Management of Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is responsible for a significant amount of morbidity and mortality throughout the world. In many countries, including the United States, a definite increase in the incidence of HCC has been observed.

Hepatocellular carcinoma (HCC) is the most common primary neoplasm of the liver, accounting for almost half a million deaths annually worldwide. Although the incidence of HCC is particularly high in parts of Asia and Africa, recent studies have documented a clear rise in the number of cases in Japan, Western Europe, and the United States.

The rising incidence in the United States, as well as other parts of the world, is attributed largely to the increase in hepatitis C-related liver disease, a known risk factor for the disease. Other risk factors for HCC include hepatitis B viral infection, alcoholic cirrhosis, aflatoxin exposure, and a variety of inherited metabolic disorders.

Complex management options confront clinicians treating patients with HCC, making a multidisciplinary team comprised of hepatologists, interventional radiologists, medical oncologists, radiation oncologists, and surgeons necessary for optimal care. Unfortunately, there are few randomized clinical trials comparing the multitude of treatment options. Furthermore, many published studies lack statistical power and fail to stratify treatment arms by known prognostic indicators. In this report, an effort is made to provide an overview of the current management modalities available for patients with HCC and to describe the most appropriate clinical contexts in which they should be employed.

Screening

Because patients with HCC most commonly manifest nonspecific symptoms of advanced disease, including abdominal pain, weakness, and weight loss, routine use of serum alpha-fetoprotein (AFP) levels and transabdominal ultrasound (US) are used to screen individuals at high risk (ie, those with chronic hepatitis and/or cirrhosis). A normal level of AFP is less than 20 ng/mL, and a measurement above 500 ng/mL is considered diagnostic. Intermediately elevated levels, although indicative of HCC, can also be associated with benign conditions.

In high-incidence regions, the sensitivity of an abnormal AFP level is 80% to 90%; however, this drops to 50% to 70% in areas of low incidence. The specificity is 90%.

Diagnosis and Staging

Many imaging modalities are available to help establish the diagnosis of HCC. Their respective sensitivities for detecting lesions ≤ 3 cm are listed in Table 1. Dynamic magnetic resonance imaging (MRI) and helical computed tomography (CT) are commonly used to screen high-risk patients for HCC because they are less invasive than other available imaging techniques.

The sensitivity of most modalities significantly drops for lesions < 1 cm. However, Lipiodol CT still has a sensitivity of about 70% for detecting lesions of this size, making it the most sensitive preoperative imaging technique currently available.

Lipiodol is an iodized oily agent that accumulates selectively in vascular HCC liver nodules after intra-arterial injection. Although used most commonly therapeutically as part of transarterial chemoembolization, some centers employ diagnostic Lipiodol CT routinely in cases of suspected HCC or to rule out multifocal or metastatic disease.

The sensitivity of intraoperative ultrasound (US) for detecting HCC tumors is 98% for lesions 1 to 3 cm in size and 86% for those < 1 cm. Therefore, exploratory laparotomy with intraoperative US remains the gold standard for determining resectability of HCC.
Recently, encouraging results of staging of liver malignancies by laparoscopy with laparoscopic US have been reported.[11] In particular, for patients with HCC, laparoscopy with laparoscopic US may avoid unnecessary laparotomy in certain instances.[12]

Preoperative needle biopsy is rarely necessary in resectable patients with a clear diagnosis of HCC (ie, AFP > 500 ng/mL and a lesion identified on imaging studies). In most cases, the diagnosis is evident, and preoperative biopsy rarely alters management. Moreover, needle biopsy can be associated with the potential risks of bleeding, tumor rupture, and dissemination of malignant cells along the needle biopsy tract.

Percutaneous biopsy is most useful if the patient has unresectable HCC or is being considered for liver transplantation.[13] In selected cases in which the diagnosis is unclear or multifocal disease is being ruled out, needle biopsy should be considered prior to major resection.[14] Other roles of biopsy include evaluation of cases in which nonoperative ablation is being contemplated and determination of the extent of cirrhosis in the nontumorous liver.

**Evaluating Hepatic Function**

Assessment of hepatic functional reserve is important for deciding whether resection, liver transplantation, or other treatment modalities should be pursued. Prognostically useful data for both surgical and medical patients may be obtained from staging using the functional Child-Pugh classification system (Table 2).[15-17]

Another method, the indocyanine green retention rate, may also provide an estimate of underlying liver function.[14] Although this test is used in some centers, it is not employed in most cases. Imaging techniques may shed light on the extent of cirrhosis in some cases. For example, a CT scan or MRI can identify the loss of liver volume or hepatic contour changes indicative of more extensive cirrhosis. Visualization of portal vein collaterals, splenomegaly, or ascites can indicate more advanced disease.

