Advances in Interventional Radiology in the Treatment of Primary and Metastatic Liver Cancer

a report by

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Hepatocellular carcinoma (HCC), a primary malignancy of the hepatocyte, is increasing in incidence worldwide. Chronic liver damage is the most important risk factor. The incidence of HCC is directly related to that of hepatitis B and C infection, and cirrhosis is present in 80% of cases.[1] It is the fifth most common primary malignancy worldwide, and the third most common cause of cancer-related death.[2] In Europe, metastatic liver disease is much more common than HCC, with 30–70% (depending on the primary site) of patients who die from cancer having liver metastases at autopsy.[3] Not only is the liver a likely target for metastatic disease because of its rich, dual blood supply, but the fenestrations in the sinusoidal endothelium also allow arriving tumour emboli to lodge in the space of Disse.

The liver is a primary target organ of gastrointestinal cancers and may be the only organ involved in colorectal primaries, HCCs and neuroendocrine tumours.[3] Even when extrahepatic spread is present, many patients die due to hepatic failure and portal hypertension. Colorectal cancer is the second leading cause of cancer-related death in Europe, with liver metastases being the most common cause of death in these patients. Although surgical resection and liver transplantation can be effective radical treatments for HCC and for liver metastases, most patients do not benefit from this due to the location or number of liver lesions, poor hepatic reserve, extrahepatic spread, co-morbid medical conditions or a shortage of donors. For example, 80% of colorectal carcinoma liver metastases are un-resectable and most resected tumours recur, with only a 30–40% five-year survival rate.[4,5] Despite recent advances in chemotherapy regimens such as fluorouracil/leucovorin and oxaliplatin[6] or the use of growth factor antibodies such as bevaciximab,[7] systemic chemotherapy and radiotherapy remain relatively ineffective, with most series having very few long-term survivors.[6,7] This has led to the advent of many locoregional therapies being developed as alternative treatment options.

Interventional radiology allows medicine and technology to combine forces and come up with revolutionary minimally invasive anticancer treatments. These therapeutic strategies can be broadly divided into two separate categories. The first category comprises image-guided ablative therapies such as cryoablation, percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), laser-induced thermotherapy and microwave ablative therapy. The second category comprises transarterial hepatic therapies such as intra-arterial chemotherapy (TAC), transarterial embolisation (TAE) and transarterial chemoembolisation (TACE).

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Cryoablation

First described in 1963, cryotherapy represents the earliest attempt at thermal ablation.[8] This technique achieves tumour cell death by lowering the temperature of tumour cells to below -20ºC. This is achieved by circulating cryogenic material such as liquid nitrogen through the probe, with thermally conductive material at the tip of the probe causing ice crystal formation. There is resultant destruction of cellular structures and rupture of cellular membranes. One limitation of this technique was that it originally required laparoscopy or laparotomy. Technical advances have allowed smaller probes, which use compressed argon gas as the cryogenic material, to be utilised. This advance has allowed percutaneous image-guided cryoablation to become a clinical reality. Additional technical difficulties include acquiring adequate cryoablation of tumours larger than 5cm or of tumours closely related to the inferior vena cava (IVC) or major hepatic branch vessels.

A tract caused by the cryoprobe or cracking of the liver surface during thawing of the iceball can cause intra-operative haemorrhage, for which liver suturing or packing is often required. A consumptive coagulopathy or thrombocytopoenia can also occur, potentially leading to delayed haemorrhage into the lesion or at a distal site. These complications are of particular concern in HCC, where patients often have cirrhosis, putting them at increased risk of haemorrhage. This has led to cryoablation more commonly being used to treat liver metastases than to treat HCC. Additionally, one study[9] reported a local recurrence rate for primary and metastatic liver tumours treated with cryotherapy versus RFA of 13.6 and 2.2%, respectively ($p<0.01$), and a much higher complication rate after cryotherapy (40.7 versus 3.3%; $p<0.01$). This and other similar studies have led to cryoablation being largely superseded by other ablative techniques.

