Image-guided therapies in the treatment of hepatocellular carcinoma: A multidisciplinary perspective

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Abstract

A multidisciplinary approach to the treatment of patients with unresectable hepatocellular carcinoma (HCC) has led to improvements in screening, detection, and treatments. Interventional techniques include thermal ablation, transarterial chemoembolization, and radioembolization whilst stereotactic body radiation therapy also uses imaging to target the radiation. Both survival rates and cure rates have improved markedly since the introduction of these techniques. This review article describes the image guided techniques used for the treatment of HCC.

Key words: Ablation; Chemoembolization; Radiation; Hepatocellular carcinoma

Core tip: This review article provides an updated description of the image guided therapies for hepatocellular carcinoma including stereotactic radiation, set in the context of a multidisciplinary approach.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of cancer related deaths[1]. Treatment depends on the stage of the tumor, performance status, and liver function, as well as on the multidisciplinary capabilities of the managing team of hepatologists, gastroenterologists, surgeons, radiologists and oncologists. Curative resection, liver transplantation, ablative therapies, trans-arterial chemoembolization (TACE), radioembolization and systemic therapy all

lie within the range of treatments available to this team[2,3].

In recent years surveillance strategies for patients with viral hepatititis or with cirrhosis have improved, leading to earlier diagnosis in many patients. These patients have a chance of gaining a curative response to treatment[4,5]. In contrast, delay in treatment leads to worse survival[6]. Resection remains the first option for patients who are suitable for surgery, as defined by the Barcelona Cancer of the Liver Clinic (BCLC) staging system. However, several different image guided minimally invasive therapies have emerged and evolved to improve the treatment of HCC at an early stage. These complement therapies provided by surgical and radiation/oncology services. Selection of treatment pathways is determined by a multidisciplinary approach[7-9] and is most commonly based on the BCLC staging system[10]. For early and intermediate stage hepatocellular carcinoma (HCC) (stages A and B) locoregional treatments including ablative therapies and TACE are used. Radioembolization is used for intermediate and advanced stage HCC who are poor candidates for TACE, and who have portal vascular invasion[11]. It is also used with limited evidence base for the downstaging of tumors so that more curative treatments can be employed[12,13].

For patients who have either failed locoregional therapies or who present with more advanced HCC, Sorafenib induces a clinically relevant improvement in time to progression and in survival.

ABLATIVE THERAPIES

Liver transplantation and surgical resection remain the primary options for curative treatment in appropriate patients. The Milan criteria[14] provide strict guidelines for transplantation eligibility, whilst surgical resection is suitable only for patients with single nodules and Child Pugh class A liver function[15]. The limitations on these treatment options offer up a substantial number of patients who can benefit from locoregional therapies. Radiofrequency ablation has become the most accepted treatment for patients with very early and early stage (BCLC 0 and A) disease who are not eligible for surgery[16,17]. In three independent meta-analyses[17-19] which include five randomized controlled trials, better local control and increased survival has been demonstrated in comparison with percutaneous ethanol ablation. When compared with surgical resection, there is conflicting evidence. In randomized controlled trials Huang *et al*[16] indicate improved results for surgery over RFA who were followed up for 5 years while Feng *et al*[20] showed that although there was a greater risk of local recurrence with RFA, there was no significant difference in overall survival. Similar conflicts are demonstrated in meta-analyses. Liu *et al*[21] found equivalent survival rates despite higher rates of local recurrence with RFA, whilst Zhou *et al*[22] found better survival rates in surgical patients for tumors measuring greater than 3 cm, and equivalent rates in smaller tumors. Survival ranges from 78%-94% at 1 year and 58%-96% at 3 years[17-22].

RFA employs low-voltage alternating current to provide sufficient heat to kill cells[21-24]. The probes are inserted under ultrasound or computed tomography (CT) guidance. The procedure is performed under moderate sedation or general anesthesia and patients can be discharged on the same day or the following day. Complication rates are lower than those of surgery and include abscess formation, tumor seeding along the electrode track, burns from the grounding pads, bile duct injury and thermal injury to adjacent organs[25]. The procedure is also less expensive than surgery.