Overall, there is no consensus on specific guidelines for evaluating hepatic function prior to treatment of HCC.

**Staging System**

Once diagnosed, the clinical staging of HCC is based on tumor size and number, whether there is vascular invasion, and the presence of regional lymph node or distant metastases (Table 3).[18] A shortcoming of the TNM staging system is the absence of liver functional status, which is an important prognostic indicator for HCC.[19] Collectively, performance status, comorbidities, liver function, and extent of disease greatly influence the range of treatment options available to a patient with HCC.

**Resectional Therapy**

**Partial Hepatectomy**

For patients without cirrhosis, surgical resection with partial hepatectomy is clearly the treatment of choice. However, no more than 30% of patients with HCC present with resectable disease, and up to 90% of patients have cirrhosis on presentation.[20,21] Extrahepatic disease, lack of sufficient hepatic functional reserve, multifocal disease within the liver, tumors in locations not amenable to resection, and main portal vein involvement, as well as comorbid disease, are all contraindications to resection.

In patients with well-compensated, mild cirrhosis (Child-Pugh class A-B) (Table 2), partial hepatectomy should be considered. Overall, the presence of cirrhosis is associated with worse long-term survival following resection.[19,22,23] In addition to cirrhosis, poor prognostic factors include large tumor size, multifocality, presence of vascular invasion, and poorly differentiated grade.[19,21,23,24] Following partial hepatectomy, overall 5-year survival rates range between 35% and 50% (Table 4).[25,19,26-31]

In recent years, improvements in operative mortality can be attributed to advances in preoperative imaging, better patient selection, development of new operative techniques and equipment, and advances in operative and postoperative anesthesia and critical care.[19] Although earlier reports demonstrated substantially increased operative mortality (up to 20%) following resection in patients with cirrhosis, more current studies from both western and eastern investigators showed similar postoperative mortality (< 5%) for patients with and without cirrhosis.[19,24,28-30] Centers in which a higher volume of liver resections are performed have a lower perioperative mortality.[32] Even among patients in whom resection is performed with curative intent, intrahepatic recurrence is seen in up to 70% of cases.[33] It is thought that some intrahepatic recurrences may actually be de novo multifocal disease or metachronous new tumors within the liver. These distinctions can be
Management of Hepatocellular Carcinoma
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difficult to make. Nevertheless, with aggressive management of recurrences, long-term survival can also be achieved in these patients.[33]

Orthotopic Liver Transplantation

In light of the high concomitant incidence of cirrhosis and HCC and the potential for multifocal malignancy, the prospect of removing the entire liver containing the tumor and replacing it with a healthy one is attractive. However, limited donor availability with attendant long waiting lists, high cost, significant morbidity, and the potential cytostimulatory effect of systemic immunosuppression remain formidable obstacles to transplantation.

Stage for stage, liver transplantation can achieve 5-year survival rates comparable or superior to those of partial hepatic resection in selected cases (Table 5).[13,25,34-39] Transplantation has a more favorable prognosis in patients with a solitary tumor < 5 cm or those with no more than three nodules, each ≤ 3 cm (the so-called “3-3 rule”).[25]

More extensive disease should be considered an absolute contraindication to transplantation. Importantly, in patients with cirrhosis, a 4-year survival rate of 75% is achievable following total hepatectomy and transplantation for unresectable tumors < 5 cm or no more than three nodules, each ≤ 3 cm.[40] Bilobar disease, by itself, is not considered a contraindication to transplantation. Contraindications to liver transplantation include the presence of extrahepatic disease and comorbid factors precluding transplantation for benign indications. Other relative contraindications include the presence of vascular invasion or a poorly differentiated grade.[13]

Due to the long wait times for cadaveric donor organs (often more than 1 year), various alternatives to standard organ availability have been considered. These include increasing the priority status of patients with HCC for transplantation, utilizing split liver techniques, or considering marginal donor organ quality for patients with a malignancy.[39] In addition, the increasing use of adult living donor transplantation may improve transplant availability for the cancer patient.