Percutaneous Ethanol Injection

Chemical ablation involves the injection of a toxic chemical into a tumour, with resultant destruction of the malignant cells. Ethanol is the most commonly used chemical. PEI involves using image guidance, usually ultrasound, to direct the injection of 95% ethanol through a thin needle. Ethanol causes dehydration and eventual fibrosis of the cytoplasm, direct chemical injury to organelles and vascular thrombosis, among other complex effects. The area of infarction and tissue destruction caused by the ethanol is not accurately predictable or reproducible. Diffusion of ethanol through a tumour depends on the tissue consistency, degree of vascularity and the presence of septa or a tumour capsule, among other factors. Clinical studies have shown that PEI is most effective for patients with a single small primary liver tumour that tends to arise in a cirrhotic liver. In this select group survival rates can be comparable to those of surgery.[10] It is thought that the soft

tumour allows the ethanol to diffuse easily through it, but not into the surrounding scarred liver. In contrast, liver metastases are usually much harder than HCCs, thus preventing uniform diffusion of the ethanol throughout the tumour. Therefore, PEI is much less effective for the treatment of liver metastases compared with the treatment of HCC. Serious complications such as intraperitoneal haemorrhage, hepatic insufficiency or infarction, bile duct necrosis or biliary fistula occur in fewer than 5% of patients.[11] However, PEI usually requires multiple treatment sessions, each one being associated with significant pain for the patient. This can lead to problems with patient compliance.[11] This, along with difficulty in achieving complete tumour destruction and a high local recurrence rate, has led to a widespread decline in the use of PEI in favour of newer single-treatment ablative techniques such as RFA.

Radiofrequency Ablation

RFA uses RF energy to destroy tumour cells. It has been the subject of increasing research and has gained widespread clinical use in recent years for the treatment of both primary and secondary liver tumours. With traditional RF systems, an electrical circuit is created within the patient by placing grounding pads on the thighs and, under image guidance such as ultrasound or computed tomography (CT), an RF electrode is positioned within the tumour. A high-frequency alternating current is then activated, leading to frictional heat caused by the movement of ions as they try to follow this alternating current. This heat causes tissue temperatures adjacent to the electrode to increase to 60–100°C, with resultant immediate induction of cell death and thrombosis of the surrounding microvasculature, referred to as coagulation necrosis. The aim is to mimic a surgical resection margin by causing thermal destruction of the tumour as well as a surrounding volume of normal liver parenchyma at least 1cm thick.

Modifications to the original technique and technical improvements are aimed at overcoming a number of limitations inherent to RFA. As the temperature adjacent to the electrode rapidly increases, water molecules begin to vaporise and tissue immediately surrounding the probe can become charred. This leads to a decrease in electrical conductivity and an impedence spike, or 'roll-off', that signals the end of active heating. As the radius of surrounding tissue that is destroyed is dependent on its impedence, it is inversely proportional to the square of the distance from the electrode.[12] Therefore, the tissue temperature falls rapidly with increasing distance from the electrode. This has led to several modifications of needle electrodes in an effort to enhance the surrounding sphere of coagulation necrosis.

Saline-enhanced probes expand the thermal zone by introducing saline into the target tissue via a cannulated RF probe.[13] The infused saline solution facilitates the conduction of thermal energy away from the electrode. However, irregular diffusion of the saline within the liver may sacrifice the uniformity or predictability of treatment. An alternative device is the multiple array electrode. This is designed with several inner hook electrodes. The needle shaft is placed within the tumour and the inner hooks are deployed. These expand in a similar way to an umbrella, effectively allowing a larger sphere of ablation.[14] Internally cooled RF probes are also designed to increase the region of effective ablation by preventing vaporisation and charring. Within these probes a chilled solution is transported to the distal tip. A separate lumen then transports the warmed solution back through the probe.[15] One recent study showed no statistically significant difference in survival at three years when small HCCs were treated with an internally cooled electrode versus an expandable electrode.[16]

