Recent Advances in Management of Hepatocellular Carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies, ranking fifth in frequency among all malignancies in the world. HCC is characterised by rapid tumour growth and a high propensity of vascular invasion. Furthermore, 80% of patients with HCC have associated liver cirrhosis related to hepatitis B or C viral infection, which often restricts treatment options because of impaired liver function. The prognosis of untreated HCC is poor, but the management approach of HCC has changed from a previously nihilistic approach to a more aggressive one with recent advances in management, resulting in improved prognosis. The wider utilisation of screening programme in high-risk patients has resulted in early detection of small HCCs, and thus improved chance of treatment.

Compared with other gastrointestinal cancers, management of HCC is more complicated because of the wide range of treatment modalities available and the underlying liver disease. Appropriate selection of patients for individual treatment according to tumour status and liver function is critical to optimise treatment outcome, and some patients may require combination of modalities in management. Treatments for HCC can be classified into curative (resection, transplantation or ablation) or palliative (transarterial chemoembolisation, radioembolisation or systemic therapy).

Surgical Resection

Hepatic resection is the treatment of choice for patients with HCC and preserved liver function. Even for patients with a large HCC > 10 cm in diameter, resection is safe and offers favourable long-term survival results. The presence of multiple tumour nodules or vascular invasion in major intrahepatic venous branches may be associated with worse prognosis. However, surgical resection is still considered the best treatment in terms of long-term survival. Extended right or left hepatic resection can be performed even in the presence of cirrhosis, provided patients are carefully selected in terms of liver functional reserve. In patients with inadequate remnant liver volume for a right or extended right hepatectomy, preoperative right portal vein embolisation can be employed to induce atrophy of the right lobe and hypertrophy of the liver remnant before resection. In centres specialised in hepatobiliary surgery, liver resection for HCC is now a safe operation with an operative mortality 2-5%. Major complications such as massive bleeding or postoperative liver failure are rare with careful patient selection and modern operative techniques.

In recent years, laparoscopic liver resection has become feasible with the development of laparoscopic instruments that allow liver transection without major bleeding. Tumours in anterior segments or left lateral segments can be resected using a laparoscopic approach, with the benefit of less postoperative wound pain, better cosmetic result, shorter hospital stay and faster recovery (Figure 1). A meta-analysis of retrospective comparison of laparoscopic and open approach has shown reduced blood loss with the laparoscopic approach, while oncologic clearance in terms of resection margin was similar between the two groups.

Bilobar HCC was used to be a contraindication for resection. However, with the advent of thermal ablation therapy, it is now possible to perform combined resection of predominant tumour mass(es) in one lobe and ablation of small tumour nodule(s) in the other lobe (Figure 2). Such an aggressive approach has increased the chance of patient receiving curative therapy for HCC and could achieve similar survival results compared with resection alone.

Figure 1. A patient with a small left lateral segment HCC (Fig. 1a) treated by laparoscopic left lateral sectionectomy (Fig. 1b). Blood loss was only 100 ml and the patient was discharged uneventfully two days after operation.

Figure 2. A patient with bilobar HCC (Fig. 2a, three tumours in right lobe and one in left lateral segment) deemed unresectable by a hepatologist and treated with TACE. He was complicated by a right lobe liver abscess in one of the tumour in the right lobe (Fig. 2a, arrow). He was subsequently treated by the author with right hepatectomy and intraoperative RFA of the left lobe tumour (Fig. 2b), and he recovered uneventfully.
Improvement in long-term survival results after resection of HCC has also been observed in recent years, with 5-year survival rate now exceeding 50%. The improvement in survival could be attributed to the increased diagnosis of early HCC and reduction in perioperative blood transfusion. Perioperative transfusion has been found to have an adverse impact on the long-term survival after resection of HCC by an inhibitory effect on immune system that leads to increased risk of recurrence. Hence, the surgeon can play an important role in improving the long-term prognosis by minimising intraoperative blood loss and avoiding perioperative transfusion. The long-term prognosis after resection of HCC has been limited by a high incidence of postoperative recurrence due to metastatic lesions or multicentric recurrences in the liver remnant. Postoperative adjuvant systemic or regional chemotherapy has so far failed to prevent recurrence in prospective clinical trials. Aggressive treatment of recurrent tumours by re-resection or non-surgical modalities such as percutaneous ablation therapy can result in prolonged survival even after the development of recurrent tumours.

