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Non-surgical treatment of hepatocellular carcinoma

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Abstract
A wide variety of non-surgical therapies can result in clinical responses in patients with hepatocellular carcinoma. Two recent studies have suggested that transarterial chemoembolisation can, in highly selected patients with good liver function, result in an improvement in survival. No other approaches have, to date, demonstrated convincing evidence of survival advantage.

Key words: *Hepatocellular carcinoma; intra-arterial chemotherapy; chemoembolisation; ablative therapy; radiotherapy; systemic chemotherapy; biotherapy*

Introduction

Surgical resection is currently considered to be the definitive treatment for hepatocellular carcinoma (HCC) and the only one that offers the prospect of cure or at least long-term survival. However, most patients have unresectable disease at presentation because of poor liver function (about 75% will have underlying chronic liver disease), bilobar disease, invasion of the major vessels or overt extrahepatic metastases. The overall resectability rate for HCC is thus only 10–25% and even among those who undergo surgical resection with curative intent, there is a recurrence rate of up to 80% at 5 years [1–3]. More recently there have been suggestions that other therapeutic modalities such as percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) are also potentially "curative". It should be noted that the term "curative" in this sense is usually meant to imply "resulting in complete local control of the original lesion". Cure in the strict and true sense of the word is seldom achieved.

Where conventional surgical resection is contraindicated because of poor underlying liver function, orthotopic liver transplantation is an option, particularly for those who have small tumours [4–6] but again recurrence remains a possibility and shortage of donor livers means that many will succumb while awaiting transplantation. It is thus apparent that the majority of patients with HCC will, at some point during the course of their disease, be candidates for non-surgical therapy. It is also apparent that they represent, by virtue of whatever factors preclude them for surgical resection, a relatively poor risk group.

Non-surgical treatment can be classified as locoregional, including intra-arterial or percutaneous local ablative approaches, a combination of the two, or systemic. When regional lymph nodes are involved or there are extrahepatic metastases, locoregional treatment is seldom indicated. Intra-arterial treatment is also contraindicated when there is involvement of the main portal venous system. Systemic chemotherapy is usually considered for the patients who are unsuitable for any of the above treatments.

It should be emphasized from the start that "liver failure" as indicated by overt jaundice, recurrent or diuretic-resistant ascites, recurrent gastrointestinal haemorrhage or encephalopathy unexplained by other factors will, in the view of most authorities, preclude any form of active treatment other than liver transplantation. In such patients prognosis is primarily defined by the underlying liver function rather than the tumour; effective anti-tumour therapy may not necessarily improve overall survival. Figures will vary from unit to unit and around the world but as a very broad generalization 15% of patients will be considered for surgical resection, 50% for non-surgical therapies and 35% will be unsuitable for any active treatment, and will receive best supportive care. These figures will change as more patients are detected in the asymptomatic stage by screening.

Intra-arterial and regional drug delivery

With the disappointing results seen with systemic therapy, several approaches that aim to target the tumour specifically have been developed. There are two ways in which targeting may be achieved. The first approach is based on the observation that primary and secondary liver tumours derive the bulk of their blood

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supply from the hepatic artery [7]. This approach to selectivity may be further enhanced by new arteriographic procedures that permit "super selective" catheterization of the tumour-feeding artery. Direct infusion of cytotoxic agents into the hepatic artery may allow an increase of the exposure of the tumour to the drug. Depending on the agent used, the time/concentration interval may increase by up to 400-fold. Dose-limiting toxicity may then become "regional" (i.e. hepatic and not systemic) [8–11].

A second source of selectivity is the use of lipiodol as a vehicle for cytotoxic chemotherapy. This oily based contrast medium, when injected into the hepatic artery at the time of arteriography, is cleared from normal hepatic tissues but accumulates in malignant tumours, probably because of the leaky character of neovascular tissue, combined with the lack of lymphatic clearance from tumour tissue [12]. The lipiodol forms an emulsion with the cytotoxic agent and then acts as a reservoir for the prolonged delivery of the agent to the tumour, and perhaps enhances uptake by the tumour cells. The extent to which the lipiodol acts as an embolizing agent in itself remains controversial.