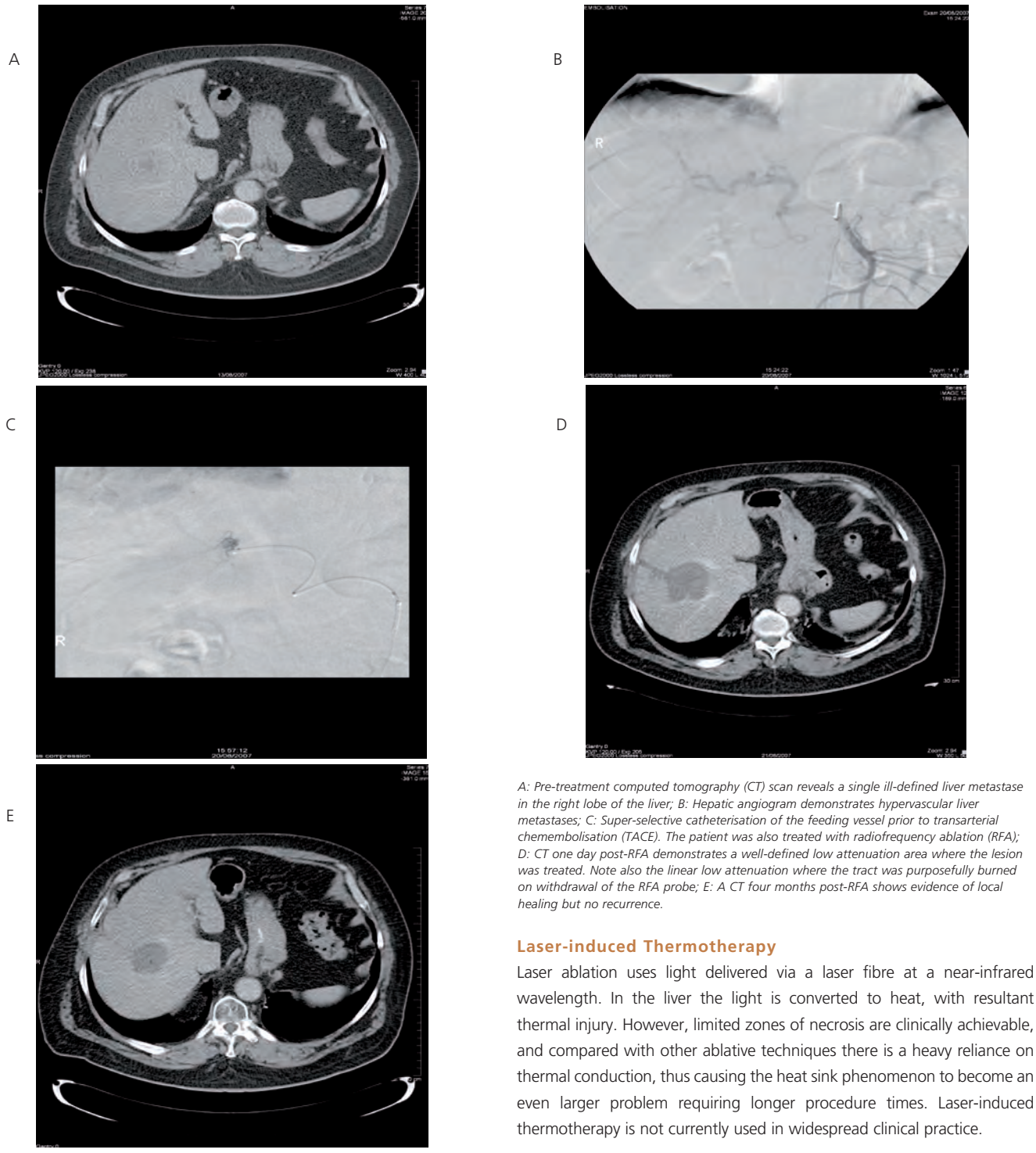
Bipolar radiofrequency systems, in which both the active and neutral electrodes are located on one application instrument separated by an insulator, are a relatively new concept. They eliminate the need for ground pads (neutral electrodes) to be placed on the patient's skin. Multiple electrode systems have also been devised in an attempt to enlarge the amount of tissue that can be successfully ablated at a single treatment. Multipolar RFA allows up to three bipolar RF probes to be placed within (or immediately adjacent to) the tumour. By having electrical current running between up to six electrodes and allowing up to 15 possible electrode combinations, more homogenous deposition of energy and potentially larger volumes of tissue ablation can be achieved. Although the author is not aware of any large series or studies with long-term follow-up, small clinical studies support the safety and efficacy of this technique.[17]

