Philippine Clinical Practice Guideline for the Diagnosis and Management of Hepatocellular Carcinoma

2021

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DISCLAIMER

This guideline focuses on prioritized clinical issues in the management of hepatocellular carcinoma in the Philippines. It is not meant to be a complete guideline on the diagnosis and management of hepatocellular carcinoma. Its target users are specialists, general practitioners, and allied health professionals largely involved in or providing care for patients with or at risk for hepatocellular carcinoma.

The contents of this CPG are not meant to restrict the clinicians in using their judgment and considering individual patient's values, needs, preferences, and institution's available resources even if adherence to this guideline is encouraged by its developers and the Department of Health. Sound clinical decision-making based on patients' current health status must be continually exercised as their responses to treatment or diagnostic tests may vary.

Policymakers and payers can also base regulations on this CPG, but nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this guideline should not also be treated as strict rules to base legal actions.

Developers of this CPG are aware of its limitations. Evidence summaries and recommendations are based on the best available scientific evidence as of the time of its formulation. The clinical trials and observational studies may not have addressed specific aspects of assessment, management, and surveillance, and as such, evidence bases are therefore not all inclusive. Nevertheless, considerations on these aspects were still deemed necessary in the current contexts of liver cancer.

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EXECUTIVE SUMMARY

The Clinical Practice Guideline (CPG) for the Diagnosis and Management of Hepatocellular Carcinoma (HCC) provides 12 recommendations for ten prioritized interventions in diagnosing and managing hepatocellular carcinoma in the Philippines. It is the first CPG for HCC developed *de novo* in the country. It is not an adaptation of existing practice guidelines developed by international organizations.

Recommendations are the product of appraisal of the best available evidence, consideration of costs, equity, feasibility, and acceptability and appropriateness of utilizing diagnostic and therapeutic interventions for HCC, incorporation of different clinical practices, and integration of patient values and preferences. This CPG is intended to be used not only by liver cancer specialists but also other clinicians and stakeholders involved mainly in caring for patients with or at risk of developing hepatocellular carcinoma. The target beneficiaries of this guideline are primarily the patients with HCC in different areas in the country as applicable.

The guideline development process followed the 2018 DOH Manual using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. This approach included (1) identification of critical research questions in PICO format (population-intervention-comparison-outcome), (2) retrieval, appraisal, and synthesis of the evidence, (3) formulation of draft recommendations, (4) formulation of final recommendations and, (5) planning for dissemination, implementation, impact monitoring, and updating.

Each recommendation is presented with the certainty of evidence (high, moderate, low, very low) and the strength of the recommendation (strong, conditional, none). Evidence with high certainty are well-established and will unlikely be changed by new research finding. Strong recommendations are those which are supported by evidence of high certainty or those which the guideline development group believes will clearly benefit or harm the target population. These can be put forth as policy. In contrast, a conditional recommendation indicates that the intervention is suggested and shared decision-making would be necessary prior to its uptake. The absence of strength indicates insufficient evidence to recommend for or against a particular intervention. Any dissonance between the certainty of evidence and the strength of recommendation is explained under the Consensus Issues.

Table 1 shows the final recommendations for this clinical practice guideline on hepatocellular carcinoma.

Table 1. Summary of recommendations

Recommendation	Strength of Panel Recommendation	Certainty of Evidence
1.1. We recommend semi-annual screening of patients at risk of developing hepatocellular carcinoma.	Strong	Low
1.2. We suggest the use of ultrasound, with or without alpha-fetoprotein test, for screening of patients at risk of developing hepatocellular carcinoma.	Conditional	Very Low
2. We recommend the use of a multiphasic, contrast-enhanced CT scan or contrast-enhanced MRI in the diagnosis of hepatocellular carcinoma.	Strong	Low
3.1. We recommend the use of core needle biopsy over fine needle aspiration biopsy among patients who do not fulfill the imaging criteria for hepatocellular carcinoma.	Strong	Low
3.2. We suggest the use of fine needle aspiration biopsy among patients who do not fulfill the imaging criteria for hepatocellular carcinoma when core needle biopsy cannot be done.	Conditional	Low
4. There is insufficient evidence to recommend liver transplantation over liver resection among patients with early stage hepatocellular carcinoma (BCLC 0-A).	None	Very Low
5. There is insufficient evidence to recommend liver transplantation over radiofrequency ablation or microwave ablation among patients with early stage hepatocellular carcinoma (BCLC 0-A).	None	Low
6. We suggest liver resection over ablation, primarily radiofrequency ablation, for patients with hepatocellular carcinoma BCLC 0-A and compensated liver function.	Conditional	Very Low
7. We recommend transarterial chemoembolization over selective internal radiation therapy in intermediate stage (BCLC B) hepatocellular carcinoma.	Strong	Very Low
8. There is insufficient evidence to recommend treatment with either selective internal radiation therapy or external beam radiation therapy for hepatocellular carcinoma patients in the intermediate stage (BCLC B).	None	Very Low
9. There is insufficient evidence to recommend the addition of targeted therapy to transarterial chemoembolization in BCLC B hepatocellular carcinoma.	None	Low
10. We suggest the use of combination therapy (atezolizumab plus bevacizumab) over sorafenib as first-line treatment for advanced stage hepatocellular carcinoma in selected patients.	Conditional	Low

