EFFECTIVENESS OF CONVENTIONAL TRANSARTERIAL CHEMO-EMBOLIZATION (cTACE) IN COMPARISON TO DRUG-ELUTING BEADS TRANSARTERIAL CHEMO-EMBOLIZATION (DEB-TACE) FOR TREATMENT OF HEPATOCELLULAR CARCINOMA IN HOSPITAL USM, KELANTAN

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LIST OF SYMBOLS, ABBREVIATIONS, AND ACRONYMS

TACE	Transarterial Chemoembolization
cTACE	Conventional Transarterial Chemoembolization
DEB-TACE	Drug-Eluting Beads Transarterial Chemoembolization
CT	Computed Tomography
PACS	Picture Archive and Communication System
RIS	Radiology Information System
LIS	Laboratory Information System
HCC	Hepatocellular carcinoma
WHO	World Health Organization
BCLC	Barcelona Clinic Liver Cancer
RECIST	Response Evaluation Criteria in Solid Tumours
mRECIST	Modified Response Evaluation Criteria in Solid Tumours
NAFLD	Non-alcoholic fatty liver disease
HIV	Human immunodeficiency virus
HCV	Hepatitis C virus
HBV	Hepatitis B virus
AFB_1	Aflatoxin B1
DNA	Deoxyribonucleic acid
AFP	Alpha-fetoprotein
MRI	Magnetic resonance imaging
TNM	Tumour, Node, Metastasis
ALBI	Albumin-Bilirubin
PT	Prothrombin time

ECOG-PS	Eastern Cooperative Oncology Group Performance Status
CR	Complete response
PR	Partial response
PD	Progressive disease
SD	Stable disease
IR	Incomplete Response
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
INR	International normalized ratio
LFT	Liver function test
ORR	Objective response rate

ABSTRAK

Latar belakang: *Transarterial Chemoembolization* (TACE) ialah rawatan standard untuk karsinoma hepatoselular peringkat B (HCC). Pada masa ini, terdapat dua teknik TACE yang boleh digunakan - TACE konvensional (cTACE) dan *drug-eluting beads* TACE (DEB-TACE). Secara teorinya, DEB-TACE sepatutnya mempunyai keberkesanan yang lebih baik dengan ketoksikan sistemik yang lebih rendah berbanding dengan cTACE. Tujuan kajian ini adalah untuk membandingkan keberkesanan dan kesan sampingan cTACE berbanding dengan DEB-TACE.

Metod: Sebanyak 161 pesakit yang menjalani TACE antara Januari 2012 hingga April 2022 telah dimasukkan dalam kajian retrospektif ini, di mana kami membandingkan pesakit HCC yang menjalani TACE dengan cTACE (n = 106) dan DEB-TACE (n = 55). Kajian ini dijalankan di Hospital Universiti Sains Malaysia (Hospital USM), Kubang Kerian, Kelantan, Malaysia. Pengimejan pra dan pasca TACE telah disemak dan tumor yang berdaya maju diukur berdasarkan kriteria mRECIST dan diberikan kepada kategori tindak balas rawatannya. Imej-imej itu dinilai selanjutnya untuk mengenal pasti kesan sampingan yang berkaitan dengan prosedur dalam kedua-dua kumpulan cTACE dan DEB-TACE.

Keputusan:

Sebanyak 12 pesakit telah dikategorikan di bawah tindak balas lengkap [8 pesakit (7.5. %) dalam cTACE; 4 pesakit (7.3 %) dalam DEB-TACE], 82 pesakit telah dikategorikan di bawah tindak balas rawatan separa [51 pesakit (48.1 %) dalam cTACE; 31 pesakit (56.4. %) dalam DEB-TACE], 21 pesakit dikategorikan di bawah

penyakit stabil [12 pesakit (11.3. %) dalam cTACE; 9 pesakit (16.4 %) dalam DEB-TACE], dan 46 pesakit telah dikategorikan di bawah penyakit progresif [35 pesakit (33.0 %) dalam cTACE; 11 pesakit (20.0 %) dalam DEB-TACE]. Secara statistik, tiada perbezaan ketara dalam keberkesanan rawatan antara cTACE dan DEB-TACE (nilai p 0.342). Walau bagaimanapun, peratusan penyakit progresif yang lebih tinggi diperhatikan dalam kumpulan cTACE berbanding kumpulan DEB-TACE. Perbezaan ketara dalam kesan sampingan tempatan diperhatikan (nilai p 0.03) kerana lebih banyak kesan sampingan tempatan didokumenkan di bawah kumpulan DEB-TACE. Kesan sampingan tempatan yang diperhatikan dalam kajian kami ialah saluran hempedu yang diluaskan (1 pesakit), trombosis vena portal (17 pesakit), dan kolesistitis (9 pesakit). Sebanyak 17 pesakit didapati mengalami sindrom pasca-embolisasi dan 20 pesakit mengalami ketoksikan hati, namun tiada perbezaan yang ketara (nilai $p < 0.05$). Tiada kesan buruk yang teruk atau kematian berkaitan prosedur diperhatikan dalam kedua-dua kumpulan.

Kesimpulan: Tiada perbezaan ketara dalam keberkesanan cTACE dan DEB-TACE dalam merawat pesakit HCC dari segi tindak balas tumor berdasarkan kriteria mRECIST. Walau bagaimanapun, lebih banyak kesan sampingan tempatan diperhatikan dalam kumpulan DEB-TACE.

Kata kunci: TACE, TACE Konvensional, DEB-TACE, Karsinoma Hepatoselular, Tomografi Berkomputer

ABSTRACT

Background: Transarterial chemoembolization (TACE) is the standard treatment for stage B hepatocellular carcinoma (HCC). Currently, there are two available TACE techniques used – the conventional TACE (cTACE) and drug-eluting beads TACE (DEB-TACE). Theoretically, DEB-TACE should have a better tumour response with less systemic toxicity as compared to cTACE. The purpose of this study was to compare the treatment response and the accompanying side effects of cTACE in comparison with DEB-TACE.