An additional limitation of RFA is the well-documented 'heat sink' effect caused by proximity to large blood vessels. Blood flow effectively carries thermal energy away from adjacent tissue faster than the RF probe can heat it. This limits coagulative potential and local tissue destruction. As a result, tumour cells nearest to blood vessels can be spared, leading to subsequent tumour recurrence. The recognition of this phenomenon has led to attempts to overcome it by reducing hepatic blood flow during RFA. These include angiographic hepatic artery balloon occlusion, temporary portal vein occlusion or selective TACE with RFA. Despite the liver also receiving a blood supply from the portal vein, there is evidence that combining RFA with TACE can increase the ability of tumours to reach tumoricidal temperatures and to increase the achievable zone of necrosis from 4 to 6.5cm.[18]

Although the most widely used approach for RFA is a minimally invasive percutaneous one, some clinicians advocate a laparoscopic or an open surgical technique. A percutaneous approach minimises access trauma and reduces intra- and post-operative complications.[19] Potential advantages of an open approach include surgical cross-clamping or wrapping of the portal vein and hepatic artery at the porta hepatis (Pringle manoeuvre) in an effort to decrease hepatic blood flow and thus also the heat sink effect. Intra-operative ultrasound improves staging and/or probe placement.[12] Additionally, better access and visualisation of disease, monitoring of ablation and easier avoidance of organs such as the diaphragm and bowel may be possible. There is as yet no consensus as to the best route of access.

The most common serious RFA complication is haemorrhage, but the risk is relatively low, with the rate of major haemorrhage occurring in most series being ~1–2%. Ablation of the tract while withdrawing the RF probe can help to decrease the risk of haemorrhage, as well as decreasing the likelihood of tract seeding with tumour cells. With centrally located tumours in particular, there is a risk of injuring the bile ducts. The predictabillity of RFA makes collateral damage to adjacent organs unusual and the heat sink effect of adjacent blood vessels, despite generally being troublesome as described above, can actually serve to protect vessels from vascular damage. RFA is the most widely used ablation technique. For HCC it can be used as a bridge to liver transplantation, allowing patients to remain on transplant lists for longer.[20] RFA improves survival and can offer the possibility of a cure in some patients with unresectable HCC if the tumour is <5cm.[20] Its use in patients with resectable HCC is controversial, but there is evidence that, for small lesions, survival at three years may be comparable to surgery.[21]

Figure 1: 63-year-old Male with Metastatic Oesophageal Cancer



A: Pre-treatment computed tomography (CT) scan reveals a single ill-defined liver metastase in the right lobe of the liver; B: Hepatic angiogram demonstrates hypervascular liver metastases; C: Super-selective catheterisation of the feeding vessel prior to transarterial chemembolisation (TACE). The patient was also treated with radiofrequency ablation (RFA); D: CT one day post-RFA demonstrates a well-defined low attenuation area where the lesion was treated. Note also the linear low attenuation where the tract was purposefully burned on withdrawal of the RFA probe; E: A CT four months post-RFA shows evidence of local healing but no recurrence.

A recent study examined patients with solitary colorectal liver metastases.[22] RFA in unresectable patients was compared with surgery in patients with resectable disease. The overall three-year survival was 52.6 and 55.4% for the RFA and surgical groups, respectively. This difference was not statistically significant, despite the fact that some of the RFA group were known to have stable extrahepatic disease. Liver metastases from neuroendocrine tumours, such as carcinoid tumours, represent a unique group of patients that can be very symptomatic due to circulating hormone levels. They can often have large, slowly growing tumours, which are unlikely to be cured by surgery. Percutaneous RFA can be highly effective in controlling symptoms in these patients, with lower complication and mortality rates than laparotomy.[20]

Laser-induced Thermotherapy

Laser ablation uses light delivered via a laser fibre at a near-infrared wavelength. In the liver the light is converted to heat, with resultant thermal injury. However, limited zones of necrosis are clinically achievable, and compared with other ablative techniques there is a heavy reliance on thermal conduction, thus causing the heat sink phenomenon to become an even larger problem requiring longer procedure times. Laser-induced thermotherapy is not currently used in widespread clinical practice.