LIST OF MEDICAL ABBREVIATIONS AND ACRONYMS

AASLD	American Association for the Study of Liver Diseases
AE	adverse event
AFP	alpha-fetoprotein
AJCC	American Joint Committee on Cancer
APASL	Asian Pacific Association for the Study of the Liver
ASR	age-standardized rate
ASCO	American Society of Clinical Oncology
BCLC	Barcelona Clinic Liver Cancer
CCT	controlled clinical trials
CENTRAL	Cochrane Central Register of Controlled Trials
CoE	certainty of evidence
CNB	core needle biopsy
CP	consensus panel
CPG	clinical practice guideline
CT	computed tomography
cTACE	conventional transarterial chemoembolization
DEB-TACE	drug-eluting beads transarterial chemoembolization
DFS	disease-free survival
EASL	European Association for the Study of the Liver
EBRT	external beam radiotherapy
ECOG	Eastern Cooperative Oncology Group
EHR	extrahepatic recurrence
EGD	Esophagogastroduodenoscopy
EORTC	European Organisation for Research and Treatment of Cancer
FNAB	fine needle aspiration biopsy
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HERDIN	Health Research and Development Information Network (Philippines)
HR	hazard ratio
IARC	International Agency for Research on Cancer
ICER	incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IHC	Immunohistochemistry
JSTOR	Journal Storage
KLCA-NCC	Korean Liver Cancer Association-National Cancer Center
LI-RADS	Liver Imaging Reporting and Data System
LR	liver resection

mRECIST	modified response evaluation criteria in solid tumors
MRI	magnetic resonance imaging
mUICC	modified Union for International Cancer Control
MWA	microwave ablation
OS	overall survival
OR	odds ratio
PhilHealth	Philippine Health Insurance Corporation
QALY	quality-adjusted life year
QoE	quality of evidence
RCT	randomized controlled trials
REILD	radioembolization-induced liver disease
RFA	radiofrequency ablation
ROB	risk of bias
RR	relative risk
SAE	serious adverse event
SC	steering committee
SIRT	selective internal radiation therapy
TACE	transarterial chemoembolization
TARE	transarterial radiotherapy
TRD	treatment-related death
TTP	time to progression
US	ultrasound
WHO	World Health Organization

Chapter 1. BACKGROUND

Liver cancers (CA) pose one of the most intensive challenges to global health, especially in developing countries. Primary cancer of the liver, which accounts for 75 to 90% of all liver cancers, is the sixth most common cancer worldwide and the second leading cause of cancer-related mortality.[1,2] In the Philippines, liver CA ranks fourth in cancer incidence, with over ten thousand new cases in 2020, and was the second leading cause of cancer death.[3] The most common histology of primary liver cancer globally is hepatocellular carcinoma (HCC), a tumor of the parenchymal cells of the liver, accounting for approximately 80% of cases.[1]

Incidence rates of liver cancer have been rising in the past three decades, with trends expected to increase from 841,080 in 2018 to 1,361,836 in 2040 (an overall change of +61.9%).[4] According to Cancer Today, an International Agency for Research on Cancer (IARC), most of the burden is in developing countries, with 80 to 85% of HCC cases reported in Africa and Asia.[4,5] However, even within these specific geographic regions, there is significant variability in the distribution and incidence of HCC, primarily due to the variable prevalence of risk factors.[6] For example, the age-standardized rate (ASR) in Cape Verde, Africa, was 10.7 (per 100,000), while in Mongolia and China, it was 93.7, which had the highest ASR in 2018. In a study, the Philippines ranked 23rd.[7]