Methods: A total of 161 patients who underwent TACE between January 2012 until April 2022 were included in this retrospective study, where we compared HCC patients who underwent TACE with cTACE (n = 106) and DEB-TACE (n = 55). This study was conducted in Hospital Universiti Sains Malaysia (Hospital USM), Kubang Kerian, Kelantan, Malaysia.

Pre- and post-TACE imaging were reviewed and the viable tumour was measured based on mRECIST criteria and assigned to its treatment response categories. The images were further evaluated to identify for side effects related to the procedure in both cTACE and DEB-TACE groups.

Results: A total of 12 patients were categorized under complete response [8 patients (7.5 %) in cTACE; 4 patients (7.3 %) in DEB-TACE], 82 patients were categorized under partial treatment response [51 patients (48.1. %) in cTACE; 31 patients (56.4 %) in DEB-TACE], 21 patients were categorized under stable disease [12 patients (11.3 %) in cTACE; 9 patients (16.4 %) in DEB-TACE], and 46 patients were categorized under progressive disease [35 patients (33.0 %) in cTACE; 11 patients

(20.0 %) in DEB-TACE]. Statistically, no significant difference in tumour response between cTACE and DEB-TACE (p-value of 0.342). However, higher percentage of progressive disease was observed in cTACE group as compared to DEB-TACE group. Significant difference in local side effects were observed (p-value of 0.03) as more local side effects were documented under the DEB-TACE group. The local side effects observed in our study were dilated bile ducts (1 patient), portal vein thrombosis (17 patients), and cholecystitis (9 patients). A total of 17 patients were found to develop post-embolization syndrome and 20 patients developed liver toxicity, however no significant difference (p-value > 0.05). No severe adverse events or procedure-related mortality were observed in both groups.

Conclusion: No significant difference in the effectiveness of cTACE and DEB-TACE in treating HCC patients in terms of tumour response based on mRECIST criteria. However, more local side effects were observed in DEB-TACE group.

Keywords: TACE, Conventional TACE, DEB-TACE, Hepatocellular Carcinoma, Computed Tomography

CHAPTER 1: BACKGROUND

1.1 Introduction

Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer, with an incidence of 9.5 patients per 100 000 person-years worldwide. It is currently ranked as the seventh most common cancer and the fourth leading cause of cancer death in the world. Currently, liver cancer is the eighth most common cancer affecting both sexes in Malaysia. It is the fifth and ninth most common cancer in males and females, respectively. It is also the fifth leading cause of cancer death in Malaysia (The Global Cancer Observatory, October 2020 – International Agency for Research on Cancer, WHO). ("Global Cancer Observatory," n.d.; Registry, 2018)

The incidence of HCC worldwide is heterogeneous due to the variable risk factors for developing the chronic liver disease. The advancement of parenchymal liver disease into liver cirrhosis increases the risk of developing HCC. Early detection based on risk factors with prompt treatment initiation will help reduce HCC morbidity and mortality. Chronic liver disease patients with a risk of developing HCC should be subjected to the HCC-surveillance program with the aim of early HCC detection and thus lead to a reduction of its mortality rate. This surveillance includes liver ultrasonography and serum α-fetoprotein level measurement six-monthly. (Arguedas, 2003; Bruix and Sherman, 2011; "EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma," 2012; Forner et al., 2018; Sarasin et al., 1996)

There are multiple staging and prognostic assessments available for HCC. The most commonly used and extensively validated is the Barcelona Clinic Liver Cancer (BCLC) system. BCLC provides treatment strategies according to the stage of the HCC at the point of diagnosis. It is based on both clinical and radiological parameters. It divides the patients into the very early stage (0), early stage (A), intermediate stage (B), advanced stage (C), and terminal stage (D). A specific treatment algorithm is suggested based on the stages (Forner et al., 2018).

Trans-arterial chemoembolisation (TACE) is the treatment of choice for intermediate stage (B) in the BCLC staging system (Forner et al., 2018). It is recommended for asymptomatic, large, or multifocal HCC without evidence of macrovascular invasion or extrahepatic metastasis (Forner et al., 2018; Sieghart et al., 2015). Careful patient selection has been proven to improve the survival rate for this category (Burrel et al., 2012; J.M. et al., 2002; Lo et al., 2002; Malagari et al., 2012; Takayasu et al., 2012). However, TACE is not recommended for stages C and D of HCC. Systemic therapy is the main treatment for stage C, while patients with stage D are treated with the best supportive care available (Forner et al., 2018).

There are two TACE techniques - conventional TACE (cTACE) and drug-eluting beads (DEB) TACE (Sieghart et al., 2015). Theoretically, the DEB-TACE is superior to cTACE in terms of better tumour response and survival rates, as well as less systemic toxicity (Lammer et al., 2010; L. Zhang et al., 2021). However, DEB-TACE is more costly compared to cTACE (Sieghart et al., 2015). Few studies have been done to compare the efficacy between cTACE and DEB-TACE. Some demonstrated the superiority of DEB-TACE, while some showed non-significant

differences between the two (Facciorusso et al., 2016; Golfieri et al., 2014; Lammer et al., 2010; Nicolini et al., 2010; Song et al., 2012; Varela et al., 2007). The purpose of this study was to compare the effectiveness of both techniques in terms of tumor response post-TACE procedure as well as to identify the common accompanying side effects of TACE in our center.

1.2 Objectives

1.2.1 General Objective:

To compare the treatment response and side effects of TACE in treating HCC in HUSM, Kelantan.

1.2.2 Specific Objectives

1. To compare the tumour response of cTACE and DEB-TACE in treating HCC based on radiological images using modified RECIST (mRECIST) criteria.

