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EDITORIAL

A Tribute to Radiologists (and the Multidisciplinary Team) in Combating Liver Cancer

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According to the Hong Kong Cancer Registry, liver cancer was the fourth commonest cancer and the third leading cause of cancer deaths in Hong Kong in 2014, indicating the dismal prognosis of this cancer.[1] Unlike many other cancers, the diagnosis of hepatocellular carcinoma (HCC) can be made radiologically based on pre-defined imaging features in the correct clinical context without histological confirmation.[2] Radiologists are key members of the multidisciplinary team responsible for managing various cancers. Indeed, few other cancers require such comprehensive involvement of radiologists as HCC does. The current clinical management of HCC has leveraged on the many advances in diagnostic, interventional, and therapeutic radiology. This is exemplified by the diversity of articles published in this issue on HCC management.

In Hong Kong and Asia, the vast majority of HCC cases develop in patients infected with hepatitis B virus (HBV), while hepatitis C virus, alcoholic cirrhosis, and fatty liver disease account for the majority of HCC cases in the West. Clinical management of HCC is challenging as the highly malignant cancer often presents late with a high propensity for vascular invasion and hence distant metastasis, and patients frequently have liver dysfunction due to pre-existing chronic liver cirrhosis. Treatment algorithms that incorporate cancer staging (tumour size, number, intra- or extra-hepatic vascular invasion or metastasis) and liver organ function (Child-Pugh score) such as the Barcelona Clinic Liver Cancer (BCLC) and the Hong Kong Liver Cancer (HKLC) staging systems are important guidelines to triage patients for the most appropriate treatment.[3,4]

In Hong Kong, early-stage tumours are usually treated with surgical resection or liver transplant if a donor is available, or ablative procedures according to the HKLC staging system.[4] Intermediate-stage tumours characterised by larger and more tumour nodules or the presence of intrahepatic vascular invasion can be treated with either surgery or transarterial chemoembolisation (TACE) depending on the Child-Pugh class.[4] Patients with locally advanced tumours are best treated with TACE, whereas those with extrahepatic vascular invasion or distant metastasis are candidates for systemic therapy or supportive care (Table).[4] Definitions of various tumour stages are shown in the Table.

Close adherence to treatment algorithms to achieve optimal clinical outcome requires consistent precision in delineating the cancerous lesions in a cirrhotic liver. Cho[5] describes the roles of gadoxetic acid–enhanced magnetic resonance imaging (Gd-EOB-MRI) and contrast-enhanced ultrasonography (CEUS), and compares them with the current established imaging tools of contrast-enhanced computed tomography, magnetic resonance imaging with extracellular agents, and conventional grey-scale ultrasonography. Gd-EOB-MRI can improve diagnostic accuracy in detecting small HCC and differentiating HCC from benign lesions in the cirrhotic liver. CEUS can play a role in HCC surveillance and diagnosis, guiding interventional procedures, and assessing treatment response.[5] Gd-EOB-MRI has been accepted as one of the primary diagnostic imaging modalities in many Asian management guidelines. Its superior spatial diagnostic resolution confers higher accuracy in the measurement of lesion size and number, thereby defining more clearly early-stage tumours from intermediate-stage tumours, which might not be the best candidates for localised ablative treatment or surgery.

Wong et al[6] critically review the hitherto exploratory role of positron emission tomography (PET) in the radiological assessment of HCC. Some success in enhancing the modest detection rate of fluorodeoxyglucose (FDG) PET has been reported in PET using dual tracers (FDG + acetate or FDG

Table. Treatment algorithm for hepatocellular carcinoma (defined as Eastern Cooperative Oncology Group score of 0-1 or Child-Pugh class of A-B) according to the Hong Kong Liver Cancer staging system.[4]

Treatment algorithm						
Presence of extrahepatic vascular invasion / metastasis	No				Yes	
Extent of tumour within the liver*	Early-stage	Intermediate-stage		Locally advanced	Any	
Child-Pugh class	A or B	A	B	A or B	A	B
Treatment recommended	Resection, liver transplant, ablation	Resection	Transarterial chemoembolisation	Transarterial chemoembolisation	Systemic therapy	Systemic therapy, supportive care

* Early-stage is defined as tumour of ≤5 cm, ≤3 tumour nodules, and no intrahepatic venous invasion; intermediate-stage as tumour of (1) ≤5 cm and either >3 tumour nodules or with intrahepatic venous invasion, or (2) >5 cm, ≤3 tumour nodules, and without intrahepatic venous invasion; locally advanced as tumour of (1) ≤5 cm, >3 tumour nodules, and with intrahepatic venous invasion, (2) >5 cm, >3 tumour nodules, and with or without intrahepatic venous invasion, or (3) diffuse tumour.

