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ROLE OF INTERVENTIONAL RADIOLOGY IN MANAGEMENT OF HEPATO-CELLULAR CARCINOMA (HCC)

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Abstract
The most typical primary liver tumour, hepatocellular carcinoma, is becoming more prevalent. The two-gold standard curative treatment options are transplantation and surgical resection, but fewer than 20% of patients qualify as surgical candidates due to severe liver disease and/or co-morbidities. For the treatment of HCC that is inoperable, numerous interventional radiological techniques have been developed and thoroughly researched. The treatment of HCC currently heavily relies on interventional radiology. These methods have considerably aided in halting disease development in liver transplant candidates and extending survival in non-candidates. These medicines stand out for their low toxicity profiles, potent tumour response, and preservation of healthy hepatic parenchyma.

Keywords: HCC, Interventional radiology, HCC treatments, Radioembolization, Radiofrequency ablation.

INTRODUCTION

A difficult global health issue, liver cancer is becoming more common everywhere. According to projections, liver cancer would afflict more than a million people annually by 2025 [1]. About 50% of cases of HCC are primarily caused by chronic hepatitis B virus (HBV) infection, while non-alcohol-related steatohepatitis (NASH) is also a major etiological concern. The sixth most common cause of cancer- related death in women and the second most common in men is hepatocellular carcinoma. According to estimates, there were 748,300 new instances of liver cancer globally in 2008, and 695,900 people died as a result of the disease [2].

In cases of Child-Turcotte-Pugh class A or B alcohol-associated cirrhosis, the annual risk of HCC is around 2.5%. Due to low cumulative survival in this group, variations in liver transplant decisions globally, and a dearth of appropriate data in the pre-transplant period, an agreement on

the development rate of HCCin Child-Pugh C hcc patients is still unclear [3].

Aristolochic acid, found in flower initiation birthwort seedlings (Aristolochia), wild ginger, which is frequently used in traditional Chinese medicine, nicotine, and aflatoxin B1 (urinary excretion of aflatoxin metabolites impose 4-fold increased risk) have been distinguished as pathophysiologic cofactors, while coffee and aspirin have been identified as precautionary factors that influence the production of liver cancer [4].

A complete clinical translation of the pathophysiology and molecular pathogenesis of HCC in relation to genotoxicity and accompanying etiologies is still pending. Traditionally, conventional criteria are used to diagnose HCC, and the severity of the underlying liver disease and the overall tumour load determine the treatment option. New research, however, emphasises the significance of histology and molecular categorizations in pathogenesis, which offers fresh therapeutic targets [5].

Role of Interventional Radiology in Hepato-Cellular Carcinoma

- **Diagnosis**

The medical staff must have a thorough understanding of the pathogenesis of hcc and its radiological aspects in order to design and evaluate treatment choices. The usual amplification appearance of the liver tumor in a solitary contrast-enhanced image acquisition was the only factor used by the American Association for the Research of Liver Diseases in 2010 to make the diagnosis of hcc [6]. Liver biopsies are occasionally required to determine the presence of hcc and, less commonly, to determine the prognosis following treatment based on the malignancy grading and vascular penetration. The ideal liver biopsy is either 20–25 mm long or has 11 full portal tracts, or both, for grading and staging a liver tumour.

The two methods of liver biopsy are fine- needle aspiration and needle core biopsy (ncb) (fna). A thin cylinder of liver tissue is removed by a ncb using a large-gauge needle (1-3 mm in diameter), whereas a fna utilises a needle that is 0.4–0.6 mm in diameter. Latest research suggested that both techniques had equivalent diagnostic yield [7]. The particularity and sensitivity of fna are 67%–100% and 98%–100%, respectively. The technique and expertise of the radiographer and the cytopathology have the biggest impact on the sensitivities of fna [8]. Ncb efficacy ranges from 62% to 93%17–19. A study indicated that the agreement amongst final operating samples and pretreatment ncbs was 91.4% [8]. However, ncb has an advantage over fna in that the specimen collected is appropriate for marker studies as well as an evaluation of architectural and cytologic aspects. When both approaches were utilised, one study revealed that the diagnostics exactness of fna and ncb, which were previously 85.4% and 83%, respectively, grew to 89.1%, and then another indicated that fna's skills are important to 88% from 78% and that of ncb was identical [9].

Several problems are said to be possible with the liver biopsy technique. Temporary hypotension and soreness are minor concerns. Intrahepatic haemorrhage, intraperitoneal haemorrhage, hemothorax, pneumothorax, and injury to nearby organs including the pancreas, colon, gallbladder, or right kidney are examples of major consequences [10]. After a liver biopsy, an intrahepatic arteriovenous fistula might also develop. 90% of problems are pain-related, with a 29% overall complication rate. Another problem that has been mentioned in the literature is tumour seeding, which has a prevalence rate of 0.003%–5%. The mortality rate after liver biopsy is reported to be 0%– 0.18%, mostly attributable to significant hemorrhage and bile peritonitis [11].