2. To identify the common side effects of TACE in both cTACE and DEB-TACE.

1.3 Research Hypothesis

Hypothesis 1: High reduction percentage of the viable liver lesion will be observed in DEB-TACE compared with cTACE.

Hypothesis 2: The adverse/side effects or complications of TACE are uncommon.

1.4 Research Questions

1. Is there any difference between the effectiveness of cTACE and DEB-TACE in the treatment of HCC based on radiological images using modified RECIST criteria?

2. How common are the adverse/side effects or complications of the TACE procedure?

CHAPTER 2: LITERATURE REVIEW

2.1 Liver Anatomy

2.1.1 General anatomy

The liver is the largest organ in the body, accounting for 2 – 3 % of average body weight. It is located in the right upper quadrant of the abdominal cavity, inferior to the right hemidiaphragm. It is divided into two lobes; right and left. The liver has a dual blood supply; 25 – 30 % of the supply is from the hepatic artery, while 70 – 75 % is from the portal vein. This blood from the arterial and portal system will ultimately be mixed within the hepatic sinusoids and later drains into the hepatic venous system. The common hepatic artery originates from the coeliac axis along with two other arteries - the left gastric and splenic arteries. This artery later branches into the gastroduodenal artery and proper hepatic artery. The proper hepatic artery will divide into the right and left hepatic arteries to supply the liver's right and left lobes, respectively. Meanwhile, the portal vein is formed from the confluence of splenic and superior mesenteric veins behind the pancreatic neck and courses cranially within the hepatoduodenal ligament towards the liver. Later, the main portal vein will divide it into the right and left portal veins near the liver hilum (Abdel-Misih and Bloomston, 2010; Germain et al., 2014).

2.1.2 Couinaud's Description of segmental Liver Anatomy

Couinaud's description of the liver segmentation system is the most widely used classification as it is well applicable for surgery and accurate localisation of liver lesions. It is based on the plane of the portal vein as well as the identification of the three hepatic veins. The middle hepatic vein divides the liver into the right and left lobes, also known as Cantlie's line. The right hepatic vein divides the right liver lobe into anterior (segments V and VIII) and posterior (segments VI and VII) segments. The left hepatic vein divides the left liver lobe into medial (segment IVa and IVb) and lateral (segment II and III) segments. The portal vein divides the right and left liver into upper (segment II, IVa, VII, and VIII) and lower (segment III, IVb, V, and VI) segments.

Segments are numbered in a clockwise direction, starting from the caudate lobe (segment I) (Germain et al., 2014).

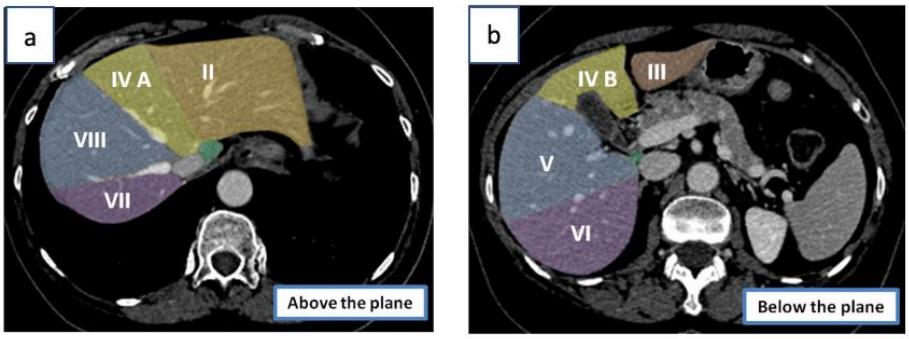

Figure 1 Images showing the liver segments above the portal vein plane (a) and below the portal vein plane (b). (Adapted from Germain et al., 2014)

2.2 Hepatocellular carcinoma (HCC)

2.2.1 Epidemiology

The development of HCC is closely related to chronic liver disease with heterogeneous incidence regions worldwide due to the variable prevalence of risk factors (Moradpour and Blum, 2005). Different regions show different risk factors for the development of HCC. Chronic hepatitis B and aflatoxin B1 exposure are the main risk factors in sub-Saharan Africa and eastern Asia (El-Serag, 2012). In patients with hepatitis B, the incidence of HCC increases with viral load, duration of infection, and the liver disease's associated severity (C. J. Chen et al., 2006). Occult hepatitis-B infection-causing DNA damage is also associated with an increased risk of development of HCC (Forner et al., 2018). The annual incidence of HCC in hepatitis B patients is more than 0.2 % (Bruix and Sherman, 2011; Forner et al., 2018).

Meanwhile, hepatitis C infection is the leading risk factor in the USA, Europe, and Japan with incidence of HCC in hepatitis C-positive varies according to regions ranging from 1 to 3 % (El-Serag, 2012). In most developed regions, non-alcoholic fatty liver disease (NAFLD) is now emerging as an important cause of HCC, however the risk to develop HCC in this group is not yet established, hence the surveillance is determined once liver cirrhosis is detected (Dyson et al., 2014; Kanwal et al., 2016). More recent evidence was collected based on retrospective assessments showing the association between metabolic syndrome, diabetes, obesity, and HCC in patients with NAFLD (Forner et al., 2018). Another risk factor identified with

associated increased risk in the development of HCC is the use of tobacco (Marrero et al., 2005). Co-infection of HIV with either hepatitis B or C virus is associated with rapid liver disease progression, hence increased risk of developing HCC (Ioannou et al., 2013). Liver cirrhosis is the other significant risk factor leading to HCC development. 70 – 90 % of HCCs developed in preexisting cirrhotic liver. The co-existence of different risk factors also increases the rate of development of HCC (Moradpour and Blum, 2005).