Cyroablation is similar in terms of technical approach to RFA, but creates tissue injury from low temperatures of -20 ℃ to -60 ℃[26]. More than one needle is usually required. The procedure can be applied with lower rates of complication than RFA when close to the gall bladder[27] or bowel loops, and is less painful when employed for lesions which are contiguous with the diaphragm[28]. The procedure can be performed under moderate sedation[29]. It is possible to follow the ablative effect on CT by visualization of the ice ball[23,28-30]. One and 3 year survival rates are demonstrated at 81.4% and 60.3%, similar to those of RFA[30]. A single meta-analysis shows an advantage for RFA over cryotherapy in terms of recurrence rate[28]. There is no study comparing the survival rates.

Microwave therapy also works by heating the local tissues. It achieves a larger ablation zone in a shorter period of time than RFA[31]. Early studies have shown that there is a larger rate of local recurrence with microwave than with RFA, but there are no large studies or randomized studies to support this.

With the advent of RFA, percutaneous ethanol injection has decreased in popularity. The procedure is low cost, but requires several sessions of treatment. It is performed with a fine needle under ultrasound guidance. Tumor recurrence rates and survival rates are inferior in comparison with those of RFA[32].

CHEMOEMBOLIZATION

HCC is preferentially supplied by the hepatic arterial inflow, in contrast to the normal liver parenchyma which is largely supplied by the portal vein. The TACE procedure exploits these blood supply dynamics. Techniques vary according to resources and expense, but the principal is that an intra-arterial catheter is placed in the vessel(s) supplying the tumor(s) and high concentrations of a chemotherapeutic agent is delivered along with an embolic agent to achieve the dual purposes of targeted chemotherapy and reduction in arterial supply to the tumor.

TACE has been performed since 1980. Chemotherapeutic drugs, most commonly doxorubicin, cisplatin and mitomycin, are delivered locally along with an embolic agent, normally lipiodol, an oil emulsifying agent, thereby avoiding systemic toxicity. Other embolic agents used are gelatin sponge and PVA particles.

Drug eluting beads (DEB-TACE), although not yet the standard, are becoming increasingly popular largely due to the decreased side effect profile in comparison with the standard TACE cocktail of drugs. DEB-TACE delivers small beads which have been soaked for several hours, normally in doxorubicin. The loaded beads occlude the feeding vessels of HCC, while the anticancer drug is released gradually, creating tumor necrosis and increasing chemotherapeutic concentrations locally. Bead size varies from 75 micron to 700 micron, the choice of size being dependent on tumor size and the desired level of concentration within the treated volume. Improved results are achieved when chemoembolization is performed selectively to segmental or subsegmental arteries feeding the tumor(s)[33].

TACE is recommended as the standard of care for intermediate stage HCC without vascular invasion or distant metastases. Although there has been some heterogeneity in the results of several randomized controlled trials, TACE has been shown to achieve at least a partial response in 15% to 62% of patients, and improves survival from 16 mo to 20 mo[34-40]. The variability in results is likely explained by the fact that intermediate stage HCC covers a broad spectrum of disease burden, that there is variability in the chemotherapeutic agents and embolization materials administered to patients, and that the procedure is performed on both Childs A and Childs B liver disease populations. DEB-TACE has been shown to achieve improved outcomes in patients with Child-Pugh B, bi-lobar disease and recurrent disease[41].

There remains debate about the optimal degree of arterial embolization to achieve tumor ischemia[42,43]. There is some evidence which indicates that complete tumor ischemia may stimulate angiogenesis, resulting in an increased susceptibility to tumor growth rather than suppression. It is therefore suggested that arterial patency be maintained, not only to prevent this angiogenic effect, but also so that patients can receive repeated treatments[44].