There seems no doubt that, compared with systemic administration [13–15], drugs given intra-arterially are more effective, although it must not be forgotten that patients treated in this manner invariably have a better performance status than those treated with systemic therapy. For this reason, better results would be expected regardless of any inherent increased efficacy of the treatment.

Transcatheter oily chemoembolization (TACE)

Following hepatic angiography to identify the arterial anatomy and the blood supply of the tumour a catheter is placed in the appropriate vessel. Not infrequently angiography identifies tumour not detected by CT scanning. In the past the entire liver has been covered by placement of the catheter in the proper hepatic artery but nowadays it is more common to use the left or right hepatic artery when the whole of one lobe is involved, or, where feasible, to selectively catheterize just the tumour-feeding arteries, and the procedure becomes "segmental". The cytotoxic drug (usually doxorubicin or cisplatin) is mixed with lipiodol and the emulsion is injected slowly. Finally, embolization with 0.5–1 mm of gelatin cubes or a similar material is undertaken [16].

The presence of Child's grade C cirrhosis is usually considered to be a contraindication, as is thrombosis of the portal vein, because the cirrhotic liver is crucially dependent on the hepatic artery in this situation, and any further interruption thereof may lead to liver failure. Thrombosis of the portal vein is also an indication of particularly bad prognosis and is associated with the development of extrahepatic disease. If the procedure is undertaken by an experienced interventional radiologist the mortality should be well below 5% and significant side effects are rare (1%) apart from occasional gallbladder infarction [17]. Effective embolization is often associated with the so-called "post embolization syndrome" of fever, pain and vomiting for up to a week, after which it subsides spontaneously. Significant deterioration in liver function may occur but usually only when Child's grade C patients are treated. Although widely regarded as standard treatment for almost 15 years, and clear evidence that tumour necrosis was indeed caused, early controlled trials did not show an increase in survival and the consensus was that although the "primary effect" (i.e. causing tumour volume reduction) is good, there is little effect on long-term survival for which other factors such as the tumour type, degree of spread and serum alpha-fetoprotein (AFP) level are more significant than the treatment [18–21].

However, more recently, two trials and a systematic review have, for the first time, provided evidence that TACE may indeed improve survival, in selected cases. In the first of these Lo *et al.* randomized 80 subjects to either TACE (with cisplatin in lipiodol followed by gelatin sponge embolization) or best supportive therapy [22]. The survival figures at 1, 2 and 3 years were 57%, 31% and 26% compared with 32%, 11% and 3%, respectively ($p = 0.006$). In the second study, from Spain, 112 patients were randomized to TACE with doxorubicin again followed by gelfoam embolization, or best supportive therapy [23]. Survival figures at 1 and 2 years were 82% and 63% in the TACE group compared with 75% and 50% for embolization alone and 63% and 27% for those receiving best supportive therapy. In both studies the procedure was repeated if there was no evidence of progressive disease. The systematic review suggested that chemoembolization, either doxorubicin or cisplatin, but not embolization alone showed a significant benefit (2-year probability of survival, compared with control, odds ratio 0.53 with 95% confidence limits of 0.32–0.89). The systematic review again suggested that benefits were mainly in those with well preserved liver function (Child's grade A) and without vascular invasion [16].

While these two studies have, according to many authorities, established TACE as the standard of care for patients with larger HCCs, we should remain cautious. Both trials were small, and some criticisms about how well the treatment and control groups were balanced have been raised. Furthermore, and of particular importance in designing further comparative studies, there remains considerable controversy as to what is actually meant by the term "chemoembolization" and the relative importance of the "embolization" and the "chemotherapy" aspects of the treatment. It is notable that different cytotoxic agents were used in the two trials. Some in the field aim to develop extensive tumour necrosis by the embolization, while others use the embolic material to slow down the blood flow to the tumour and not to

permanently occlude the vessels and thereby permit repeat procedures.

Local ablative therapies

As noted above, the definitive local therapy is surgical resection, but newer ablative therapies, that aim to ablate the lesion using a variety of technologies, are now being widely used. The results achieved are starting to challenge surgical resection.