- **Treatment**

After a liver biopsy, there is no recorded mortality rate. Locoregional techniques are crucial in the management of hcc in patients with early- or intermediate-stage disease because they slow the disease's course until decisive intervention or raise a patient's eligibility for a curative treatment. The major goals of treatment for individuals with advanced disease are to manage symptoms, extend

life, and enhance quality of life. Direct ablation, portal vein embolization,transarterial endovascular, transarterialchemoembolization, drug-eluting beads, and transarterial radioembolization are some of the image- guided treatments that are offered (tare) [12].

Ablative Therapy

In order to create necrosis, ablation entails the thru application of chemicals or heat energy to the tumour. There are two varieties of thermoablative therapeutic interventions:

- ✓ Hyperthermic [radiofrequency ablation (rfa),microwave ablation (mwa), and laser ablation] and
- ✓ Hypothermic (cryotherapy).

Chemical ablation uses percutaneous ethanol injection (pei) or percutaneous acetic acid injection (pai) [13].

Thermoablative Therapy

For early-stage, localised, advanced or metastatic hcc, percutaneous thermal ablation is thought to be the best locoregional therapeutic option [14]. The methods that are currently accessible are predicated on limiting collateral damage to healthy hepatic tissue and surrounding components while minimizing tissue damage by providing energy to the lesion.

As a source of thermal energy that results in cell death, a needle delivering high-frequency electrical current is used in rfa. The cell-kill zone is affected by the maximum temperature attained and the length of heat exposure, but a significant restriction is the potential for a heat-sink effect caused by big capillaries (>3 mm) close to the ablation zone. The blood current may result in positive margins by preventing total necrosis of surrounding tumour cells. In other instances, the vascular supply to the tumour is embolized beforehand to overcome the heat-sink effect [15].

Elevated efficiency, preserving of ordinary liver parenchyma outside the burn zone, and the ability for safe repetition numerous times are all benefits of rfa [16]. RFA exposes the patient to a slight risk of injury to the following structures: pneumothorax (less than 1%), biliary injury (less than 1%), abscess (less than 1%), severe bleeding (less than 1%), and tumour seeding (less than 1%). However, rfa has a major complication risk that ranges from 2.4% to 13.1%, whereas surgical resection has a major complication rate that ranges from 9% to 22% [17]. Due to the potential for extreme discomfort, rfa treatment of subscapular tumours may necessitate general anaesthesia.

Initial ablation following rfa was beneficial in 96% of cases, according to Salmi *et al.*, prospective's study. Local tumour progress rates were 4% and 14% at 1 and 5 years, respectively, and survival rates were 92% at 1 year and 63% at 5 years. The ablated tumours in the study had sizes ranging from 1.2 cm to 3.5 cm [18].

Irreversible Electro-Poration (ire)

Irreversible Electro-Poration (ire) is a new technology that has recently been applied in hcc treatment. It functions by sending pulses of electricity to tumour cells up to 3 kV, creating an electrical field that causes nanopores to form in cell membranes. The cell's equilibrium is impacted by this irreparable damage, which also leads to apoptosis, or cell death. The two benefits of this technique are that it has no heat-sink effect and does not impact the extracellular matrix, protecting the structural integrity of the surrounding blood arteries and bile ducts. Therefore, irreversible electroporation can aid in thetreatment of tumours in challenging places. The treatment zone can be examined earlier than it can with other ablation techniques since the procedure does not result in fibrosis and scarring following ablation. However, ire necessitates deep neuromuscular block and general anaesthesia for the patient in both openand ct-guided percutaneous procedures. The use of ire in the management of hcc is still in its early stages, and no long-term results are available [19].

Chemoablative Therapy

A tried-and-true method for treating hcc tumours smaller than 3 cm is percutaneous ethanol injection. It is carried out with a thin needle under imaging guidance, and because of its cytotoxic effects, it results in coagulative necrosis (cytoplasmic dehydration, denaturation of protein, and small-vessel thrombosis). Alcohol consumption is largely constrained to tumour tissue due to cirrhotic borders surrounding hcc tumours, preserving normal parenchyma [20]. The procedure has the benefits of a straightforward methodology, minimal cost, and safety. Even tumours smaller than 3 cm require more than 4 sessions of pei to treat each mass. Because rfa requires fewer sessions to complete treatment, it is therefore more limited in its use than other modalities. Risks of bleeding, intestinal necrosis, gallbladder damage, and portal vein thrombosis, bowel necrosis, gallbladder injury, and liver necrosis have likewise been revealed to upsurge with pei [21].

A randomised trial with 187 patients examined the tumour recurrence and survival rates for rfa, pei, and pai in the treatment of hcc 3 cm in size or smaller, Child-Pugh A and B. Local recurrence rates for radiofrequency ablation were shown to be superior, at 10% and 14% at 1 and 3 years, as opposed to 16% and 34% for the pei group and 14% and 31% for the pai group [22]. The rfa, pei, and pai groups, respectively, had survival rates of 93% and 74%, 88% and 51%, and
90% and 53% after 1 and 3 years. At 1 and 3 years, the rfa group had a cancer-free survival rate of 74%, the pei group had a rate of 70%, and the rfa group had a rate of 71% in the pai cluster. Large tumour size (>2 cm) and high tumour grade were independent factors that correlated with local recurrence [23].