Liver Transplantation

In the 1980s, advanced unresectable HCC was a common indication for transplantation but the results were disappointing, with a 5-year survival rate of around 20%. The presence of circulating tumour cells associated with large HCC leads to a high incidence of postoperative recurrence in the setting of immunosuppressive therapy used to prevent graft rejection. A landmark study published in 1996 showed that for solitary HCC < 5 cm or < 3 tumour nodules each of size < 3 cm, the long-term survival rate of liver transplantation was favourable. It is now well-accepted that Child’s C cirrhotic patients with HCC < 5 cm or < 3 tumour nodules each of size < 3 cm (Milan criteria) and without radiological evidence of venous invasion or distant metastasis should be treated by transplantation, as hepatic resection is usually contraindicated in this group of patients with poor hepatic function. Some centres adopted expanded criteria of solitary tumour ≤ 6.5 cm or ≤ 3 nodules with the largest lesion ≤ 4.5 cm and total tumour diameter ≤ 8 cm (UCSF criteria) for liver transplantation. With such stringent selection criteria, the 5-year survival rate is about 60-75%. Tumour recurrence is an important cause of long-term mortality after liver transplantation. Currently there is no effective adjuvant therapy to reduce the risk of tumour recurrence.

Whether Child’s A cirrhotic patients with preserved liver function and a small HCC should be treated with transplantation or resection is a controversial issue. Some Western centres recommended liver transplantation for small HCC even in child’s A patients because of the lower tumour recurrence rate compared with resection. However, in most Asian centres including Hong Kong where there is a severe shortage of liver graft donors, hepatic resection remains the first-line treatment for such patients because similar overall survival results of about 70% in 5 years can be achieved for small HCCs. A significant proportion of HCC patients listed for liver transplantation may drop out of the waiting list because of tumour progression. Furthermore, specific long-term complications of liver transplantation such as recurrent viral hepatitis, graft rejection, opportunistic infection or secondary malignancies as a result of immunosuppression may lead to mortalities. Resection followed by salvage transplantation for intrahepatic recurrence or deterioration of liver function may be a more effective strategy for patients with small HCC and preserved liver function.

Adult live donor liver transplantation is an appealing alternative for patients with HCC because it reduces the chance of dropout from the waiting list for deceased donor liver grafts. However, the benefit of live donor liver transplantation for HCC patients has to be balanced against a risk of about 0.5% mortality and 20% morbidity in the live donor undergoing right lobe donor heptectomy. Furthermore, there is some concern of the effect of regeneration of the partial liver graft in stimulating the growth of microscopic metastasis, although there are not enough clinical data on this issue. Hence, most centres consider that the selection criteria for HCC patients to undergo live donor liver transplantation should be similar to that of deceased donor liver transplantation. Even with the use of live donor liver transplantation, less than 5% of HCC patients at the author’s institution are treated by liver transplantation.

Local Ablative Therapies

Local ablation is a potentially curative therapy for small HCCs not amenable to resection. Patients with HCC ≤ 5 cm and up to 3 nodules are the best candidates for ablative therapies, although larger tumours can also be ablated in selected cases. While there is some preliminary evidence suggesting that ablative therapies may achieve similar survival results compared with surgical resection, the evidence is not yet strong enough to recommend local ablation as the first line therapy for patients with a resectable small HCC. However, for patients with borderline liver function, local ablation is a safer option especially if the tumours are centrally located. Local ablative therapies are useful in treating recurrent HCC after previous resection, which occurs mostly in the liver remnant. Local ablative therapy may also be employed as a bridging therapy for control of tumours before a liver graft is available even if liver transplantation is contemplated.