Microwave Ablative Therapy

Microwave ablation works through a process known as dielectric hysteresis. The microwaves cause dipolar molecules (mainly water) to alternate along with the field. As the molecules cannot alternate as fast as the field there is conversion of some of the microwave energy into heat. As described above, RFA systems require an electrical current and therefore low impedence within the patient. Microwave antennae, on the other hand, radiate microwave fields. Heating of tissues is not inhibited by charring or vaporisation of tissue more proximal to the ablation probe (antenna), thus the impedence spike that cuts off RF heating does not occur. This allows a larger volume of active heating. As microwave ablation heats tissue much more quickly than RFA, this technique should also be less susceptible to

vascular heat sink effects, allowing increased cell death of peri-vascular tumour. Heating up to 100 times faster than RFA would also mean quicker procedure times. Engineering difficulties, such as making smaller-diameter antennae systems powering several antennas from a single high-powered generator and systems that do not cause too much heating of the proximal antenna or power distribution cables, are being overcome.[23] It is likely that the theoretical advantages of microwave systems will be translated into clinical practice in the near future.

Transarterial Hepatic Therapy

The liver has a unique dual blood supply, with the portal vein supplying approximately 70% of the organ and the hepatic artery supplying the remainder. Both primary and secondary hepatic tumours derive more than 90% of their blood from the hepatic artery.[24] Transarterial hepatic therapy offers a unique opportunity to exploit these facts. TAC allows high doses of chemotherapeutic agent to be infused directly into the tumour feeding artery. Bland TAE involves injection of embolising agents into the hepatic artery, causing ischaemic necrosis of the liver tumour while normal liver parenchyma continues to be supplied by the portal vein. TACE attempts to combine these methods by injecting anticancer drugs followed by embolic material. TACE affords concentrations of chemotherapeutic agents to reach one to two orders of magnitude higher within the tumour than with infusion alone, and prolongs dwell time, with measurable drug levels achieved months later.[18] This causes less systemic toxicity, achieves more extensive tumour necrosis and can prolong survival compared with TAC.[25]

In HCC, TACE prolongs survival compared with best supportive care.[26,27] TACE is a widely used technique for treatment of colorectal liver metastases. Studies of TACE in these patients suggest a longer survival time than one would expect for systemic therapy in patients who have failed standard chemotherapy.[28] TACE can prolong survival in patients with liver metastases from ocular melanoma,[29] demonstrate a response to treatment in patients with sarcomas metastatic to the liver[30] and downstage cholangiocarcinoma in selected cases so that previously unresectable patients can become surgical candidates.[31] Considering the dismal prognosis and the lack of alternative effective treatments, TACE is an important treatment option for these patients.

Intra-arterial hepatic therapy is also commonly used to treat liver metastases from carcinoid and islet cell tumours. The primary aim of this therapy is to produce symptom relief. These hypervascular neuroendocrine tumours can cause pain and produce hormones such as serotonin, gastrin, glucagons and other polypeptides. TACE or TAE typically produces symptom-free intervals in 90–100% of patients and in one study demonstrated a mean time to symptomatic progression of 19 months.[32] TACE is generally a well tolerated procedure. The most common side effect of TACE, occurring in 60–80% of patients, is a self-limiting post-CE syndrome. This consists of transient abdominal pain, fever, nausea and vomiting. If this is treated symptomatically, most patients can go home the day after the procedure. Severity of cirrhosis is predictive of a post-TACE deterioration in liver function. In patients with an advanced Childs class, approximately 3% develop irreversible hepatic decompensation as a result of the procedure.[33] A recent large systematic review reported complications such as hepatic or splenic abscesses, bile duct injuries, upper gastrointestinal bleeding secondary to gastroduodenal ulceration and irreversible renal dysfunction occurring in less than 3% of patients each, and an overall median 30-day mortality rate of 2.4%.[25]