2.2.2 Pathogenesis

The development of HCC is a complex phenomenon involving a multistep process, including sustained inflammatory damage, hepatocyte necrosis, and regeneration, with associated fibrotic deposition. Various risk factors affect the development of HCC. The sustained chronic liver injury will induce an increased liver cell turnover rate, resulting in genetic alterations. Genetic alterations include activation of cellular oncogenes, inactivation of tumour suppressor genes, DNA mismatched repair defects, impaired chromosomal segregation, over-expression of growth and angiogenic factors, as well as telomerase activation. The malignant transformation of the hepatocytes can also occur regardless of the risk factors. (Forner et al., 2018; Moradpour and Blum, 2005)

2.2.3 Surveillance and diagnosis

Enrollment of patients into the surveillance program is determined by the risk of developing HCC, life expectancy, and the financial cost to be invested (Arguedas, 2003). Surveillance is recommended for patients with liver cirrhosis (irrespective of aetiology) and patients with hepatitis B and C (even without evidence of liver cirrhosis) (Bruix and Sherman, 2011). The incidence of HCC in patients with non-viral chronic liver disease without cirrhosis is not well established yet. Hence no recommendation for surveillance in this group has been made (Forner et al., 2018).

Prior studies have shown that high-risk patients enrolled in the HCC surveillance program were diagnosed at an earlier stage and received early treatment. These patients had a better survival rate as compared to the unenrolled patient (Sherman, 2014). A randomised control trial of a surveillance system was done in China with 18 816 patients with hepatitis B. They were divided into two main clusters; the screening and control clusters. This trial showed a reduction of HCC-related mortality in the screening cluster (B. H. Zhang et al., 2004), as shown below.

Table 1: Summary of the randomised control trial results showing reduced HCC-related mortality by 37 % in the screening cluster compared to the control cluster. (B. H. Zhang et al., 2004)

	Screening Cluster (9373)	**Control Cluster (9443)**
Screening methods	6-monthly α-fetoprotein test and ultrasound assessment	None
HCC-related mortality	83.2 per 100 000	131.5 per 100 000
Mortality rate ratio	0.63 (95% CI 0.41 – 0.98)	

Ultrasound is the standard tool used for the early detection of liver lesions in the surveillance program as it is readily available and well-tolerated (Forner et al., 2018). It is safer as no ionising radiation is involved. Screening the population at risk of developing HCC using ultrasound can be done every six months (Bruix and Sherman, 2011). However, it is limited by the operator's experience and has an unsatisfactory diagnostic accuracy in an inexperienced performer (A. G. Singal et al., 2013). When an expert does it, the ultrasound's sensitivity for lesion detection is 60 – 80 %, with more than 90 % specificity (Forner et al., 2018). When ultrasound is used alone for surveillance, the detection rates ranging from 73 to 93 %, false positive rate of 2.7 to 3.1 %, and positive predictive value of 4.7 to 8.5 % (A. Singal et al., 2009). US LI-RADS (Ultrasound Liver Imaging Reporting and Data System) is one of ultrasound module for screening and surveillance used that aims to standardized the imaging technique and reporting of liver ultrasound. It has two components – US category and US visualization score. However, dedicated training for this module must be conducted in order to achieve similar diagnostic accuracy among the ultrasound operators (Fetzer et al., 2022). Currently, this module is not used in our department.

The most commonly used serum tumour marker for HCC is α-fetoprotein (AFP). The AFP level is used as an alternative surveillance method for early diagnosis of HCC (Forner et al., 2018). In retrospective patient-control studies that evaluated the accuracy of α-fetoprotein in the diagnosis of HCC, with a cut-off of 10 – 20 ng/ml, the reported sensitivities were approximately 60 % and low specificities of approximately 80 % (Lok et al.,

2010; Marrero et al., 2009). When serum AFP is used alone for surveillance, the detection rates ranging from 54 to 80 %, false positive rate of 4.7 to 5.3 %, and positive predictive value of 2.2 to 4.4 % (A. Singal et al., 2009). The AFP response is assessed in another study by referring to a baseline of >20ng/ml. This study defines the response rate as a more than 50 % decrease in the AFP serum level three months after TACE. This study proved the superiority of DEB-TACE as it shows a significantly greater AFP response rate in the DEB-TACE group compared to the cTACE group (Song et al., 2012). HCC patients successfully detected by AFP surveillance usually indicate a chronic disease rather than an early stage (Bruix et al., 2015). However, approximately one-third of patients with HCC demonstrate non-elevation of serum AFP which generally have favorable prognosis. Hence, serum AFP cannot be used in monitoring treatment response in this group (Hanif et al., 2022).

A combination of ultrasonography and serum α-fetoprotein could increase the lesion detection rates. When ultrasound is combined with serum AFP for surveillance, the detection rates ranging from 80 to 97 %, false positive rate of 7.1 to 7.9 %, and positive predictive value of 2.2 to 3.8 % (A. Singal et al., 2009; B. Zhang and Yang, 1999).

The ideal interval of surveillance for HCC is based on an assumed tumour growth rate as described in previous studies. As mentioned in previous study, 6-monthly ultrasound interval is the recommended ultrasound surveillance based on the basis of tumour doubling times described in old series and data. It is more effective in early detection of the lesion and better

survival rate compared with the 12-monthly interval. 12-monthly interval is usually related with late detection causing low survival rate. Meanwhile, 3-monthly interval may increase detection rate for small nodules, however it has no impact on survival rate (Forner et al., 2018).

