, radiofrequency ablation (RFA), or transarterial chemo-embolization (TACE). If the lesions are accessible, then either percutaneous ethanol injection (PEI) or RFA, depending on the operator skill and interest, would seem to be equivalent, and for small lesions at least, resection seems to be equal to PEI. The choice of treatment is also impacted by the severity of cirrhosis. Additionally, given the favorable curative new Model for Endstage Liver Disease (MELD) criteria, liver transplantation is a reasonable treatment option in this situation, especially in the presence of cirrhosis. We have a multidisciplinary weekly liver tumor conference, where all new and difficult cases are reviewed, before a treatment decision is made.

7. WHAT ARE THE TREATMENT OPTIONS FOR ONE TO TWO LESIONS OF ANY SIZE, WITH OR WITHOUT CIRRHOSIS AND WITH NORMAL LIVER FUNCTION TEST RESULTS?

A single lesion of any size in a noncirrhotic liver, or one with Child’s A cirrhosis, and a small contralateral lesion has several treatment methods. Depending on the exact location and proximity to major blood vessels, resection of the single lesion and possibly either resection or RFA of the contralateral lesion may be a reasonable choice. If the main lesion cannot be resected, then TACE or hepatic $^{90}$Yttrium microspheres are our preference. If cirrhosis is present, liver transplantation should be considered, given the favorable MELD score and the chance for cure.

8. WHO SHOULD OR CAN RECEIVE A LIVER TRANSPLANTATION?

The current guidelines include HCC as a single lesion less than 5 cm maximum in diameter or three HCC lesions, each 3 cm or smaller without gross vascular invasion of a main portal vein or portal vein branch or hepatic vein branch, and without metastases, regardless of the degree of cirrhosis. These patients have the highest possibility of complete cure because the liver transplantation treats both the cirrhosis as well as the HCC, unlike the above treatments. The United Network for Organ Sharing (UNOS) (cadaveric) and MELD scoring systems are updated regularly.

MELD was instituted on February 27, 2002, with a 6- to 40-point scale based on serum total bilirubin, international normalized ration (INR), and creatinine
levels, with more severe disease having a higher score (http://www.unos.org/resources/meldpeldcalculator.asp). For patients with radiographic evidence of stage I HCC (one tumor up to 2 cm), 24 MELD points were assigned, and for those with stage II HCC (one tumor up to 5 cm, or up to three lesions all smaller than 3 cm, without gross vascular invasion or extrahepatic spread), 29 points were assigned. After 1 year, it became evident that this was too high a priority, and the points were decreased to 20 for stage I HCC and to 24 for stage II. Recently, the stage I HCC priority has been criticized, and a proposal to eliminate the stage I priority has been adopted.

9. WHAT ARE THE TREATMENT OPTIONS FOR ONE LESION MORE THAN 5 CM OR THREE LESIONS WITH ONE OR MORE BEING LARGER THAN 3 CM?

We approach this with TACE or hepatic $^{90}$Yttrium in an attempt to downstage the size or the lesion in question. As soon as the patient has been restaged and can fit within the MELD score criteria for transplantation, then the patient undergoes a liver transplantation evaluation and is listed, if appropriate. Alternatively, the patient can undergo transplantation as a primary treatment (depending on the philosophy of the individual transplantation center), but the patient will not receive any additional MELD listing points.

10. A PATIENT WITH MULTIPLE LESIONS, ANY MORE THAN 5 CM AND WITHOUT METASTASES, WHO HAS A BLOOD GROUP-MATCHED FAMILY MEMBER WILLING TO ACT AS A LIVING-RELATED DONOR

Live donor transplantation has been used frequently in the past for patients with HCC because of the shortage of organs and rapidity of HCC growth. However, with the recent advent of the allowance of extra MELD listing points for patients with HCC (single lesion $\leq 5$ cm or three lesions none $\{GT\}3$ cm), the incidence of live donor transplantations for this group of patients has decreased. For those patients with single lesions larger than 5 cm or with more than three lesions, live donor transplantation is an option but is individualized within each transplantation program. Because the risk of recurrence in this group of patients is much higher, many programs will not offer live donor transplantations to this group. However, as we have recently found, patients with multiple lesions may have either multiple de novo tumors or intrahepatic metastases; these groups can be distinguished using currently available genotyping techniques. Patients with multiple small de novo could be considered for live donor transplantation, whereas the recurrence rate for patients with intrahepatic metastases is probably prohibitive. If the patient has a single, peripheral lesion larger than 5 cm without
metastasis or hepatic or portal vein involvement, then the patient could be considered for live donor transplantation.

11. MULTIFOCAL HCC WITH TUMORS CONFINED TO THE LIVER WITH OR WITHOUT PORTAL VEIN THROMBOSIS AND BILIRUBIN LEVELS LESS THAN 2.0 mg/dL

These patients are treated with hepatic artery chemotherapy or chemoembolization (TACE) or $^{90}$Yttrium glass microspheres into the hepatic artery. Patients seem to prefer the latter, because of the minimal side effects and the small total number of treatments that are usually required.

12. A PATIENT WITH ANY TUMOR, NOT FOR TRANSPLANT, WITH CHILD’S B OR C CIRRHOSIS, ENCEPHALOPATHY, OR BILIRUBIN LEVELS MORE THAN 3.0 MG/DL

These patients are normally referred for palliative or supportive care, or possibly phase II studies with noncytotoxic drugs, such as hormones or growth factor modulators.

13. CLINICAL EVALUATION AND WORK-UP FOR LIVER TRANSPLANT

The patients are evaluated by a multidisciplinary team at most transplantation centers that consists of transplantation surgeons, hepatologists, anesthesiologists, nurses, and social workers. The evaluation includes a thorough history and physical examination as well as an evaluation of the patient’s cardiac and pulmonary functions. All patients undergo an endoscopy to assess for esophageal varices. Further, age-appropriate screening for other carcinomas should be performed (e.g., colonoscopy, mammography, pap smear, etc.). Blood work for tissue typing, tumor markers, viral disease (e.g., HBV, HCV, human immunodeficiency virus, cytomegalovirus, Epstein–Barr virus, etc.) and autoimmune markers are performed. All patients with HCC being considered for transplantation must have a current CT and MRI of the abdomen and pelvis as well as a CT of the chest. After the medical testing and fiscal clearance is obtained, the patient is presented at the transplant evaluation conference for listing.