Percutaneous ethanol injection therapy was used to be the main local ablative therapy in the 1990s. However, radiofrequency ablation (RFA) has replaced ethanol injection to be the most widely used ablative modality for HCC. Randomised controlled trials have demonstrated that RFA is superior to ethanol injection in that it requires fewer treatment sessions, and it achieves a higher complete ablation rate, lower tumour progression rate and higher overall survival rate. RFA is associated with a mortality rate of 1% or lower, and it can be performed through percutaneous, laparoscopic, and open approaches. The choice of treatment approach depends on the size and location of the tumour(s) and patients’ comorbid condition. Patients with tumour ≤ 3 cm in diameter located in the periphery of the liver are the best candidates for percutaneous RFA under ultrasonographic guidance.
or computed tomography guidance. Laparoscopic RFA allows the ablation of liver tumours in close contact with the surrounding organs, such as bowel, kidney, gallbladder and diaphragm, for which percutaneous RFA carries the risk of bowel perforation or visceral damage. Open surgical approach is indicated in patients with large tumours or multiple tumour nodules located at the superior or posterior portion of the liver (Figure 3). There is a higher degree of freedom for accurate introduction of the RF needle into the tumour in open RFA compared with other approaches, so that more effective ablation can be carried out to minimise the chance of residual tumour at the treatment site. For HCC > 3 cm in diameter, a previous study by the author showed that open approach achieved better long-term survival compared with percutaneous RFA. Recent studies have shown that 5-year survival of 40-60% can be achieved with RFA for small HCCs, but the recurrence rate remains high. The author is conducting randomised controlled trials to evaluate the benefit of combining transarterial chemoembolisation (TACE) or heat-activated liposomal doxorubicin (Thermovex) in combination with RFA to reduce recurrence rate. Thermovex contains doxorubicin encapsulated in a heat-sensitive layer of liposome that releases the doxorubicin at temperature > 42°C. This allows delivery of high concentrations of doxorubicin to the ablation zone with minimal systemic toxicity. An early phase trial jointly conducted by the author and the National Cancer Institute of the USA showed that this is a promising strategy in enhancing cancer killing at the ablation zone.

High intensity focused ultrasound (HIFU) is a new modality of ablation that is totally non-invasive. Ultrasound focused by a transducer can kill cancer cells by caviation effect in addition to thermal ablation effect. Currently, Queen Mary Hospital is the only hospital in Hong Kong with a HIFU system for treatment of liver cancer. Since 2007, more than 100 cases of HIFU for HCC have been performed under ultrasound imaging guidance, with complete ablation rate close to that of RFA. As no electrode needle puncture is required, it eliminates the small risk of bleeding or needle track tumour cell seeding associated with RFA. Furthermore, the ablation is more precise than RFA and it may be used in tumours located near major bile duct or vessels. It is also possible to ablate large tumours > 5 cm (Figure 4).

**Transarterial Therapies**

For patients with large tumour or multifocal tumours confined to the liver but not suitable for resection, transplantation or ablation because of inadequate liver function reserve or poor general condition, transarterial chemoembolisation (TACE) is the standard of care. In this treatment, cisplatin or doxorubicin mixed with Lipiodol is injected to the hepatic artery supplying the tumour(s) via a catheter placed through the femoral artery, followed by embolisation using gelfoam or embosphere particles. Meta-analyses of prospective randomised trials have demonstrated the efficacy of TACE in prolonging the survival of patients compared with conservative management, but the tumour response rate is only about 35%. Revascularisation by angiogenesis in the periphery of tumour after initial response leads to disease progression. Molecular targeting agents such as bevacizumab, which is a monoclonal antibody against vascular endothelial growth factor, have been developed to inhibit angiogenesis. Anti-angiogenic therapy has been proven to be a useful treatment to inhibit cancer growth in several human cancers. The author is conducting a trial of combining bevacizumab with TACE to enhance its efficacy.

Doxorubicin-eluting bead is a new development that aims to enhance the efficacy of TACE and reduce its toxicity. The beads are microspheres pre-loaded with doxorubicin that releases the doxorubicin slowly in the tumour when injected transarterially and the beads also serve as embolising particles. A phase I/II study conducted by the author showed that doxorubicin-eluting bead could significantly reduce the systemic exposure to doxorubicin while delivering higher concentration of doxorubicin to the tumour compared with conventional Lipiodol-doxorubicin TACE, and the tumour response rate appeared superior. A randomised trial in Europe has shown that doxorubicin-eluting beads reduced liver toxicity and increased tumour response in more advanced HCC compared with conventional Lipiodol-TACE.