Survival rates of HCC, even in recent studies, are lacking due to the advanced stage of the disease when diagnosed. The median survival of untreated HCC ranges from 3 to 9 months, with 5-year mortality rates as high as >95% annually and mean age-standardized survival rate at five years of approximately 12%.[2,8] Geographic distribution of mortality in HCC is similar to that of incidence.[2,4]

Hepatocellular cancer occurs more often in males than in females (2.4:1), and the incidence increases with age, with the highest seen in the 60-70 years age group.[2,4] However, in populations where hepatitis B and C infection is hyperendemic, the disease can develop at a younger age, most often around the age of 40.[5,7]

Several important risk factors have been identified, including chronic hepatitis B infection, chronic hepatitis C infection, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, alcoholic liver disease, and any other condition of sustained inflammatory damage leading to hepatocyte necrosis, regeneration, fibrotic deposition, resulting in cirrhosis.[4,6] Other risk factors include exposure to aflatoxin, tobacco, obesity, diabetes, birth control pills, insulin resistance, hypothyroidism, and hyperlipidemia.[2] In the majority of cases of HCC (75 to 80%), the association with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections has been well-established.[5] Indeed, variations in the age-, sex-, and race-specific rates of HCC in different geographic regions are likely to be related to differences in the prevalence of viral hepatitis in these populations.[5]

In the Philippines, there is a paucity of local data on epidemiology, incidence, and treatment outcomes of HCC. There is no local CPG to guide the approach to diagnosis and treatment.

Management is primarily based on individual physician preferences, which may be influenced by specialty and institutional protocol, resulting in significant variation in practice that potentially affects clinical outcomes. Although several clinical practice guidelines on the management of HCC have been published worldwide[9-11], their applicability in the local context may not be appropriate. In 2019, the Department of Health commissioned the Rizal Medical Center in Pasig, Metro Manila, to formulate an evidence-based clinical practice guideline on hepatocellular carcinoma to standardize the approach to the diagnosis and treatment of HCC.

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Chapter 2. GUIDELINE DEVELOPMENT METHODS

Organization of the Process

The guideline development process followed the methodology outlined in the CPG Development Manual of the Department of Health[1]. First, the DOH selected one of its tertiary hospitals to organize the Lead CPG Developer or the Steering Committee (SC). The SC created a roster of physicians, hospitals, and organizations that provide liver cancer care and invited them as stakeholders in the development of this CPG. The SC was tasked to oversee the CPG formulation process, including setting up the working groups (i.e., Evidence Review Experts and Consensus Panel). The SC was also responsible in setting the scope of the CPG by identifying and prioritizing clinical questions and formulating these questions, with specific population, intervention, comparator, and outcomes of interest (PICO), before sending to the Evidence Review Experts.

The EREs were tasked to perform a systematic literature search, review existing CPGs, appraise and synthesize relevant evidence, draft the evidence-based recommendations, and present them to the consensus panel.

Lastly, the Consensus Panel was assigned to choose the critical and important outcomes, review the evidence summaries and draft recommendations, discuss the merits of the evidence, consider other factors (cost, patient's values and preferences, feasibility) during an *en banc* meeting, and formulate the final recommendations and strength.

Composition of the CPG Consensus Panel

The Consensus Panel is a multisectoral group of content experts and key stakeholders in the care of patients with HCC. Selecting the members of the consensus panel was guided by the recommendations of DOH.[1] The key stakeholders who joined the series of online *en banc* meeting were general and hepatobiliary surgeons, medical and surgical oncologists, liver pathologists, interventional radiologist, family physician, infectious disease specialist, a patient representative, private and public physician practitioners, medical training officer, and a government representative.

Declaration and Management of Conflicts of Interest

Each prospective member of the working groups of the CPG was required to declare his/her financial and intellectual conflicts of interest (COI) that may lead to biased decisions. The SC assessed the declared COIs and disqualified from the Consensus Panel anyone with major potential COIs. Those with other COIs were to inhibit themselves from the discussion should this be related to their declared COI.

The Steering Committee facilitated the whole CPG process, but its members had no direct participation in assessing and synthesizing the evidence, generating the evidence summaries, draft recommendations, and strength of recommendations of the EREs, and in voting on or

discussing the final recommendations during the *en banc* review or in the Delphi of the Consensus Panel.

The summary of declaration of COIs is shown in Appendix A.