DEB-TACE causes fewer side effects than conventional TACE. Side effects associated with both DEB-TACE and conventional TACE include nausea, vomiting and right upper quadrant pain (post embolization syndrome), cardiac toxicity related to the doxorubicin, bone marrow aplasia, hepatic abscess and cholecystitis[36,38,45]. Two recent randomized controlled trials have shown improved side effect profiles[46,47]. One trial showed equivalent survival rates[42,46] whilst the other showed longer time to progression for DEB-TACE in comparison with conventional TACE[47]. A single meta-analysis demonstrated equivalent tumor response rates[48].

RADIOEMBOLIZATION

Radioembolization for primary hepatic cancer with Yttrium-90 (90Y) was first described in 1965 who used isotope embedded 50 μm ceramic microspheres to embolize hepatic cancer *via* a surgically placed catheter based in the hepatic artery[49]. Today, the technique has evolved away from an open surgical approach to a minimally invasive fluoroscopically guided microcatheter based technique using either 90Y embedded non-biodegradable glass microspheres measuring 25 ± 10 μm (Theraspheres, Nordion Incorporated, Ottawa, Ontario, Canada) or 90Y embedded non-biodegradable glass resin based microspheres measuring 29-35 μm (SIR-Spheres, Sirtex Medical Incorporated, Lake Forest, Illinois). Radioembolization, similar to TACE, exploits the preferential arterial blood supply of an HCC by delivering radiotherapy in an embolic agent directly to the tumor bed while preserving the blood flow to the normal liver parenchyma, which is supplied primarily by the portal vein. Unlike TACE, which uses 75-700 μm beads to occlude medium to large sized arteries leading to tumor ischemia, 90Y radioembolization uses these smaller beads to act as a microembolic agent to deposit radiotherapy directly within the tumor *via* an intratumoral vessel. Once deposited at the target lesion, 90Y delivers tumoricidal doses of a pure high energy beta emitter (937 KeV) with a short tissue penetration (mean 2.5 mm and maximum 11 mm) and short half-life of 2.67 d. The short tissue penetration and half-life of 90Y make it an ideal radioisotope for intra-arterial radiotherapy as there is minimal dose deposited in the adjacent liver parenchyma and the patient can immediately be safely discharged home without fear of radiation being delivered to others.

Radioembolization with 90Y has generally been reserved for patients who have intermediate/advanced BCLC stage hepatocellular carcinoma and who are not candidates for TACE due to portal vein invasion[10,50,51]. Sorafenib is generally considered the treatment of choice for advanced HCC[52]. However, Sorafenib is often not well tolerated[53], and 90Y radioembolization is a suitable alternative for patients with advanced HCC given the equivalent median overall survival of 13.2 mo in the radioembolization group *vs* 14.4 mo in the Sorafenib group[54]. 90Y radioembolization has also been proposed as an alternative treatment option to prevent progression of disease in eligible transplant patients and to downstage patients in order to become eligible transplant recipients based on the Milan criteria[12-14].

According to the Radioembolization Brachytherapy

Oncology Consortium, it is recommend that patients undergo preembolization planning and treatment simulation with intrarterial injection of technectium-99m labeled macroaggregated albumin (^{99m}Tc-MAA) and CT to rule out > 30 Gy radiation exposure to the lung from hepatopulmonary shunting and to measure liver volumes[51]. There is currently no consensus on the recommend radiation dose to deliver to effectively treat HCC. In patients with advanced stage inoperable HCC, however, Lau *et al*[55] did demonstrate a median survival benefit of 55.9 wk *vs* 26.2 wk in patients receiving > 120 Gy *vs* < 120 Gy, respectively. A randomized controlled trial is underway examining the efficacy of radioembolization when compared with chemo-embolization (Seinstra)[56].