Attempts have been made to restrain HCC growth while patients await transplantation. Many institutions have published small series employing preoperative chemotherapy, radiotherapy, and/or transarterial chemoembolization administered prior to transplantation; these studies have had mixed results.[41-44] Similarly, the role of postoperative adjuvant chemotherapy is undefined.[45]

At present, conclusions cannot be made, and definitive recommendations for the use of preoperative or adjuvant therapy await the results of ongoing, multicenter, randomized clinical trials.[13] Currently, only selected patients with small tumors and moderate to severe cirrhosis should undergo liver transplantation.

Ablative Approaches

Percutaneous Ethanol Injection

Despite a lack of randomized controlled trials comparing percutaneous ethanol injection to hepatic resection for HCC, some consider ethanol injection to be an alternative to surgery for patients with resectable disease, particularly those with associated chronic viral disease. The reason for this is that percutaneous ethanol injection is associated with less damage to surrounding nontumorous tissue than resection, and, therefore, repeat treatment is better tolerated in this population at high risk for recurrent and second primary tumors. In general, however, percutaneous ethanol injection is recommended for patients with small unresectable lesions and those who are at adverse risk for surgery.[46]

Percutaneous ethanol injection entails injecting 95% or absolute ethanol directly into the tumor, usually using local anesthesia with sedation. Typically, no more than 3 lesions, each < 3 to 5 cm are treated. When more extensive percutaneous ethanol injection is used, general anesthesia is required.[46-48]

The goal of therapy is to achieve complete necrosis of the tumor with extension into the perineoplastic tissue.[49] Typically, multiple injections are needed to obtain complete tumor necrosis. Unlike intravascular therapies, percutaneous ethanol injection–induced necrosis is not influenced by the degree of vascularity of the tumor.

Five-year survival rates up to 60% have been reported following percutaneous ethanol injection, although intrahepatic recurrence rates of 50% to 75% have been cited.[46,48-50] Common side effects include fever, pain, and elevated transaminases. Procedure-related mortality is rare.[46,48-50]

Percutaneous ethanol injection is contraindicated when gross ascites, coagulopathy, or obstructive jaundice is present. Superficial lesions are usually avoided because of the potential for ethanol to leak into the peritoneal cavity.
Despite multiple reports of encouraging long-term results with percutaneous ethanol injection, no randomized trials have compared this ablative therapy to resection. Until such a trial is conducted, liver resection should remain the treatment of choice in eligible patients. The minimal invasiveness, simplicity, safety, repeatability, low cost, and high efficacy of percutaneous ethanol injection make it an attractive form of therapy for patients with HCC who are not candidates for partial hepatectomy or liver transplantation.

**Cryosurgery**

Hepatic cryosurgery involves the in situ destruction of the tumor and surrounding tissue produced by an intratumorally placed probe through which liquid nitrogen circulates.[51] Usually, the procedure requires an open laparotomy, although laparoscopic approaches have been used.[52] Relative indications for this technique are unresectable lesions and contralateral nodules detected during resection; cryosurgery also has been used as an adjunct to resection for devitalizing narrow tumor margins.

Although cryosurgery has been reported to produce survival rates comparable to those achieved with resection,[51] rigorous clinical trials are still lacking. Heat from local vascular structures and difficulties in documenting adequate margins of therapy limit the effectiveness of cryosurgery. Overall, cryosurgery is safe. Fever and elevated transaminases may accompany cryosurgery; however, care must be taken to avoid renal insufficiency and liver cracking.

As with other ablative techniques, the role of cryosurgical ablation in the treatment of HCC is unclear. The need for an operative approach with cryosurgery, unlike the other ablative approaches, limits its use in unresectable patients. The principle role for cryosurgery may prove to be as an adjunct to liver resection for operative ablation of residual tumor or narrow tumor margins.

**Radiofrequency Ablation**

In radiofrequency ablation, an electric current that is passed into the tumorous tissue via an electrode tip results in heat generation and coagulative necrosis.[53] This technique can be safely used to treat unresectable HCC via a percutaneous, laparoscopic, or open approach.[53-57] Compared to percutaneous ethanol injection, percutaneous radiofrequency ablation requires fewer treatment sessions and may achieve superior tumor necrosis of small (≤3 cm) HCC.[56] In a nonrandomized study involving 39 patients, rates of local recurrence and overall survival following percutaneous radiofrequency ablation of small (≤3 cm) HCC were comparable to those reported for similar patients treated by surgery or percutaneous ethanol injection.[54]

Increased tumor necrosis can be achieved using expandable electrodes resulting in effective treatment of lesions up to 5 cm in a single session. When radiofrequency ablation is performed through the percutaneous approach, mild to severe pain may limit the duration of treatment.[56,57] In another nonrandomized study, patients (N = 26) with small (<3 cm) peripherally located HCC were treated by percutaneous radiofrequency ablation and others (N = 22) with more extensive disease were treated by intraoperative radiofrequency ablation, with or without resection, intraoperative US, and vascular inflow occlusion.[57] No procedure-related deaths occurred, but one patient required transarterial embolization to control hemorrhage. After a median follow-up of 15 months, only one local recurrence was reported.