Lipiodol (ethiodised oil) is a contrast agent that was commonly used as a vehicle in an attempt to carry and localise chemotherapeutic agents within liver tumours. However, recently it has fallen out of favour as there is no evidence that it can slowly release the chemotherapeutic agent within the tumour. It can also mask assessment of residual tumour vascularity on post-procedural computed tomography (CT) scans, and there is evidence that it may be associated with post-procedural bilomas.[34]

The most widely used embolic agent used in published clinical trials is gelatin sponge. This causes a transient vascular thrombosis of approximately two weeks. In recent years a number of new agents have been developed. Theoretically, embolising agents such as polyvinyl alcohol (PVA) particles, which can cause permanent thrombosis, should be more effective. Theoretical advantages should also pertain to deformable particles that have a standardised size and are less inclined to aggregate due to smooth and hydrophilic surfaces. Embosphere® (BioSphere Medical, US) microspheres (100–700µm) is one such agent that can result in a lower rate of catheter occlusion and more distal penetration into smaller vessels.[35] Novel systems such as drug-eluting beads (e.g. DC Bead™ Biocompatibles UK) and HepaSphere™ (BioSphere Medical, US) microspheres have unique fluid-absorbing properties that are specifically designed to release chemotherapeutic agent into the targeted tumour at a slow rate, as well as causing small-vessel occlusion. Another form of intra-arterial locoregional therapy is radioembolisation, or selective internal radiation therapy (SIRT). It involves injection of embolising microspheres that also contain yttrium-90. This results in a form of brachytherapy that can improve survival when combined with systemic chemotherapy versus systemic chemotherapy alone for patients with colorectal liver metastases.[36]

Embolising the tumour-feeding arteries blocks the nutrient supply to the tumour, rendering it ischaemic. When combined with regional chemotherapy infusion in TACE, tissue levels of the chemotherapeutic agent have been demonstrated to persist for several months and to be up to 40 times higher in the tumour compared with the surrounding liver.[37] Considering the importance of preserving as much of the remaining liver function as possible, this highlights the need for selective catheterisation of the hepatic artery branch feeding the tumour when possible. In addition, embolisation can theoretically help overcome tumour drug resistance by causing adenosine 5'-triphosphate (ATP)-dependent transmembrane pumps, which are known to actively expel drugs such as doxorubicin, to fail. Therefore, the tissue hypoxia can cause increased intacellular retention of the chemotherapeutic agent.

Surprisingly, despite the theoretical advantages of TACE compared with TAE, no study has yet proved a survival advantage of one method over the other.[25] There is also a concern that ischaemia produced by embolisation can promote angiogenesis in tumour cells.[38] This is leading to increasing interest in using antiangiogenic agents, such as sorefanib, in TACE. As yet, no one chemotherapeutic agent, or combination of agents, used in TACE has been shown to be more beneficial than the others.[25] Some of the more commonly used regimens involve doxorubicin, cisplatin, mitoxantrone or a combination of these agents for treatment of HCC. The ideal drug for use in TACE should have preferential hepatic excretion and be most active at high concentrations, i.e. concentrations not obtainable from systemic administration. Newer agents will continue to be evaluated for use in TACE. Irinotecan shows some promise of being beneficial for treating colorectal liver metastases.[39]

Tumour response to chemotherapy and radiation is a function of the tumour cells present that are sensitive to the treating agent. Large tumours are less likely to be totally killed than small tumours. In fact, for both chemotherapy and radiation therapy, the log of a surviving fraction of a homogenous population of sensitive tumour cells is a linear function of treatment dose.[40] It is on this basis that systemic dosing and scheduling regimens for chemotherapy are based. Systemic therapy is usually given continuously or in up to three weekly intervals. Although it is generally accepted that TACE is most beneficial when repeated, it is usually repeated every two to three months. From an oncological point of view, chemotherapy given at these intervals is unlikely to be beneficial. Although clinicians must be wary of the underlying liver function, the efficacy of more concentrated regimens with more frequent repetition of TACE should also be evaluated.