COMBINATION TACE AND RFA

Ablative techniques demonstrate diminished efficacy when tumor diameter is greater than 3 cm[57,58]. This failure to achieve complete tumor necrosis is largely attributed to the "heat sink" effect: cooling by blood flow resulting in a reduction in temperature adjacent to vessels within or adjacent to the ablation zone[59].

Adjuvant locoregional therapies have been employed to achieve higher rates of efficacy in the treatment of larger tumors (3-5 cm). The most common of these is chemoembolization. The embolic effect of the lipiodol or beads decreases the "heat sink" effect caused by local vessels, whilst the addition of the chemotherapeutic drug improves overall tumor kill efficacy[60-62]. A single randomized controlled trial has shown decreased rates of tumor progression in the combination group in comparison with the RFA only group[63], although no significant difference in survival was demonstrated.

SURGICALLY ASSISTED RFA

Radiofrequency ablation was widely adapted in the 1990's as a method to treat lesions deemed unresectable at the time of open hepatectomy. As technology improved, RFA moved from the operating room to the IR suite where percutaneous ablations could be performed without the morbidity of a laparotomy. While percutaneous image guided ablative therapies are a useful tool in the armamentarium for the loco-regional treatment of liver lesions, there are some limitations. These include difficulty in localizing lesions, potential for injury to extra hepatic structures and decreased efficacy in close proximity to liver vasculature. Many of these limitations can be addressed by performing surgically assisted RFA using a laparoscopic approach[64].

Because percutaneous ablation relies on the ability to localize lesions with ultrasound, obese patients with thick abdominal walls can provide a challenge, particularly with lesions in the dome.

While this has in large part been abrogated by use of CT and magnetic resonance imaging (MRI) guidance, some tumors are difficult to localize on cross sectional imaging. The ability to perform ultrasound directly on the liver surface allows for more accurate tumor localization and may result in more efficacious tumor treatment when compared to percutaneous ablation[65,66]. The most widely used technique for laparoscopic assisted RFA is with insufflation of the abdomen after induction of general anesthesia. A laparoscopic ultrasound probe is then introduced and used to guide a percutaneously placed RFA needle. Additional laparoscopic ports can be introduced to manipulate the liver as well as other extra-hepatic structures. The ability to manipulate the peri-hepatic environment can protect structures such as the colon, stomach, small bowel and diaphragm from transmitted heat. It also allows for potential removal of the gallbladder prior to RFA, preventing injury and heat sink. Other techniques to protect peri-hepatic structures include instillation of artificial ascites which can absorb heat without transmission to surrounding viscera[67].

An additional benefit of surgically assisted RFA is the ability to occlude hepatic vascular inflow, which in theory reduces the heat sink from major vessels. With minimal mobilization of the liver, a temporary ligature can be placed around the porta hepatis and tightened immediately prior to application of energy. In-vivo animal studies have indicated an increase in tumor necrosis around blood vessels, although human data is lacking[68,69].

TACE + RADIOTHERAPY FOR HCC

Locoregional relapse remains an important issue for HCC. In early stage HCC stereotactic body radiotherapy (SBRT) has been used in conjunction with TACE in an effort to improve cure rates[70,71]. In the locally advanced setting, three dimensional conventional radiation therapy (3DCRT) has shown promising results following TACE in promoting tumor necrosis and reducing local relapse.

SBRT entails the delivery of highly conformal, high dose, ablative radiotherapy to a liver lesion in a short period of time (typically over 1-2 wk). Selection criteria for liver SBRT is similar to that of TACE: Childs A liver function, 1-3 lesions, more than 700 cc uninvolved liver, tumors less than 5 cm, and well controlled extrahepatic disease[72]. Prior to SBRT patients undergo a 4 dimensional CT planning scan to delineate the target lesion and its real time movement across several phases of respiration. Ultrasound guided insertion of tumor fiducial markers is often useful for image guided radiotherapy where the markers act as a surrogate for tracking the lesion's location for radiation delivery. Liver SBRT prescriptions can vary from 50 Gy/5 fractions to

60 Gy/3 fractions, in contrast to 3DCRT where the conventional daily dose of radiation is 1.8 to 2.0 Gy/fraction and the total dose is 45-50 Gy in 25 fractions. Care is taken to avoid excess dose to adjacent bowel and the remaining liver during SBRT given the potential for severe complications with high doses.