Although definitive conclusions regarding the role of radiofrequency ablation in the management of HCC await the results of randomized trials, this technique appears to be safe and may prove to be superior to percutaneous ethanol injection or cryosurgery.

**Other Ablative Techniques**

Microwave coagulation therapy, laser coagulation, intraslesional chemotherapy, and intratumoral yttrium-90 glass microsphere injection are other ablative techniques that have been employed in the treatment of HCC. With microwave coagulation therapy, microwaves emitted from an electrode implanted intratumorally produce heat and coagulative necrosis in water-containing tissues.[58] However, it is difficult to monitor tumor destruction because of the production of water vapor.[59] Moreover, multiple applications are required due to the small zone of distribution.[60]

Limited studies suggest that microwave coagulation therapy is safe and devoid of significant procedure-related morbidity.[58-62] In nonrandomized trials, microwave coagulation therapy may achieve better local control than percutaneous ethanol injection for tumors ≤2 cm that are not well differentiated. Survival following microwave coagulation therapy is reported to be similar to that following resection.[59,63]

Yttrium-90 emits high-energy beta radiation with a half-life of only 64 hours.[64] Ultrasound guidance is used to target glass microspheres containing yttrium-90 directly into the tumor. Intratumoral injection of yttrium-90 glass microspheres provides an opportunity to ablate the entire tumor, including its periphery, which is more difficult to achieve via the intra-arterial route.
In uncontrolled reports in limited numbers of patients, this therapy appears to achieve tumor control.[65] One concern is that significant potential complications may result from intraperitoneal spillage of the radioisotope or shunting to the lungs. Therefore, the safety of intratumoral yttrium-90 glass microspheres injection should be studied more fully before it is used widely. These and other ablative techniques may show promise for the treatment of patients with HCC, and each may have potential advantages. Yet, despite the extensive use of these approaches worldwide, it is imperative that randomized controlled trials be carried out comparing them to each other, as well as to resectional therapy.

Transarterial Chemoembolization

The rationale for transarterial chemoembolization rests on the observation that nearly all of the blood supply to HCC is derived from the hepatic artery; in contrast, normal liver tissue receives 80% of its blood supply from the portal vein. During transarterial chemoembolization, interventional radiology is used to embolize the blood supply to the tumor with a combined emulsion of Lipiodol, gelatin-sponge particles, and chemotherapeutic agents. Worldwide, transarterial chemoembolization is the most common therapy used in unresectable patients, and in parts of Asia, transarterial chemoembolization is considered standard therapy in many cases. Although promising results of retrospective clinical trials employing transarterial chemoembolization have been reported, several randomized clinical trials have found that transarterial chemoembolization offers no improvement in survival compared to supportive therapy alone.[66-68] These studies have been criticized for various limitations, however, including small sample sizes and variable techniques. Transarterial chemoembolization requires hospitalization, and its cost and side effects are not insignificant. Nevertheless, in some cases, a significant reduction in tumor size can be achieved and subjective improvement can occur in symptomatic patients.[69-71] Confusion about the effectiveness of this therapy has been compounded by variations in the embolic material and technique employed, and whether chemotherapy is used at all. Currently, despite its widespread use, the role of transarterial chemoembolization in patients with unresectable disease remains unclear.

Radiation Therapy

External-Beam Radiation

The potential benefits of radiation therapy in HCC are offset by its hepatotoxicity. For adequate doses of radiation to be delivered to the tumor, unacceptable injury to the surrounding liver parenchyma is risked. Thus, to avoid producing radiation hepatitis, only limited amounts of radiation are administered. As a result, external-beam radiation is not commonly used alone in the treatment of HCC. Rather, it is sometimes combined with chemotherapeutic regimens as palliative therapy for selected patients. Improved techniques of conformational highly targeted external-beam radiation therapy may result in its increased use in the future, however.