A widely recognised problem when evaluating the literature for TACE is that patients included in earlier studies had more advanced cancer and more decompensated liver disease. It is likely that this reflects the more widespread use of TACE in recent years as a result of advances in technique and growing confidence in its efficacy. However, most studies continue not to be strictly comparable. Studies continue to examine different chemotherapeutic agents, different embolic agents, different doses of drugs, different scheduling of repeat treatments, patients with operable and inoperable tumours, different underlying liver function and co-morbidities and, in HCC, a different underlying aetiology, e.g. viruses. Global effort is needed to ensure that high-quality trials are performed.

Combination Therapies

With increasing evidence of the safety and efficacy of radiologically guided ablative and intra-arterial therapeutic techniques has come a trend towards combinations of these therapies being employed to treat primary and secondary liver tumours. Theoretically, these combinations may be synergistic rather than merely additive in their combined benefits. For example, TACE performed prior to PEI may render the tumour necrotic, and thus allow enhanced diffusion of the ethanol. This should allow effective treatment of tumours larger than can be successfully treated with PEI alone. As discussed, regional blood flow promotes heat loss and has a detrimental effect on the efficacy of RFA. Therefore, TACE performed prior to RFA should enhance the overall treatment. A recent systematic review supports the efficacy of these theoretical advantages in practice.[41] Another study demonstrated improved local tumour control and long-term survival when RFA was combined with PEI compared with RFA alone in patients with HCC.

Conclusion

Prognosis and treatment options remain limited for most primary and secondary liver cancers. As technical improvements and new chemotherapeutic agents become available, radiologically guided treatment of liver tumours will continue to play an increasingly important role in the effective and safe treatment of these malignancies. ■

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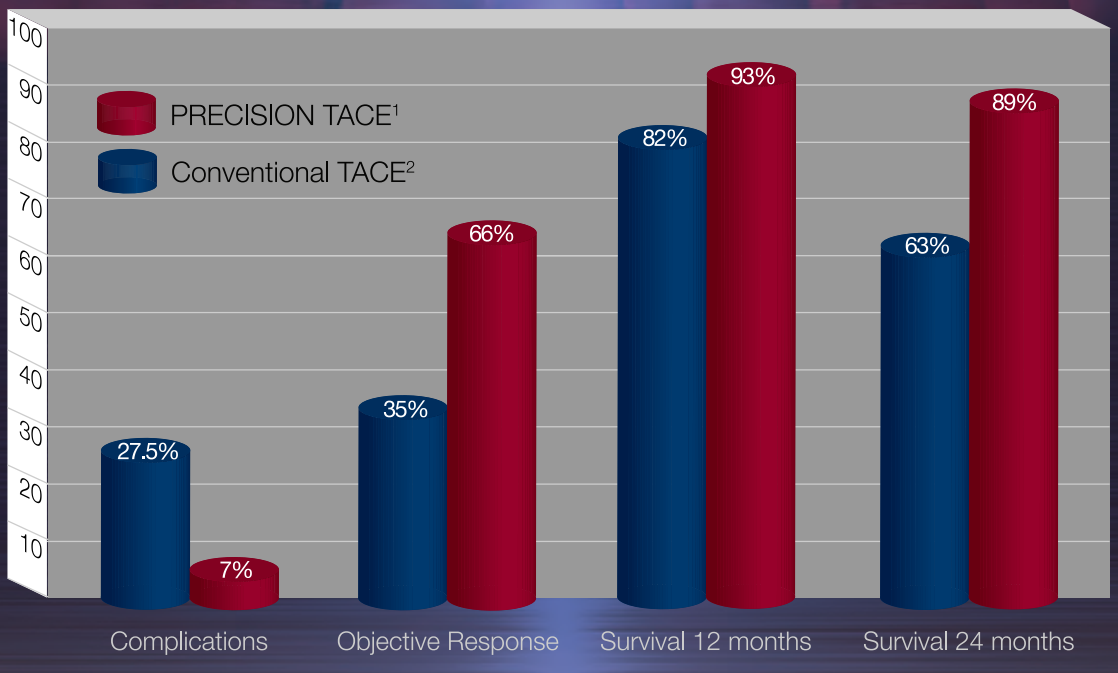

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