Creation of the Evidence Base

The ERE conducted a systematic search in electronic (MEDLINE via PubMed, CENTRAL, Google Scholar and *ClinicalTrials.gov*) and local databases using keywords based on the PICO for each question (Table 2). To ensure a comprehensive search, the ERE contacted authors, consulted local experts on the topic, and hand searched articles for other relevant references. The last search was conducted from March to April 2021.

The EREs were tasked to look for international CPGs published over the past five years that answer their respective clinical questions. Two methodologists appraised the relevant CPGs using the AGREE tool and assessed for possible adaptation.

For questions on therapeutic interventions, randomized controlled trials (RCTs), controlled clinical trials (CCTs), systematic reviews or meta-analyses were sought. In their absence, quasi-randomized and observational studies were considered. For questions on diagnostic tests, the included studies were those that reported sensitivity and specificity or had data for their computation. Cost-effectiveness studies, if available, were included.

Two members of the ERE independently appraised each individual study for methodological quality. Results from studies with similar outcomes were pooled and estimates of effect were determined. Review Manager version 5 was used for quantitative synthesis of clinical outcomes identified for each of the ten questions. The ERE determined the certainty of evidence for each outcome (benefit or harm) after assessment of directness, risk of bias, consistency, and precision of results using the GRADE approach (Table 3). The evidence obtained from the review became the basis for the draft recommendations.

Table 2. PICO questions of this guideline

1. *Among patients at increased risk for hepatocellular carcinoma (those with liver cirrhosis secondary to alcohol, hemochromatosis, non-alcoholic fatty liver disease, and other metabolic disorders, hepatitis B and hepatitis C infection), should we use a biannual liver ultrasound (US) or a combination of biannual liver US and alpha-fetoprotein (AFP) to improve HCC-related survival rate?*

2. *Among patients with suspected hepatocellular carcinoma, should we use multiphasic computed tomography scan versus contrast-enhanced abdominal magnetic resonance imaging in diagnosing hepatocellular carcinoma?*

3. *Among patients suspected of having hepatocellular carcinoma but do not fulfill the imaging criteria for diagnosis, should we use fine needle aspiration biopsy versus core needle biopsy in diagnosing hepatocellular carcinoma?*

4. *Among patients with early-stage hepatocellular carcinoma (BCLC 0-A), should we do liver transplantation versus liver resection to improve progression-free and overall survival, morbidity, and mortality?*

5. *Among patients with early stage hepatocellular cancer (BCLC 0-A), should we do liver transplantation versus ablation (microwave ablation or radiofrequency ablation) to improve progression-free and overall survival, morbidity and mortality?*

6. *Among patients with early stage hepatocellular cancer (BCLC 0-A), should we do liver resection versus ablation (microwave ablation or radiofrequency ablation) to improve progression-free and overall survival, morbidity, and mortality?*

7. *Among patients with intermediate stage hepatocellular carcinoma (BCLC B), should we use transarterial chemoembolization versus selective internal radiation therapy to improve progression-free and overall survival, morbidity, and mortality?*

8. *Among patients with intermediate stage (BCLC B) hepatocellular carcinoma, should we use selective internal radiation therapy (SIRT) versus external beam radiotherapy to improve in terms of progression-free and overall survival, morbidity, and mortality?*

9. *Among hepatocellular carcinoma patients with intermediate stage (BCLC B), should we use the combination of targeted therapy (e.g., sorafenib, lenvatinib) plus transarterial chemoembolization versus transarterial chemoembolization alone to improve response rate, progression-free and overall survival, preservation of liver function, and quality of life?*

10. *Among hepatocellular cancer patients with advanced stage (BCLC C), should we use sorafenib versus combination immunotherapy (e.g., atezolizumab, pembrolizumab, nivolumab, ipilimumab) plus bevacizumab to improve progression-free and overall survival and quality of life?*

Table 3. Basis for assessing the certainty of evidence using GRADE approach[2]

Observational studies	Certainty of Evidence	Randomized trials
Extremely strong association and no major threats to validity	High (Further research unlikely to change our confidence in estimate of effect)	No serious flaws in study quality
Strong consistent association and no plausible confounders	Moderate (Further research is likely to have an important impact)	Serious flaws in design or execution or quasi-experimental design
No serious flaws in study quality	Low (Further research is very likely to have an important impact)	Very serious flaws in design or execution
Serious flaws in design and execution	Very low (The estimate of effect is very uncertain)	Very serious flaws and at least one other serious threat to validity
Additional factors that lower certainty of the evidence are: ● Important inconsistency of results ● Some uncertainty about directness ● High probability of reporting bias ● Sparse data ● Major uncertainty about directness can lower the quality by two levels Additional factors that may increase certainty are: ● All plausible residual confounding, if present, would reduce the observed effect ● Evidence of a dose-response gradient		