Percutaneous alcohol injection

Ultrasound or CT-guided percutaneous injection of sterile absolute alcohol into liver tumors, via a 19–22 gauge needle, under local anaesthetic consistently induces vascular thrombosis and coagulative necrosis. A total of between 2 and 100 ml of alcohol is injected during the course of several sessions (depending on the tumour size) and distributed as uniformly as possible throughout the lesion. The most suitable patients are those with less than three small (<3 cm) tumours with good underlying liver function (Child's grade A). In such patients complete response is obtained in around 80% with survival figures in the range of 3 and 5 years in the order of 75% and 50%, respectively [24]. In such patients it seems likely that results are at least as good as surgical resection [25]. The benefits of PEI decrease markedly in larger lesions; the procedure becomes more tedious and it is more difficult to generate complete necrosis, in part because of the presence of septa within the lesion but also because of "run off" of the alcohol into the vasculature. Most units will not consider PEI for lesions >5 cm [26].

The procedure is cheap, simple to perform, does not require a general anaesthetic and is virtually free of any associated mortality. The only complications are intense pain if the alcohol is allowed to leak out into the peritoneal cavity, transient pyrexia, very occasional episodes of haemoperitoneum (<5% of cases) and, very occasionally, tumour seeding along the needle tract. Nonetheless, as with surgical resection, in 50–70% of cases there will be intrahepatic recurrence. This is particularly so in larger lesions and those that are multifocal to begin with. Most will occur within 2 years of the initial procedure [27,28].

How should one decide between surgical resection and PEI in a patient with a solitary small liver tumour before prospective randomized clinical trials directly comparing the procedures are available? There are no hard and fast rules and it is probably fair to say that there is a trade-off between more early morbidity and mortality with surgical resection and more late deaths with PEI. If the patient is young, there are no co-existing medical conditions and liver function is good, most would still favour surgical resection. This has the added theoretical benefit of removing surrounding tissue that may be the site of micro-metastatic disease. If there is any factor indicating significant operative risk, co-morbidity, or the patient is elderly and frail, then PEI is probably preferable. In the future it is likely that the current position of PEI will be challenged by radiofrequency ablation, largely on the grounds that the lesions can be dealt with in a fewer number of sessions.

Thermal and laser ablation

Both heating and cooling, locally administered under ultrasound control, have been used to induce tumour necrosis. "Cryotherapy", which relies on a "freeze-thaw" process is undoubtedly effective in delivering local tumour control even in larger lesions (up to 8 cm) but the probe needs to be large (up to 10 mm in diameter) and the treatment needs to be delivered under general anaesthetic [29]. The latter, in which heat is developed from an alternating electric current in the radiofrequency range, can result in complete necrosis of a 3-cm tumour in <1 hour and in one session. RFA is considered to be "minimally invasive", the needle electrodes being only 15-gauge. Depending on tumour size and site it may be administered percutaneously, intra-operatively or laparoscopically. Some lesions, particularly those near to large vessels, may be technically difficult to access.

Overall, the complication rate is <10%, rather lower than that reported for cryotherapy, as is the mortality. Such opinions should be taken cautiously as the size of tumour treated with RFA tends to be smaller than with cryoablation and thus the inherent risks of the procedure are also smaller. Nonetheless there is a general trend toward RFA and away from cryotherapy. Moreover, the more rapid achievement of complete tumour necrosis and easier access to tumour margins has also led to a general trend towards RFA over PEI [30–34]. Indeed, such is the enthusiasm for RFA that prospective randomized trials comparing RFA with surgical resection are currently underway.

Other technologies are being developed to achieve similar ends to RFA and PEI and these include photodynamic therapy and laser thermal ablation. The latter has yielded encouraging results, and has the advantage that it can be carried out under magnetic resonance guidance, the whole procedure being monitored with near real-time thermal imaging to assess the efficacy of tissue necrosis [35,36].

Radiotherapy

The application of external beam irradiation for the treatment of liver tumours has been severely limited by the radiosensitivity of normal hepatocytes. Maximum tolerance of normal liver to radiation is generally accepted to be between 2500 and 3000 cGy; above this level the risk of radiation hepatitis (veno-occlusive disease with perivenular congestion and fibrosis) increases rapidly [37].