+ choline).[6] Further evidence from larger studies is eagerly awaited to confirm the preliminary results of PET in predicting the outcome of liver transplantation and evaluating treatment outcome after TACE or selective internal radiotherapy (SIRT).

Among local ablative procedures (percutaneous or surgical radiofrequency ablation [RFA], microwave ablation, percutaneous ethanol injection, high-intensity focused ultrasound) for treating early-stage HCC, RFA (mainly performed by radiologists through a percutaneous route) has been confirmed in multiple randomised studies and meta-analyses to have similar efficacy to surgical resection.[7] Cheng et al[8] report a respectable overall survival rate of 80% at 3 years following RFA in 22 patients with stage I / IIa HCC. Half of those 14 patients who had recurrence by 3 years had local 'infield' or 'scar' recurrences that were further salvaged by either repeated RFA or other procedures.[8] Severe adverse events were few and there was no procedure-related mortality.[8] Microwave ablation and high-intensity focused ultrasound have also been reported to achieve outcomes comparable with RFA.[9,10]

TACE remains the treatment of choice for most patients with intermediate-stage HCC; it is performed by radiologists with special expertise in interventional radiology.[3,4] Success of TACE is closely associated with identifying the lesions and their respective feeding arteries through accurate pre-procedural imaging using multi-detector computed tomography (MDCT), conventional digital subtraction angiography (DSA), or cone-beam computed tomography (CBCT). Chan et al[11] recommend CBCT over MDCT or DSA. CBCT angiography offers better delineation of subsegmental tumour-feeding arteries and extrahepatic arterial feeders; this facilitates planning of targeted embolisation and allows detection of smaller occult HCCs.[11]

Newer modalities of local ablative therapy have been explored in early- and intermediate-stage HCC due to the inherent risks associated with surgery, patient preference for less invasive procedures, and shortage of liver donors. In fact, only about 30% of HCC patients ever undergo any surgical resection.[4] There is an unmet need for more effective local therapy for intermediate-stage and locally advanced HCCs when TACE is contraindicated or fails. Both stereotactic body radiotherapy (SBRT) and SIRT have shown promising early results, attributable to technological advances in high-precision external radiation delivered under image guidance and selective delivery of radioactive beads targeting the tumour through the tumour-feeding arteries, respectively.[12-14]

Lam et al[15] report results of SBRT in 39 patients treated according to institutional guidelines. Almost all patients had failed prior local therapies but still had a relatively small volume of localised recurrent or progressive tumour.[15] The 1-year local control rate was 82.8%, but a significant proportion of patients (21 of 39) had 'outfield' intrahepatic recurrence and the 2-year overall survival was modest (56.1%); the outcomes were not atypical of patients with recurrent or progressive HCC.[15] Tai et al[16] report respectable clinical outcomes in 62 patients treated by SIRT with yttrium-90. Most patients were selected according to a stringent set of criteria. Radiologists were responsible for pre-procedural treatment planning and screening for SIRT; they also perform the major part of the SIRT. Overall, preliminary results confirmed that both SBRT and SIRT were relatively safe and efficacious as first- or second-line therapy with or without prior TACE.[15,16] The promising results also emphasised the importance

of patient selection by a multidisciplinary team that pooled expertise from various disciplines often led by radiologists.

With concerted efforts from radiologists, clinical and medical oncologists, surgeons, and hepatologists in the multidisciplinary team in a high-volume centre, HCC patients can be offered various treatment options according to the current BCLC or HKLC guidelines, based on customised clinical decisions supported by precise radiological staging and patient assessment. Wider use of state-of-the-art radiological imaging and novel local therapies reported by radiologists and clinical oncologists in the current issue is expected to further improve the outcomes of localised HCC. For recurrent, metastatic, or localised HCC not amenable to any local therapy, besides the targeted drug of sorafenib as standard first-line systemic therapy, the new first-line targeted drug such as lenvatinib, the second-line targeted drug of regorafenib, and the immune checkpoint inhibitor of nivolumab further strengthen the armamentarium of systemic therapeutic agents.[17-20] Oncologists still have a long way to go to achieve the same success as radiologists in combating HCC.

On the preventive side, universal HBV vaccination for newborns (introduced in 1988 in Hong Kong) has slowly reduced the HBV carrier rate in Hong Kong and other regions.[21,22] Together with wider prescription of anti-viral therapy for HBV carriers and introduction of targeted screening for HBV carriers or cirrhotic patients, the age-standardised incidence, cancer burden, and overall mortality of HCC in Hong Kong can be further reduced.[23]

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