Formulation of the Recommendations

During the *en banc* consensus panel meeting, the draft recommendations and supporting evidence were presented and discussed. The nominal group technique was used, wherein each panel member had the opportunity to clarify matters about the evidence presented and to systematically contribute his knowledge and opinions about the issues under discussion. After considering the certainty of the evidence, trade-offs between benefits and harms, cost, equity, feasibility, acceptability in the current local setting, patient values and preferences, the CP members voted to approve of the recommendation and its strength. A consensus was reached when an approval vote of at least 75% was achieved. In case consensus was not reached in the first round of voting, discussions occurred to determine reasons for dissenting opinions and to revise the recommendation statement until it was approved. Two further rounds of voting on the issue were allowed. If consensus was not reached, the final approval was obtained through a modified Delphi process.

Each recommendation may be for or against a specific intervention or diagnostic test and can be strong or conditional. The panel can also opt not to make a recommendation. A strong recommendation for an intervention or diagnostic test sets it as a standard of care for most patients and it may be adopted during health policy-making. In contrast, a conditional recommendation indicates that the intervention or diagnostic test is suggested and may be useful in certain situations. Shared decision-making would be crucial for its implementation.

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Chapter 3. FINAL RECOMMENDATIONS and EVIDENCE to DECISION ISSUES

The recommendations and evidence summaries are briefly outlined in the following pages. More details of the evidence can be found in a separate document (Evidence Base).

BIANNUAL LIVER ULTRASOUND vs. LIVER ULTRASOUND and ALPHA-FETOPROTEIN *for Screening*

Recommendations

1.1. We recommend semi-annual screening of patients at risk of developing hepatocellular carcinoma. ***(strong recommendation, low certainty of evidence)***

1.2. We suggest the use of ultrasound, with or without alpha-fetoprotein test, for screening of patients at risk of developing hepatocellular carcinoma. ***(conditional recommendation, very low certainty of evidence)***

Ultrasonography or US is a non-invasive imaging procedure that uses soundwaves to produce images of organs inside the abdomen or pelvis. Among adults, AFP is a tumor marker from the liver, testicles, or ovaries. Semiannual US with or without AFP determination has been recommended as a non-invasive surveillance strategy in a number of HCC clinical practice guidelines.[1]

Evidence to Decision

Benefits and Harms

There was no randomized controlled trial directly comparing US to US plus AFP test in HCC surveillance among patients with cirrhosis, hepatitis B, and/or hepatitis C infection with mortality or survival as an outcome measure. One RCT compared overall survival between the biannual US + AFP screening with usual care (no screening).[2,3] The investigators recruited 18,816 participants with hepatitis B, 9,373 were randomized to semiannual screening, and 9,443 served as controls. From this study, the authors extracted the accuracy estimates for US alone, AFP alone, and US + AFP from the screening arm.

Based on this single RCT[3], the reported sensitivity estimates of US alone, AFP alone, and US + AFP were 84%, 69%, and 92%, respectively.[2] Moreover, screening patients at risk for HCC using US + AFP was associated with a 40% lower risk of HCC-related mortality (95% CI 8 to 61%) compared to unscreened individuals. There was no significant difference between the screened group and the unscreened group regarding the number of cancers detected. However, there was a significantly higher proportion of HCC detected at an early stage in the screened group. Surveillance improved four-year survival in more than half of patients and five-year survival in more than 40% of patients.[3]

Confirmatory US and contrast-enhanced CT scans carry a 10% risk of mild adverse events.[4] Needle track seeding of cancer cells, a potential risk associated with biopsy of hepatic tumors, can be as high as 0.9% per annum.[5] Less well-known is the psychological distress that a presumptive or a missed diagnosis of HCC will inflict on screened patients.[6,7]

Certainty of Evidence

1.1.The overall certainty of evidence for the first recommendation was deemed to be low because of serious risk of bias and indirectness.[2]

1.2. The overall certainty of evidence for the second recommendation was very low due to very serious risk of bias and indirectness.[3]

Other Considerations

Cost

There is no local cost-benefit analysis of HCC screening among at-risk patients. Based on an informal survey of four stand-alone laboratories in Manila, liver US (single organ) ranges from PHP 600 to PHP 700, and quantitative AFP determination ranges from Php 850 to PHP 2,000. A rapid qualitative AFP test kit costs PHP 10 to PHP 70 each (wholesale or retail value, respectively) exclusive of delivery, personnel salary, and other costs.