Data is also emerging that SBRT may be an effective salvage strategy for patients who experience local failure post TACE. Patients with Childs A disease and tumors measuring less than 10 cm who have undergone partial or incomplete TACE may have 2 year local control rates as high as 94.6% when salvaged with SBRT[73-75]. High grade toxicity resulting in duodenal or gastric perforation is rare (approximately 5%) if dose constraints are respected[73]. However, the presence of tumor vascular thrombosis is a risk factor for severe and even mortal toxicity[76,77]. Combination TACE + SBRT appears to be a potentially promising treatment for early stage HCC and likely merits a multi-institutional phase III study as the existing literature consists of single institution retrospective data or small phase I/II trials[78].

In locally advanced HCC, 3DCRT or chemoradiation post TACE or partial TACE may confer better outcomes than Sorafenib. One study compared 67 patients with BCLC stage C disease who received TACE + 3DCRT with a cohort that was given Sorafenib as first line treatment. While this study did not examine local control, the median survival of the TACE + RT group was 14.1 mo compared to 3.1 mo in the Sorafenib group[79,80]. Combining TACE and conventional radiation treatments for locally advanced HCC may also be an effective treatment in patients with extensive portal vein thrombosis[74,81-85]. One year progression free rates in patients who receive TACE + 3DCRT for unresectable HCC can be as high as 70% compared to TACE alone (40%)[85]. Patients who have failed 1-2 TACE treatments and who received subsequent 3DCRT have been reported to have as high as 68% response rate post radiotherapy with 70% achieving stable disease at 1 year[86,87]. As prognosis for locally advanced HCC remains poor, the use of local therapies in conjunction with chemotherapy is also being explored. Clinical trials of concurrent chemoradiation and TACE in advanced disease have shown promise in improving local control and progression free survival[88,89].

IMAGING AFTER IMAGE-GUIDED THERAPIES

With the variety of image-guided liver directed therapies available, it is important to know the different expected post-therapy appearances and be able to differentiate these from abnormal imaging findings. Contrast-enhanced CT or MRI are the preferred imaging modalities for post therapy surveillance. Post therapy imaging should be performed at scheduled intervals, although a standard interval has not been established. At our institution, we perform contrast enhanced CT or MRI at 6 wk and then at 3, 6, 9 and 12 mo intervals.

ABLATION

An ablation zone encompasses the tumor with a variable margin, and is therefore usually larger than the tumor on initial imaging. Unenhanced CT and MRI images are obligatory as the ablation zone may be hyperattenuating or have intrinsic hyperintensity on pre-contrast T1-weighted images due to coagulative necrosis and hemorrhage making evaluation for arterial enhancement more difficult. Subtraction MRI is particularly useful when there is T1 hyperintensity on unenhanced images. In a completely treated lesion, contrast enhanced images demonstrate a non-enhancing well-defined ablation zone.

Familiarity with normal periablation changes is also important. Transient hyperemia and edema can be present around the ablation zone due to thermal injury to the surrounding parenchyma, manifesting as a concentric thin rim of enhancement on arterial and sometimes portal venous phase contrast enhanced CT and MRI and a hyperintense rim on T2-weighted images. Peripheral geographic arterial enhancement can also be seen post ablation, often related to injury to the portal vein branches and subsequent increase in perfusion from the hepatic artery. These changes usually resolve within several months[90,91]. Residual disease in contrast demonstrates an area of irregular or thick, peripheral arterial enhancement.