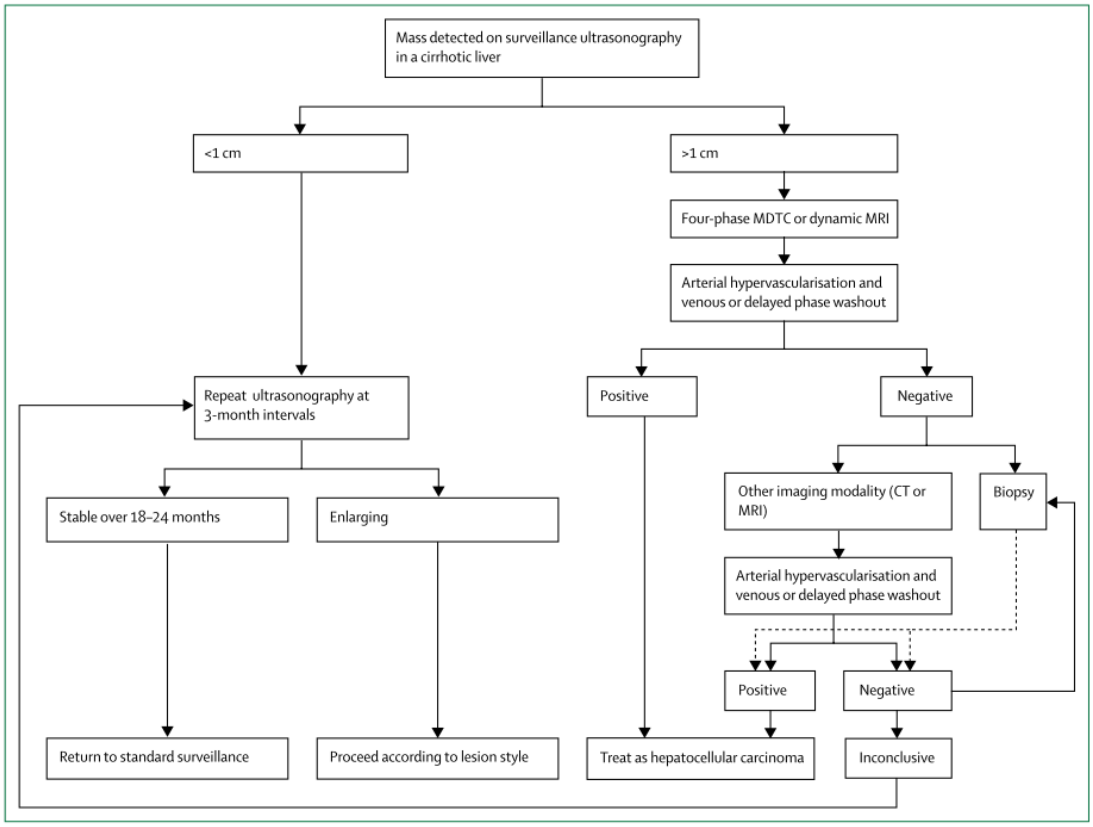

Figure 2 Diagnostic algorithm for HCC (adapted from Forner et al., 2018).

A confident diagnosis of HCC with nodules larger than 1cm can be made by referring to the specific imaging pattern in either Computed Tomography (CT) Multiphase or Magnetic Resonance Imaging (MRI) Primovist (Forner et al., 2018). The classical pattern includes intense contrast enhancement during the arterial phase followed by rapid washout during the venous and delayed phases. In nodules between 1 – 2cm, these imaging pattern has a specificity and positive predictive

value of nearly 100 % with a sensitivity reaching 71 % (Forner et al., 2008; Khalili et al., 2011; Leoni et al., 2010; Sangiovanni et al., 2010).

These non-invasive diagnostic criteria are only valid in a patient with cirrhosis. In the non-cirrhotic liver, a diagnostic biopsy is advised. A diagnostic biopsy should also be performed when the imaging fails to demonstrate the typical lesion enhancement pattern of HCC (Forner et al., 2018). However, the false-negative rate of biopsies can reach up to 30 %. Hence, a negative biopsy does not rule out HCC (Forner et al., 2008).

Another management recommendations for HCC lesions based on LI-RADS are also available which consist of four individual imaging algorithms designed for different clinical contexts which are US LI-RADS for surveillance, CT/MRI LI-RADS for diagnosis and staging, contrast material-enhanced US LI-RADS for diagnosis, and treatment response LI-RADS to assess response to local regional therapies. CT/MRI LI-RADS is used for diagnosis and staging of the liver lesion which will categorize the lesion based on the available features to different LI-RADS (LR) categories. Specific plan of managements and recommendations are given according to each LR categories. However, this management recommendation is not widely used in our department currently (Chernyak et al., 2018). (Figure 3)