Recommendations from Other Groups

APASL, KLCA-NCC, AASLD and LI-RADS recommend US together with AFP every 6 months for HCC surveillance. The EASL did not recommend use of AFP due cost-effectiveness issues.[1] In general, CPGs from the Americas and Europe recommend US while CPGs from Asia recommend US and AFP for semiannual screening.[8-11]

It is generally accepted that groups with hepatitis B and/or C infection, those with cirrhosis of any cause, individuals with a family history of liver cancer, those with prolonged heavy alcohol consumption, and men older than 40 years are at an increased risk of developing HCC.[12]

Consensus Issues

The CP members identified at-risk patients as those with liver cirrhosis of any etiology, hepatitis B, with a family history of hepatocellular carcinoma, males aged 40 years and above, and females aged 50 years and above. They were convinced of the net benefit of selective screening, thus the strong recommendation despite the low certainty of evidence. Moreover, despite the higher costs associated with screening (increased number of patients eligible for early management e.g., transplantation and immunosuppression), its positive impact on a patient's life (e.g., increased societal participation and fulfilled roles in the family), was highly valued and difficult to equate with economic gains.

Members of the panel favored using US alone, which will cost less and is more available. However, combining US with AFP when the latter test is available and affordable is also acceptable in most urban places in the country.

GRADE Evidence Profile

P *patients at increased risk for hepatocellular carcinoma*
I *combination of biannual liver US and alpha-fetoprotein (AFP)*
C *biannual liver ultrasound (US)*
O *HCC-related survival rate, diagnostic accuracy*

Table 4. Summary of findings on HCC screening vs. no screening

Outcomes	Importance	Basis	Effect Estimate	95% CI	Interpretation	Overall CoE
Mortality	Critical	1 RCT (n = 18,816)	RR 0.60	0.39 - 0.92	Benefit	Very Low
Proportion of resectable tumors	Critical	1 RCT (n = 18,816)	RR 8.06	3.18 - 20.41	Benefit	Very Low
Detected Stage 1 HCC	Critical	1 RCT (n = 18,816)	RR 82.07	5.16 - 1305.59	Benefit	Very Low
Sn (US)	Critical	1 CS	84.3%	71.4 - 93.0%	-	Low
Sp (US)	Critical	1 CS	97.0%	96.8 - 97.2%	-	Low
PPV (US)	Critical	1 CS	6.6%	5.8 - 7.6%	-	Low
False positive rate (US)	Critical	1 CS	2.98%	2.75 - 3.23%		Low
Sn (US + AFP)	Critical	1 CS	92.2%	81.1 - 97.8%	-	Low
Sp (US + AFP)	Critical	1 CS	92.5%	92.1- 92.9%	-	Low
PPV (US + AFP)	Critical	1 CS	3%	2.7- 3.3%	-	Low
False positive rate (US + AFP)	Critical	1 CS	7.5%	7.1 - 7.9%	-	Low

Sn – sensitivity, Sp – specificity, PPV – positive predictive value, RCT – randomized controlled trial, CS – cross-sectional derived from the RCT, US – ultrasound, AFP – alpha-fetoprotein, HCC – hepatocellular carcinoma, RR – relative risk, COE – certainty of evidence

Table 5. Comparison of survival rate between HCC screening vs. no screening

Outcomes	Importance	Basis	Screened Group (n = 9,373)	Usual Care Group (n = 9,443)	Overall COE
1-year survival	Critical	1 RCT	65.9%	31.2%	Very Low
3-year survival	Critical	1 RCT	52.6%	7.2%	Very Low
5-year survival	Critical	1 RCT	46.4%	0	Very Low

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MULTIPHASIC CT SCAN vs. CONTRAST-ENHANCED ABDOMINAL MRI *for Diagnosis*

Recommendation

2. We recommend the use of a multiphasic, contrast-enhanced CT scan or contrast-enhanced MRI in the diagnosis of hepatocellular carcinoma. ***(strong recommendation, low certainty of evidence)***