Embolization

✓ **Venous Embolization**

The predicted liver leftover was observed to be dramatically improved by portal vein embolization (pve) in a retrospective assessment of patients with hcc who underwent prolonged liver excision (flr). In order to safely perform extensive liver surgical resection, pve is utilised to cause gradual atrophy of the embolized region and hypertrophy of the remaining non-tumor- containing parenchyma. The flr increase is significantly less in cirrhotic patients than in those with moderate to mild fibrosis, although this procedure can be used when the flr is less than 20%–30% of the initial total normal liver volume or less than 50% in fibrotic and cirrhotic livers [24].

For distally embolization, liquid agents (glue or alcohol) and materials for small-particle embolization are utilised. Some teams also use coils to occlude major central vessels. It is important to avoid placing the coils too close to the hepatic hilum because doing so could make surgical ligation more challenging. A temporary rise in white blood cell count, fever, and gastrointestinal discomfort has all been noted as pve adverse effects [25].

In 34 patients who underwent curative liver resection after pve and in 102 patients who underwent resection without pve, Siriwardana *et al.*, prospectively examined the impact of pve on hcc recurrence. The flr went from 23% to 34% with the use of pve. The study came to the conclusion that pve has no harmful oncologic effects after large hcc resection and can raise the resectability rate of hcc tumours initially thought to be unresectable due to insufficient flr [26].

Simoneau *et al.,* evaluated the effect of pve on the growth of liver metastases from colorectal cancers. 109 individuals who had right pve and 11 patients who did not were prospectively monitored for tumour development. Tumor volume increased by 33.4% in the right lobe of the liver and by 49.9% in the left lobe of the embolized group, whereas it decreased by 34.8% in the right lobe of the liver and by 33.2% in the left lobe of the non-embolized group (p 0.001 in the right lobe, p
= 0.022 in the left lobe) indicating a significant difference in tumour growth between the groups.

However, resectability was unaffected by those findings. There are no comparable statistics for patients with hcc [27].

✓ **Arterial Embolization**

TAE Trans artery embolization (Bland Embolization): In this procedure, the hepatic artery is blocked either by installing microsphere-like equipment or by introducing an intravascular substrate. A catheter is used during the procedure, which is done under fluoroscopy. Embolization is successful in treating hcc mainly due to hcc's reliance on arterial blood flow [28]. It is thought that embolization of the feeding arteries causes ischemic tumour necrosis and intra- arterial infusion of various medications or devices enables preferential distribution to tumours.

According to Nicolini *et al.,* treatment utilising microspheres can result with a complete response (cr), with evidence of the tumor's devascularization in 89% of instances. The definition of cr is an absence of peripheral enhancement in arterial-phase ct imaging [29]. However, the authors noted that 62% of patients experienced local recurrence, and 56% of patients developed new tumours. Between the assessment of cr and the local recurrence of the tumour, 3 to 6 months elapsed [30]. The limited study sample and the potential for ct overestimation of tumour response were mentioned as potential causes for the high recurrence rate by Nicolini *et al.,* Nevertheless, the study demonstrated that it is a well-tolerated technique for individuals with early or moderate hcc and does not result in a clinically significant decline in liver function [31].

TACE

Tace is administered to the cancer using a transarterial approach, merging embolization and the injection of cytotoxic drugs [32]. Iodinated poppy seed oil was the first chemoembolic agent employed; because to its viscosity and water insolubility, it is a great agent for intra-arterial embolization [33]. It obstructs the descending capillaries, kills tumour cells more quickly than hepatocytes, and is radiopaque, allowing for radiologic viewing while being injected. The anticancer drugs cisplatin, doxorubicin, carboplatin, epirubicin, mitoxantrone, and mitomycin C12 can all be used with iodinated poppy seed oil. Through a catheter inserted into the proper subsegmental branches of the hepatic artery supplying the tumour, the combination is administered [34].

There is some debate regarding tace's function in neoadjuvant therapy. Although tace is advised as first-line palliative therapy for nonsurgical cases with large or multifocal lesions and no vascular penetration of distant metastases, tace administration prior to resection (compared to resection alone) may result in a survival advantage. By shrinking the tumour or limiting its growth, transarterial chemoembolization can also be utilised as a bridging therapy before transplantation [35].

In animal tests, tace was discovered to supply medication concentration 1-2 orders of magnitude greater to the target organ and to sustain a noticeably longer dwell time than systemic chemotherapy infusion alone. Furthermore, because the majority of the medication was kept in the liver, it decreased systemic toxicity [36].

Survival rates in the tace arm were reported to be 64% and 38% at 1 and 2 years in a French multicenter trial of 127 patients with advanced illness, compared with just 18% and 6% in comparable unprocessed controls [37]. Those with Okuda stages 1 and 2 (but not stage 3) illnesses had a much higher survival rate after receiving treatment than they had without it. In a subsequent study, the mean overall survival for hcc patients who received chemoembolization compared to controls who received symptomatic care revealed a significant difference at 2 years, with the former having a 54% survival rate and the latter, 26% [38].

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