Internal irradiation with intra-arterial radioisotopes

Therapeutic doses of radioisotopes can be administered into the hepatic artery using ^{90}Y tagged to resin-based or glass microspheres or ^{131}I in conjunction with lipiodol. Lipiodol-^{131}I emits mainly γ-radiation. The volume of radioactive lipiodol administered is limited by the size and vascularity of the tumour; thus in practice, radioactive lipiodol is used only in patients with tumours <5 cm in diameter [38]. About 40% of patients will gain objective remissions with minimal toxicities while keeping the radiation dose to a normal liver below 2000 cGy. ^{90}Y, a pure β-emitter, is more powerful than ^{131}I with a mean tissue penetration of about 2.5 mm. Optimal tumour regression and reduction of serum AFP level are seen when the average radiation dose to the tumour is $>12\,000$ cGy. The partial response rate is $>50\%$ [39]. Despite the presence of cirrhosis, there is little evidence of radiation hepatitis, even when the non-tumorous liver receives up to 7000 cGy. Leakage of the microspheres into the right gastric artery or gastroduodenal artery may occasionally cause radiation gastritis or duodenitis. Systemic leakage of the microspheres to involve the lungs, which are also sensitive to irradiation, may occur if there is extensive arteriovenous shunting within the tumour. For this reason, the degree of lung shunting must be determined before administration of the radioisotope by using a ^{99m}Tc macroaggregated albumin (^{99m}Tc-MAA) scan with γ-camera scan [40].

Systemic chemotherapy

Almost all the cytotoxic agents used in oncologic practice have been evaluated, and none has been shown (as a single agent or in combination with other agents) to improve survival or to achieve a consistent response rate of $>20\%$ [41–43]. The most widely used agent has been adriamycin (doxorubicin). In a review of several published trials involving >600 patients, the objective response rate was 19% with a median survival of 4 months. A reasonable approach is to administer three courses and to reassess at 2 months. If there is evidence of a response, in terms of a $>50\%$ fall in serum AFP or a decrease in liver or tumour size as determined by ultrasound or CT scanning, then treatment should be continued to a maximum dose of 550 mg/m^2. Above this cumulative dose, cardiotoxicity becomes increasingly more frequent.

It is noteworthy that the most common primary liver tumour in childhood, hepatoblastoma, is significantly more chemosensitive (using various combinations of cisplatin and doxorubicin), and it is now common practice to administer chemotherapy before surgical resection. Around 90% of cases will achieve remission, and initially unresectable tumours can usually be successfully resected or transplanted [44,45]. In a similar manner, a regimen known as PIAF (platinum, interferon, adriamycin, and 5-fluorouracil) has recently been shown to convert about 10–20% of unresectable adult HCCs to resectable ones, but this regimen should remain experimental until controlled trials are completed [46].

Hormonotherapy and biotherapy

There has been recent interest in altering the hormonal environment of the tumours and small studies suggested survival benefit from both anti-androgenic and anti-oestrogenic agents. However, recent large-scale prospective randomized controlled studies have failed to find any support for these contentions [47–49]. A recent small prospective randomized study [50] found significant improvement in survival for patients receiving octreotide, a somatostatin analogue, but this has not been subsequently confirmed [51].

Conclusions

Locoregional therapies and surgical resection, the definitive locoregional treatment, are all capable of delivering complete local control in a percentage of cases, the percentage decreasing as the tumour size increases. It seems likely that all these would, in patients without underlying liver disease, or with well compensated liver disease, result in improvement in survival but this has, to date, only been demonstrated in two small series of patients receiving TACE. The treatment of choice will depend on the ease and cost of the therapy, its complication and acceptability rate and any benefit that can be shown in prospective randomized clinical trials. The problem with all these approaches remains the fact that recurrence is the rule. What is needed therefore is effective systemic therapy to supplement and enhance the local control. To date this has not been demonstrated but remains the long-term goal. However if, as seems the case, therapeutic benefit can only be demonstrated in patients with good underlying liver function (Child's grade A), and such patients will invariably receive some form of locoregional therapy, there would appear to be very little scope for testing novel systemic therapies.

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