MRI is particularly helpful for residual disease evaluation, as this demonstrates focal hyperintensity on T2-weighted images and often increased signal on diffusion-weighted images. Recurrent disease has similar imaging characteristics to residual disease, but can occur within or adjacent to the ablation zone. New disease occurs in other areas of the liver or in extra-hepatic locations. In some cases, it may be difficult to differentiate expected a post ablation peripheral rim of enhancement from residual or recurrent tumor. In these cases, closer follow-up imaging may be necessary. Risk factors for residual or recurrent disease include large tumor size, aggressive histology, difficult location, and heat sink effect, specifically in radiofrequency ablation[92].

Transient bile duct dilatation peripheral to the ablation zone is often seen. Leakage of bile from injured ducts can result in a biloma, which appear as a non-enhancing fluid collection.

If there is injury to larger vessels, parenchymal or intraperitoneal hemorrhage can occur and be detected on CT or MRI. If both the portal and hepatic arteries are injured, hepatic infarction can occur, which

appears as non-enhancing parenchyma peripheral to the ablation zone. Other vascular complications, such as arteriovenous fistula or pseudoaneurysm can also be identified on arterial phase imaging.

Hepatic abscess is an additional complication which can be seen after ablation. This usually presents a few weeks after the procedure and demonstrates peripheral enhancement and development of gas within or adjacent to the ablation zone. Injury to adjacent structures is an additional complication to be aware of after ablation: for example, adjacent bowel or the diaphragm[92].

TACE, CONVENTIONAL TACE, AND RADIOEMBOLIZATION

Imaging following TACE and transarterial radio-embolization is similar to ablation with a few additional caveats. The treated lesion again should demonstrate lack of enhancement, but also may demonstrate a peripheral rim of enhancement, geographic arterial enhancement or both. After transarterial radioembolization, there may be heterogeneous parenchymal enhancement in a perivascular distribution due to radiation effect. This can mimic tumor and may need shorter term follow-up. In patients treated with lipiodol MRI has been shown to be superior to CT given the ability to perform diffuse weighted images and image subtraction[93]. Residual or recurrent disease appears as nodular arterially enhancing tumor, often in the periphery, similar to ablation.

SBRT

Treatment response assessment for SBRT is evolving. As with other image guided therapies, tumor response after SBRT is recognized as non-enhancement of tumor. However there are other unique imaging characteristics. After SBRT, recurrence can occur within the planned target volume, suggesting that an inadequate dose was used, or can occur along the margin of the high dose region, suggesting incomplete coverage of the tumor margin. This marginal recurrence may be due to patient respiratory motion. Additionally, focal peritumoral enhancement may be seen on any phase of imaging, likely representing radiation induced changes and inflammation of the surrounding normal liver parenchyma. These areas of enhancement can persist for months and should not be confused with recurrent tumor. Additionally, it can take time for the initial tumor enhancement to disappear, and therefore continued follow-up is necessary. Sanuki *et al*[94] demonstrated in 38 patients a median time of 5.9 mo to reach complete treatment response with a range of 1.2 to 34.2 mo.

RESPONSE ASSESSMENT

Different criteria have been developed to evaluate tumor treatment response. Conventional size measurement, such as Response Evaluation Criteria in Solid Tumors (RECIST), is predominantly useful for evaluation of cytotoxic systemic agents but does not work well for evaluation after locoregional therapy, as tumor necrosis is the goal and may not always manifest as a decrease in lesion size. The European Association for the Study of the Liver (EASL) measures the arterially enhancing area in two dimensions, while a modified RECIST classification uses a single largest diameter of arterially enhancing tumor. The modified RECIST criteria has been recommended as the preferred criteria for tumor response by the EASL and European Organisation for Research and Treatment of Cancer[95].

CONCLUSION

Most patients presenting with HCC are ineligible for surgical curative treatment. Advances In locoregional therapy, both catheter based and ablative, have led to improvements both in cure rates and in survival. A multidisciplinary approach is optimal for the planning of treatment given that there are treatment contributions from gastroenterology, surgery, interventional radiology, and oncology.

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