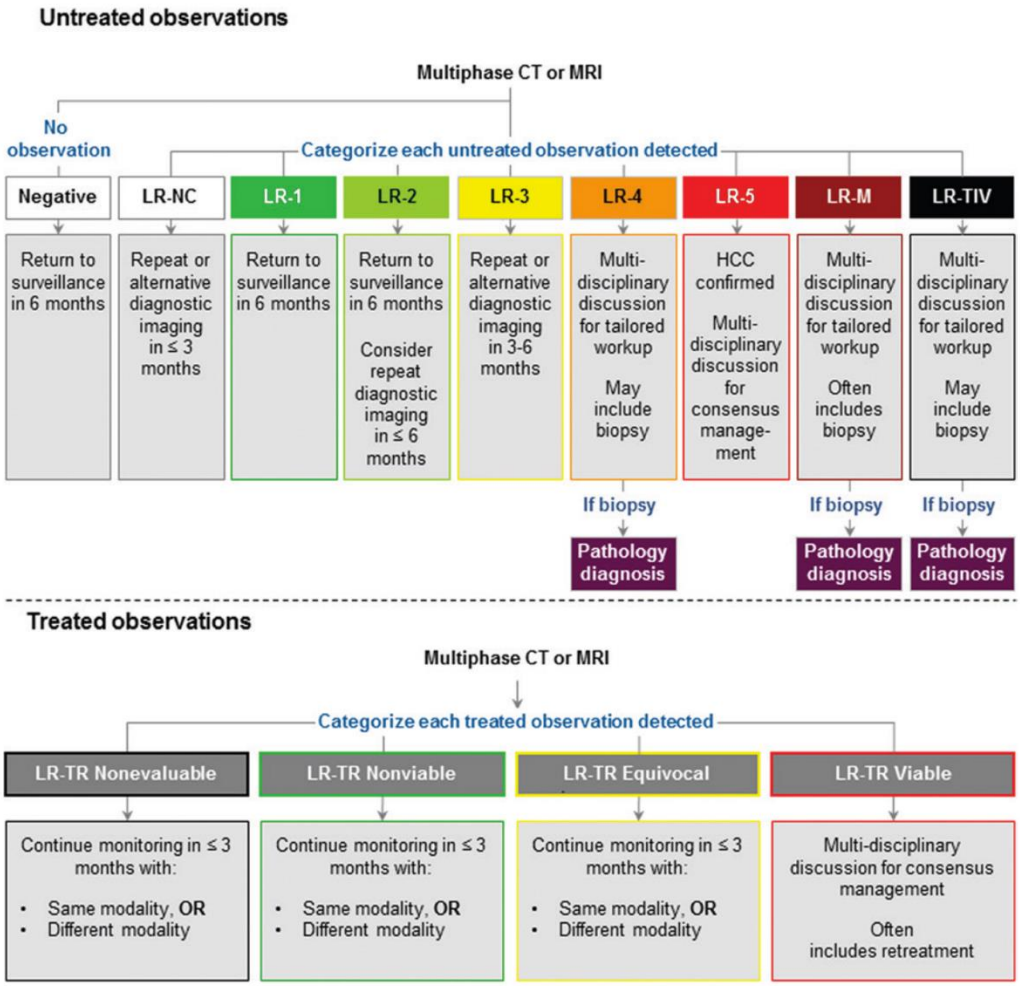

Figure 3: Summary of management recommendation and treatment response based on LI-RADS. (Chernyak et al., 2018)

2.3 Staging of Hepatocellular Carcinoma

There are multiple staging and treatment systems available for HCC, such as Barcelona Clinic Liver Cancer (BCLC), Cancer of the Liver Italian Program, Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire; Tumour, Node, Metastasis (TNM); the Chinese University Prognostic Index; Japanese Integrated Staging; the Taipei Integrated Scoring System and Hong Kong Liver Cancer staging system (Forner et al., 2018; Yau et al., 2014). The most commonly used staging system is BCLC, which has been extensively validated since its initial publication in 1999. Since then, this system has been updated a few times based on recent evidence in untreated and treated patients (Forner et al., 2018; Reig et al., 2022).

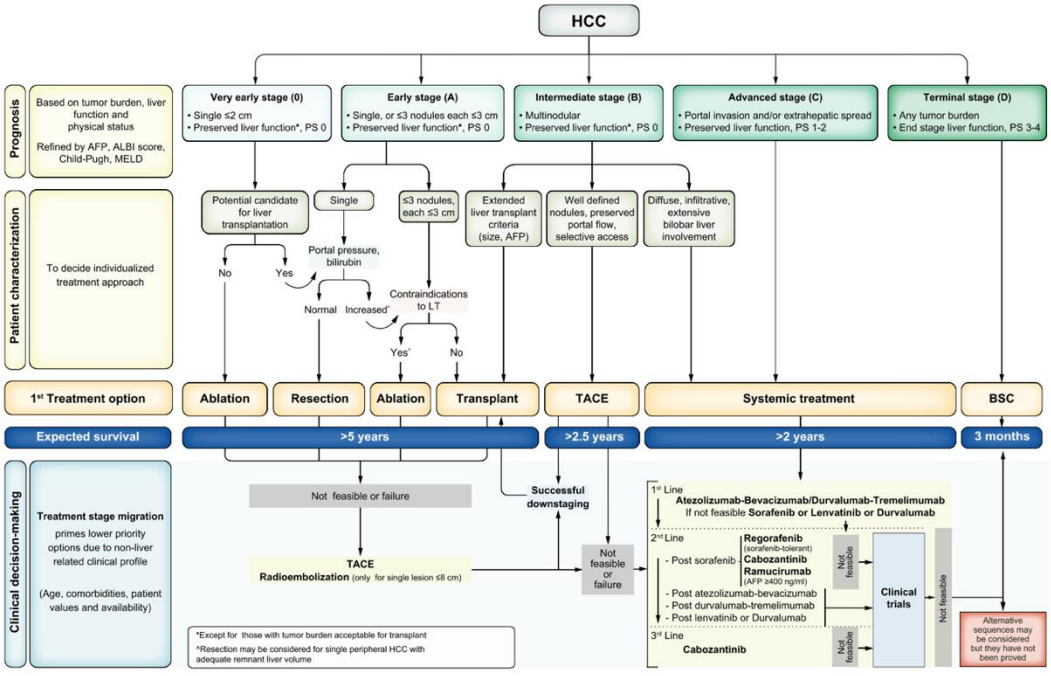

Figure 4: BCLC Staging System and Treatment strategy (Reig et al., 2022)

Table 2: Summary of the components that could help in the HCC staging assessment (Forner et al., 2018; Johnson et al., 2015; Pinato et al., 2017).

Components	
Liver function	It is usually assessed by using the Child-Pugh classification. However, this classification has low predictive power as it cannot fully assess conditions that could indicate terminal liver disease (such as renal failure, spontaneous bacterial peritonitis, recurrent encephalopathy, malnutrition, and hyponatremia).
Albumin-bilirubin (ALBI) score	Shown to stratify patients across the BCLC staging system. However, its role is not adequately determined as its components are already used to evaluate a patient's condition. Hence, it might be clinically irrelevant to be used in decision-making.
Serum α-fetoprotein	An increased level is associated with poor prognosis; however, no data is available to define the cut-off value for decision-making in the treatment of HCC.

The Child-Pugh class score is a clinical score used for liver cirrhosis (Forman and Lucey, 2001). It consists of three continuous variables (prothrombin time, bilirubin, and albumin) and two discrete variables (ascites and encephalopathy) (Ministry of Health, 2019; Thüring et al., 2020).