Intra-arterial Iodine-131-Lipiodol and Yttrium-90 Microspheres

Like transarterial chemoembolization, the premise of intra-arterial iodine-131-Lipiodol and yttrium-90 microspheres is based on the finding that nearly all of the blood supply to a tumor is derived from the hepatic artery. In addition, Lipiodol is retained selectively in HCC following intra-arterial injection.[72] Thus, theoretically, radiation can be specifically targeted to unresectable tumors using these therapies. Moreover, both techniques are performed percutaneously. Possible contraindications include a complicated arterial blood supply, a high degree of shunting to the lungs or gastroduodenal region, and an unfavorably high ratio of radioisotope uptake by the normal liver tissue compared to the tumor.[73] Limited studies suggest that both intra-arterial iodine-131-Lipiodol and yttrium-90 microspheres are well tolerated.[74-76] Problems with radiation hepatitis and liver failure have not been encountered following intra-arterial yttrium-90 microsphere treatment; moreover, a small number of instances of complete pathologic remission and conversion to resectable disease have been reported.[72] In a randomized, controlled trial of patients with locally advanced HCC in the presence of portal vein thrombosis, treatment with intra-arterial iodine-131-Lipiodol resulted in a significant, but modest, prolongation of survival compared to supportive therapy alone (median survival durations, 24 and 8 weeks, respectively).[77] Others have shown that, in patients with unresectable HCC, intra-arterial iodine-131-Lipiodol treatment is safe and produces a 52% response rate, with survival rates similar
to those achieved with transarterial chemoembolization.[72,78-80]

One drawback of intra-arterial radioisotope therapy is the isolation period required to allow for decay of the radioisotope.[76] Before treatment with iodine-131–Lipiodol or yttrium-90 microspheres is widely adopted for unresectable HCC, the efficacy and cost of these modalities should be more rigorously compared to other therapies.

**Adjuvant and Neoadjuvant Therapy**

The high relapse rates following curative therapy for HCC underscore the need for an effective adjuvant therapy. Unfortunately, in numerous randomized trials, systemic chemotherapy has not proven to increase survival, either when administered as primary treatment for HCC or when given after curative resection.[81] In addition, significant side effects greatly limit its usefulness. Because of the limited efficacy of current systemic chemotherapy and the high incidence of recurrence within the liver, several investigators have focused on regional adjuvant therapy.

**Hepatic Arterial Infusion Chemotherapy**

One preliminary study suggested a positive effect on survival when hepatic arterial infusion chemotherapy with doxorubicin and mitomycin (Mutamycin) was administered with intravenous fluorouracil (5-FU) to patients deemed at high risk for recurrence following resection for HCC.[82] In another nonrandomized study, hepatic artery infusion of cisplatin (Platinol) or 5-FU, doxorubicin, and mitomycin following resection of stage III or IV HCC appeared to improve 3-year survival (71% for treated vs 32% for untreated).[83] In contrast, a prospective, randomized study, found no effect on survival when epirubicin (Ellence) was administered intra-arterially and intravenously in combination with oral 1-hexycarbamoyl-5-FU following resection.[84]

Based on the data accumulated to date, the routine use of adjuvant hepatic arterial infusion chemotherapy cannot be justified.

**Transarterial Chemoembolization as Adjuvant Therapy**

Three randomized clinical trials have evaluated the role of transarterial chemoembolization as adjuvant therapy. In one of these studies, the efficacy of transarterial chemoembolization as neoadjuvant therapy prior to partial hepatectomy for large (≥ 10 cm), resectable HCC proved disappointing. Patients treated with preoperative transarterial chemoembolization had a significantly worse overall survival during a 10-year period, as compared with those treated with surgery alone.[85] In patients who received transarterial chemoembolization preoperatively, surgery was delayed for 4 months and a higher incidence of distant metastases was reported.

A recent retrospective analysis found preoperative transarterial chemoembolization to be an unfavorable prognostic factor for survival in patients with Child-Turcotte class B or C cirrhosis.[22]

Another randomized trial studies the effect of postoperative adjuvant transarterial chemoembolization.[86] Following curative resection of HCC with vascular invasion and/or intrahepatic metastases, patients were randomized to receive no treatment (N = 27) or transarterial chemoembolization (N = 23). No improvement in survival was detected in the group that was given postoperative transarterial chemoembolization. However, this study was criticized because, in the treatment group, chemoembolization was performed with gelatin-sponge particles and Lipiodol in 7 patients, whereas only Lipiodol was used in 16.

Currently, no convincing data exist showing that transarterial chemoembolization should be used in the adjuvant setting, either before or after resection.