Diagnosis of HCC through non-invasive techniques has been advocated by different liver cancer technical groups and societies. Unique vascular derangements of the tumor can be visualized through multiphasic CT scan or MRI with extracellular contrast.[1,2] Using CT and MRI with extracellular contrast, definite HCC diagnosis is characterized by the presence of arterial phase hyperenhancement with washout in the portal venous or delayed phases. MRI with hepatobiliary contrast will show arterial phase hyperenhancement with washout in the portal venous, delayed, or hepatobiliary phases in HCC.[3]

Evidence to Decision

Diagnostic Accuracy and Harms

Seventeen cross-sectional studies that compared contrast-enhanced abdominal MRI and multiphasic CT were reviewed. Using lesion per lesion analysis, contrast-enhanced abdominal MRI has higher pooled sensitivity (84% versus 67%) but with similar pooled specificity (90% versus 93%) compared to multiphasic CT scan. Using lesion per patient analysis, contrast-enhanced abdominal MRI has higher pooled sensitivity (86% versus 73%) and specificity (85% versus 78%).

Contrast agents are considered safe but adverse effects can present as mild allergic-like reactions to rare but severe complications like contrast-induced nephropathy and nephrogenic systemic fibrosis.[4] The incidence of adverse events is 1.5 events per 1000 doses (2.62% of which are serious) with low-osmolar iodinated contrast and 0.4 events per 1000 doses (6.25% of which are serious) with gadolinium-containing agents.[5] A Canadian review (2017) reported that a previous reaction to contrast is the greatest predisposing risk factor for an adverse reaction. Other known risk factors were rate and route of administration, larger contrast dose and type of non-ionic contrast use.[6]

Certainty of Evidence

The overall certainty of evidence is low because of inconsistency and serious risk of bias. The biases stem from different reference standards used, unclear interval between performance of the index tests and reference standard, and unclear method of patient sampling. [7-17]

Other Considerations

Cost

A cost-utility analysis in 2019 concluded that the most cost-effective strategy is to use CT scan for HCC surveillance and diagnosis, and complete MRI for inadequate CT performance in an optimal scenario involving patients with compensated cirrhosis with 100% compliance rate.[18]

From an informal survey in Metro Manila (March 2021), cost of imaging varies greatly. In a government hospital, the cost of multiphasic CT scan and extracellular contrast-enhanced abdominal MRI is PHP 9,695 and PHP 15,330, respectively, and an additional PHP 12,500 is needed for gadoxetic acid (*Primovist*) MRI contrast.

Recommendations from Other Groups

2018 KLCA-NCC: Diagnosis of HCC can be made, with either pathology or noninvasive imaging, in high-risk groups (chronic hepatitis B, chronic hepatitis C, or cirrhosis) (*strong recommendation, high quality of evidence*). Multiphase CT or multiphase MRI with extracellular contrast agents or hepatobiliary contrast agents should be performed as a first-line examination especially in at risk patients with a lesion ≥ 1 cm in size on surveillance tests *(strong recommendation, high quality of evidence)*.[3]

2018 EASL: In addition to imaging, histopathology confirmation is required for non-cirrhotic patients *(strong recommendation, moderate quality of evidence)*.[19]

Consensus Issues

There was unanimous strong recommendation from the panel members for use of either of the two imaging tests, without prioritizing one imaging test over the other. The majority of CP members who favored MRI did so because of its higher sensitivity, ability to detect tumors of smaller size, and no exposure to radiation. Furthermore, using MRI as a first-line confirmatory test may turn out to be less expensive if the diagnosis is arrived at earlier and the cost of a failed CT scan is avoided.

However, CT scan was favored by some because it is (1) already commonly used as initial diagnostic test by specialists (2) more commonly available (3) able to provide faster results, and (4) less costly. In addition, MRI is dependent on technical expertise and high-resolution machine to produce good quality images, technology which is not widely available in the country.

GRADE Evidence Profile

P *patients with suspected HCC*
I *multiphasic computed tomography scan*
C *contrast-enhanced abdominal magnetic resonance imaging*
O *diagnosing hepatocellular carcinoma*

Table 6.Summary of findings on multiphasic CT scan vs. contrast-enhanced abdominal MRI in diagnosis of hepatocellular carcinoma: Lesion per lesion analysis

Multiphasic CT Scan		Contrast-enhanced abdominal MRI	
Sensitivity	0.67 (95% CI: 0.59 to 0.74)	Sensitivity	0.84 (95% CI: 0.77 to 0.89)
Specificity	0.78 (95% CI: 0.89 to 0.96)	Specificity	0.90 (95% CI: 0.82 to 0.94)