Table 3: Cut-off values for all parameters in the Child-Turcotte-Pugh score for grading severity of liver disease (Ministry of Health, 2019)

Variable	1	2	3
Ascites	None	Mild	Moderate/severe
Encephalopathy	None	Mild	Marked
Bilirubin (μmol/L)	<34	34 - 50	>50
Albumin (g/L)	>35	28 - 35	<28
Prothrombin time (seconds over normal)	<4	4 - 6	>6

Class A: 5 – 6 points, Class B: 7 – 9 points, Class C: 10 – 15 points

According to the West-Haven criteria, the encephalopathy score was obtained by transferring the daily clinical assessment into a cognitive status (Cash et al., 2009; Ferenci et al., 2002). The Ascites score was obtained by measuring the perihepatic ascites expansion in the transverse plane at the portal vein bifurcation (Forman and Lucey, 2001).

Eastern Cooperative Oncology Group Performance Status (ECOG-PS) is a standard scale used in the Oncology department. It helps make clinical decisions and provides prognostic values as it is correlated with cancer morbidity, mortality, and post-chemotherapy complications (Neeman et al., 2019).

Table 4: Definition of ECOG performance status score (Neeman et al., 2019).

Grade	ECOG performance status
0	Fully active; able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework or office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50 % of waking hours
3	Capable of only limited self-care; confined to bed or chair for more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

2.4 Modified Response Evaluation Criteria in Solid Tumours (mRECIST) guideline

The Response Evaluation Criteria in Solid Tumours (RECIST) guideline is introduced to measure tumour response (Lencioni et al., 2010). In this guideline, tumour response is measured by a simple measurement of the size of the target and non-target lesions in a single linear summation (Lencioni et al., 2010). The RECIST guideline utilises the sum of the unidimensional measurements of the largest tumour diameter for up to five target lesions (Forner et al., 2008; Santi et al., 2010). Based on the tumour size alone, it is assumed to sufficiently evaluate tumour response, as most responsive tumours will shrink upon treatment with cytotoxic drugs (Lencioni et al., 2010).

However, certain tumours do not show their response to their specific treatment if it is based on size reduction only. In HCC, previous studies showed that for advanced HCC, RECIST guidelines failed to demonstrate the actual tumour response based on the decrease in size alone (Forner and Bruix, 2008; Llovet et al., 2008). Treatment of HCC mainly reduces the tumour's vascularity and produces an avascular necrotic area within the lesions without necessarily causing a reduction in the overall tumour size (Lencioni et al., 2010).

Hence, mRECIST is introduced for HCC, in which this guideline will only quantify the viable portions of the tumour (Lencioni et al., 2010). A viable tumour is defined as the portion of the tumour which shows uptake of contrast media in the arterial phase of dynamic CT or MRI (Bruix et al., 2001). The measurement of tumour burden and tumour response is described in the table below.

Table 5: Assessment of tumour lesions at baseline using RECIST and mRECIST (Lencioni et al., 2010).

Measurement of Tumour Burden at Baseline		
	RECIST v1.1	**mRECIST**
Measurable disease	The lesion can be accurately measured in at least one dimension > 1cm and is suitable for repeat measurement.	The lesion can be accurately measured in at least one dimension >1cm and is suitable for repeat measurement, and the lesion shows intratumoral arterial enhancement.
Non-measurable disease	All other lesions, including small ones (<1cm) and non-measurable ones.	All other lesions, including small ones (<1cm) and non-measurable ones.
Number of lesions	Up to 5 (2 per organ)	Up to 5 (2 per organ)
Measurement	Sum of longest diameters of individuals lesions	Sum of longest diameters of individual lesions showing arterial enhancement.

Table 6: Comparison between RECIST and mRECIST criteria in assessing the target lesion response (Lencioni et al., 2010).

Target Lesion Response Definitions		
	RECIST v1.1	**mRECIST**
Complete Response (CR.)	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial Response (PR.)	≥ 30 % decrease in the sum of the longest diameters of target lesions compared with the baseline	≥ 30 % decrease in the sum of the longest diameters of viable (arterially enhancing) target lesions compared with the baseline.
Progressive Disease (PD.)	≥ 20 % increase in the sum of the longest diameters of target lesions compared with the smallest sum of longest diameters recorded (nadir).	≥ 20 % increase in the sum of the longest diameters of viable (arterially enhancing) target lesions compared with the smallest sum of the longest diameters recorded (nadir).
Stable Disease (SD.)	Neither PR nor SD	Neither PR nor SD

Table 7: Comparison between RECIST and mRECIST criteria in assessing non-target lesion response (Lencioni et al., 2010).

Non-Target Lesion Response Definitions		
	RECIST v1.1	**mRECIST**
Complete Response (CR.)	Disappearance of all non-target lesions	Disappearance of any intratumoral arterial enhancement in all non-target lesions
Progressive Disease (PD.)	Unequivocal increase in the size of non-target lesions or new lesions.	Unequivocal increase in the size of non-target lesions or new lesions meeting specific criteria.
Incomplete Response or Stable Disease (IR/SD)	Persistence of one or more non-target lesions.	Persistence of arterial enhancement in one or more non-target lesions.