**Iodine-131–Lipiodol**

One randomized trial examined the use of adjuvant intra-arterial iodine-131–Lipiodol following curative resection for HCC.[88] Patients were given 50 mCi of intra-arterial iodine-131–Lipiodol or no treatment within 6 weeks after surgery. Interim analysis in a small number of patients suggested that adjuvant therapy reduces local recurrence (12.5% vs 62.5%) at 2 years after surgery.

**Polyprenoic Acid Chemoprevention**

Following partial hepatectomy for HCC, second primary tumors are thought to develop in up to 50% of patients at 2 years.[87] In an effort to reduce this high incidence of second tumors, Japanese investigators recently reported the results of a prospective, randomized trial in which 89 patients who had undergone successful treatment with either partial hepatic resection or percutaneous ethanol injection received chemoprevention with the vitamin A analog, polyprenoic acid.[87]

Posttreatment administration of polyprenoic acid significantly reduced the incidence of second primary tumors compared to placebo (16% vs 44%) but did not decrease local recurrence. This is consistent with the hypothesized role of the retinoids in inhibiting tumor initiation but not disease progression.
Although these results with polypreroidic acid chemoprevention are promising, many clinicians are awaiting further confirmatory reports before adopting its use. In addition, it would be of interest to determine whether similar positive results might be obtained in Western countries where lower incidences of cirrhosis and HCC are found.

**Treatment of Advanced Disease**

**Systemic Therapy**

As mentioned above, no survival benefit has been demonstrated with any systemic chemotherapeutic regimen given as primary therapy for HCC in randomized clinical trials. Recently, encouraging results have been reported using a combination of Platinol, interferon-alfa-2b, Adriamycin, and 5-FU (PIAF) as primary therapy for patients with unresectable HCC, including some with distant metastases.[89] In this phase II trial, a partial response based on radiologic criteria was achieved in 26% of patients. Subsequently, 9 of 50 patients underwent partial hepatic resection, with 8 achieving a complete remission of up to 25.8 months.

The major toxicity of PIAF was myelosuppression, mainly leukopenia (34%) and thrombocytopenia (22%). Two patients died from neutropenic sepsis. Although moderate toxicity is associated with this regimen, the encouraging results should prompt further studies to determine the role of this or other similar combination chemotherapeutic regimens for patients with advanced disease.

An association between estrogens and HCC based on animal and epidemiologic studies has led to the study of tamoxifen (Nolvadex), an antiestrogen compound, in the treatment of HCC. Initial studies yielded conflicting results. However, these studies had insufficient sample sizes and were limited to patients with advanced disease.

In order to clarify the effect of tamoxifen on HCC, a multicenter, randomized clinical trial was conducted in Italy.[90] No restrictions were placed based on disease stage or prior treatment. Patients who had received prior tamoxifen therapy or individuals who had been diagnosed with HCC more than 2 years prior to the study were excluded. Compared with supportive care, tamoxifen therapy did not prolong survival during this 30-month study period.

At present, there is no clear justification for the use of tamoxifen in the management of HCC.

**Downstaging**

Patients with extrahepatic disease should receive palliative care. However, those with locally advanced HCC should be offered treatment aimed at prolonging survival. Moreover, as described above, selected patients with advanced disease confined to the liver may respond to treatment regimens that convert unresectable to resectable disease, therefore providing an opportunity for cure.[72,89,91]

Many different treatment regimens have been reported to downstage HCC, allowing for subsequent partial hepatectomy, with varying degrees of success. These include preoperative transarterial chemoembolization, intratumoral ablation, radiation therapy, and chemotherapy.[89,91,92]

However, heterogeneous inclusion criteria (ie, disease stage, Childs class, prior treatment), small sample sizes, and the multitude of treatment combinations prevent definite conclusions from being made regarding the best method for particular circumstances.

**Conclusions**

The management of HCC remains one of the most complex problems that a clinician can face. Only a multidisciplinary team can effectively deal with the diverse issues involved in treating a patient with this cancer. **Figure 2** outlines a recommended management strategy. Clearly, for patients who have resectable disease and can tolerate surgery, partial hepatic resection or, in selected cases, liver transplantation remains the treatment of choice and provides that best chance for cure. As more data become available, nonoperative ablative therapy likely will play an increasingly important role in the management of HCC.

Well-designed trials need to be carried out comparing various ablative approaches and comparing ablation to resection. In addition, improvements in systemic and regional therapy are important both in advanced disease and as adjuvants in combination with ablation or resection. Promising early results with novel chemotherapeutic regimens (eg, PIAF) and combined modalities need further study to maximize the number of patients with locally advanced HCC whose disease may be converted from unresectable to resectable.
References:


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