Transarterial radioembolisation using Yttrium-90 labelled spheres is an alternative to TACE that has become more popular in recent years, though its use is still limited compared with TACE. The efficacy and safety of transarterial radioembolisation appears to be similar to TACE, but there are no randomised trials comparing it with TACE in the literature. Transarterial radioembolisation appears to be more effective in inducing shrinkage of tumour thrombus in the portal vein compared with TACE. The author prefers to use transarterial radioembolisation rather than TACE in patients with portal vein tumour thrombus and has experience of successful shrinkage of tumour thrombus in main portal vein followed by resection.

**Systemic Therapy**

For patients with advanced HCC that is not amenable to locoregional therapy, systemic chemotherapy has so far demonstrated low efficacy and toxicity is significant because of the underlying cirrhosis in most patients. Systemic chemotherapy using conventional agents...
such as 5-FU, doxorubicin and cisplatin either alone or in combination has not been shown to prolong patient survival in prospective randomised trials.\textsuperscript{25,26} HCC is a highly vascularised tumour, and previous studies by the author have demonstrated that significance of angiogenesis and vascular endothelial growth factor in HCC.\textsuperscript{27,28} Recently, a molecular targeting agent that inhibits receptor of vascular endothelial growth factor and a signalling protein Raf kinase in the HCC cells has been shown to be effective in prolonging survival of patients with advanced HCC in two large phase 3 randomised placebo-controlled trials.\textsuperscript{29,30} The drug Sorafenib prolonged patient survival by approximately three months in these trials, but tumour response rate was less than 3\%. Hence, the benefit is limited. The use of Sorafenib is also hindered by significant side effects such as hand-foot skin reaction and the high cost.

Currently many other molecular targeting drugs that target different pathways such as the mTOR pathway, c-MET and fibroblast growth factor are under clinical trials in direct comparison with Sorafenib, in combination with Sorafenib or as a second-line therapy after Sorafenib failure.\textsuperscript{31} Some novel drugs such as Everolimus and Brivanib have demonstrated favourable safety and also efficacy in phase II trials in HCC and are now being evaluated in phase III trials.\textsuperscript{31} In the author’s institution, several clinical trials on the novel drugs are on-going (information available on www.livercancer.hku.hk) and provide an alternative option for patients who cannot afford Sorafenib or who have failed Sorafenib therapy. The author has also completed a phase II trial of combining Sorafenib with newer chemotherapeutic agents Capecitabine and Oxaliplatin (SECOX) for advanced HCC. Our data showed that the regimen is well-tolerated in HCC patients and appears to be substantially superior to Sorafenib monotherapy in tumour response rate, disease stabilisation rate and overall survival. An international multi-centre phase III randomised controlled trial will be conducted to further evaluate the benefit of this regimen compared with Sorafenib monotherapy. Finally, the role of molecular targeted agents in earlier stage HCC is also being evaluated. The author is participating in a large-scale international multi-centre phase III randomised trial of Sorafenib versus placebo as adjuvant therapy after resection or ablation of HCC, with a target sample size of 1100 patients. There are also on-going trials of combination of Sorafenib or novel targeting agents such as Brivanib with transarterial chemoembolisation for intermediate stage HCC.

Conclusions
The management of HCC has changed dramatically in recent years with improved outcomes. The improved safety and long-term survival after hepatectomy for HCC and the development of minimally invasive liver resection have reinforced the role of liver resection as the first-choice treatment. Local ablative therapies have provided an important alternative for curative treatment for patients who have inadequate liver function reserve for resection. Recurrence after resection or ablation remains a major problem, but active studies are being conducted to evaluate novel adjuvant therapies to improve the prognosis of patients. TACE or radioembolisation is the mainstay of palliation for patients whose HCCs are confined to the liver that is not amenable to resection or ablation. Occasionally, patients with initially unresectable disease can be downstaged to resectable disease after transarterial therapies. Development of novel techniques such as drug-eluting beads and combination with molecular targeting drugs may further enhance the efficacy of TACE. Molecular targeted therapy is an important break-through that has shown for the first time as a systemic therapy to improve survival of patients with advanced HCC. It has triggered major interests in development of new drug therapies that hopefully will help conquer a disease once deemed to be associated with uniformly grim prognosis.

References
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