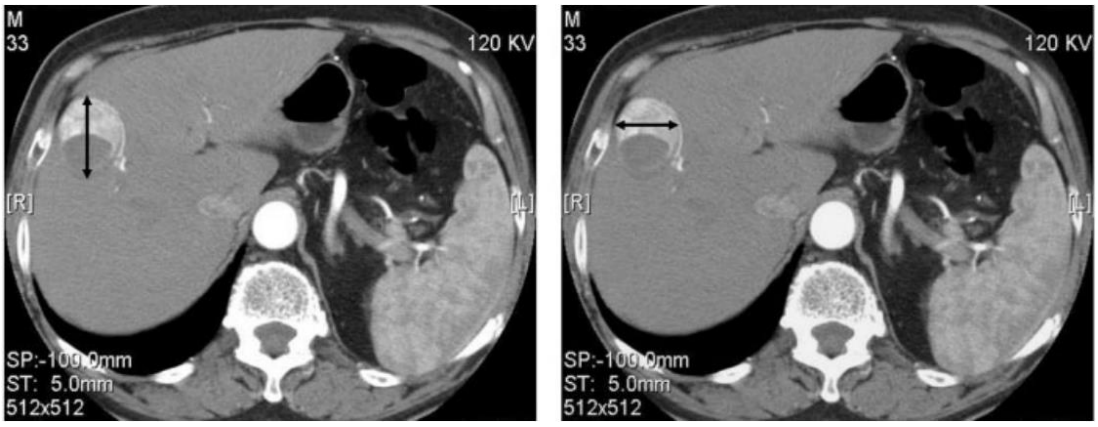

Figure 5 The difference in method to measure target tumour response on arterial-phase computed tomography (CT) scans.

(Left Image) Lesion measurement in conventional RECIST guidelines, where the longest overall diameter of the lesion is measured, and (Right Image) Lesion measurement according to mRECIST guidelines, where the longest viable tumour diameter is measured (Lencioni et al., 2010).

2.5 Trans-Arterial Chemo Embolization (TACE) treatment in HCC

Based on the BCLC staging and treatment system, TACE is recommended for a patient diagnosed with stage B. TACE aims to induce tumour necrosis. It is done by selective intravascular delivery of drugs or embolic material, which causes blockage of the arterial blood supply (Forner et al., 2018). More than 50 % of patients achieved extensive tumour necrosis post-TACE with improved survival rates (J.M. et al., 2002; Lo et al., 2002). Appropriate patient selection and optimal delivery of the chemo embolic material increase survival rates from 20 months to 30 – 40 months (Burrel et al., 2012; Malagari et al., 2012; Takayasu et al., 2012). Patients with vascular invasion (stage C) are not indicated for TACE, as they are associated with poor tolerability and impaired outcomes (Forner et al., 2014). However, in some centers (including our center), TACE is also performed to patient with stage C as a palliative, disease-modifying, or symptom-improving option as most of these patients are unable to afford the high cost of systemic therapy. However, not all stage C patients are suitable for TACE procedure, where only relatively healthy patient with segmental portal vein thrombosis were chosen. Ill patients with extensive main portal vein thrombosis were not offered for TACE procedure. TACE is also offered in stage C patients in combination with systemic therapy to improve clinical outcomes (S. Chen et al., 2018; Patidar et al., 2022). Many other guidelines (other than BCLC) also consider TACE as one of the treatment option for advanced stage (S. Chen et al., 2018; Khan et al., 2021).

After the first TACE treatment, there might be incomplete tumour devascularisation, so the procedure will need to be repeated. TACE will not be usually

repeated if follow-up treatment fails to obtain noticeable necrosis at sites that have shown progress during the initial treatment. If substantial tumour necrosis is still not achieved after two rounds of treatment, TACE is suggested to be discontinued (Forner et al., 2018). Another treatment algorithm needed to be considered at this time. There are two TACE techniques - conventional TACE (cTACE) and drug-eluting beads (DEB) TACE (Sieghart et al., 2015).

2.5.1 Conventional TACE (cTACE)

Conventional TACE (cTACE) uses a combination of cytotoxic and ischemic effects to achieve tumour necrosis (L. Zhang et al., 2021). A mixture of concentrated chemo-embolic material (e.g. Mitomycin, Doxorubicin, etc.) and iodised oil (Lipiodol) is injected intraarterially (Sieghart et al., 2015; L. Zhang et al., 2021). Preferential tumour uptake of lipiodol makes it an optimal agent used ("EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma," 2018). However, cTACE is limited due to its inconsistency in drug delivery as well as retention limits of the drugs used (Gaba et al., 2012).

Mitomycin and Doxorubicin are our centre's most common chemotherapeutic agents used in cTACE treatment. Both drugs will be mixed with lipiodol or contrast media before injection (Gruber-Rouh et al., 2018). Other drugs that could be used include 5-fluorouracil and cisplatin.

Lipiodol is a common radio-opacifying contrast agent used in interventional radiology, which developed from a poppy-seed oil. It can be used in TACE and lymphangiography. Due to the presence of the iodine component, lipiodol is also

useful in monitoring tumour changes in post-treatment CT studies, as it will be clearly visible (Gruber-Rouh et al., 2018).

2.5.2 Drug-Eluting Beads TACE (DEB-TACE)

Meanwhile, drug-eluting beads (DEB)-TACE is the new alternative approach that theoretically should produce a better outcome as compared to cTACE (Kang et al., 2020; Prajapati et al., 2014; Sun et al., 2020). An embolic microsphere loaded with a chemotherapeutic agent (e.g., Doxorubicin) will be injected intraarterially in this approach (Sieghart et al., 2015). The microsphere has the ability for slow drug release. This will ensure high local drug concentration with low systemic drug concentration (Kishore et al., 2020). However, this procedure is costly (Sieghart et al., 2015).

Variable sizes of drug-eluting embolic materials (e.g. HepaSphere, DC bead) used in DEB-TACE treatment such as > 300 μm [58], 100 – 300 μm and the smallest is 30 – 60 μm (Malagari et al., 2014). Recent studies have shown that smaller diameters (100 – 300 μm) produced better outcomes as compared to the larger size (> 300 μm) (Malagari et al., 2008; Padia et al., 2013). Smaller calibres can cause more distal embolisation within the tumour (Malagari et al., 2011). The size of HepaSphere 30 – 60 μm will be expanded to 166 – 247 (197 ± 31) μm in saline and 145 – 213 (148 ± 45) μm after loading with Doxorubicin (Malagari et al., 2014). The other microspheres available are DC beads and tandem beads, but these are not commonly used in our centre.