Prevalence or Pre-test probability: 7.8%

Outcome	Importance	Basis	Effect per 1,000 patients tested Pretest probability of 7.8%		Interpretation	Certainty of Evidence
			multiphasic CT scan	contrast-enhanced abdominal MRI		
True positives	Critical	13 Cross-sectional studies (cohort type accuracy study) n = 1,069	52 (46 to 58)	66 (60 to 69)	14 fewer TP in multiphasic CT scan	Low
False negatives	Critical		26 (20 to 32)	12 (9 to 18)	14 more FN in multiphasic CT scan	
True negative	Critical	13 Cross-sectional studies (cohort type accuracy study) n = 1,609	857 (821 to 885)	830 (756 to 867)	27 more TN in multiphasic computed tomography scan	Low
False positives	Critical		65 (37 to 101)	92 (55 to 166)	27 fewer FP in multiphasic computed tomography scan	

Table 7.Summary of findings on multiphasic CT scan vs. contrast-enhanced abdominal MRI in diagnosis of hepatocellular carcinoma: Lesion per patient analysis

Multiphasic CT Scan		Contrast-enhanced abdominal MRI	
Sensitivity	0.73 (95% CI: 0.63 to 0.80)	Sensitivity	0.86 (95% CI: 0.78 to 0.91)
Specificity	0.78 (95% CI: 0.68 to 0.86)	Specificity	0.85 (95% CI: 0.53 to 0.97)

Outcome	Importance	Basis	Effect per 1,000 patients tested Pretest probability of 7.8%		Interpretation	Certainty of Evidence
			multiphasic CT scan	contrast-enhanced abdominal MRI		
True positives	Critical	5 Cross-sectional studies (cohort type accuracy study) n = 309	57 (49 to 63)	67 (61 to 71)	10 fewer TP in multiphasic CT scan	Low
False negatives	Critical		21 (15 to 29)	11 (7 to 17)	10 more FN in multiphasic CT scan	
True negative	Critical	5 Cross-sectional studies (cohort type accuracy study) n = 309	720 (626 to 790)	787 (488 to 892)	67 fewer TN in multiphasic CT scan	Low
False positives	Critical		202 (132 to 296)	135 (30 to 434)	67 more FP in multiphasic CT scan	

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FINE NEEDLE ASPIRATION BIOPSY vs. CORE NEEDLE BIOPSY *for diagnosis of patients who do not fulfill the imaging criteria for HCC*

Recommendations

3.1. We recommend the use of core needle biopsy over fine needle aspiration biopsy among patients who do not fulfill the imaging criteria for hepatocellular carcinoma. ***(strong recommendation, low certainty of evidence)***

3.2. We suggest the use of fine needle aspiration biopsy among patients who do not fulfill the imaging criteria for hepatocellular carcinoma when core needle biopsy cannot be done. ***(conditional recommendation, low certainty of evidence)***

The imaging criteria are globally accepted in diagnosing HCC even in the absence of biopsy results. However, images are less readily seen when the size of a liver lesion is small and/or when the liver is cirrhotic. In such cases, a biopsy is needed to come up with a definitive diagnosis of the liver mass, which could be benign regenerating nodules or early HCC.[1]

Evidence to Decision

Diagnostic Accuracy and Harms

We reviewed three retrospective cohort studies comparing the diagnostic accuracy of fine needle aspiration biopsy (FNAB) and core needle biopsy (CNB) in the diagnosis of liver masses seen on prior imaging of the liver.[2-4] These tests were compared with an accepted reference standard (histopathology and/or fulfillment of clinical criteria). FNAB and CNB were shown to have similar sensitivity, specificity, and accuracy for diagnosing benign and malignant liver masses. The FNAB had an 83% sensitivity (95% CI 79%, 86%) while CNB had a 79% sensitivity (95% CI 76%, 83%). Specificity for both FNAB and CNB was at 100%.

The three cohort studies did not report any adverse events. However, fine needle aspiration biopsy (FNAB), because it uses a smaller gauge needle (≥ 20), is considered a safer procedure than CNB when tissue diagnosis is needed in the definitive diagnosis of HCC. However, there may be need for multiple passes, with a higher risk of seeding and bile leak if the patient has portal hypertension.[5] Core needle biopsy (CNB), with the availability of more material on a single pass, provides tissue for immunohistochemical studies, but it may lead to more bleeding complications especially in patients with chronic liver disease.

Certainty of Evidence

The overall certainty of evidence is low because of serious risk of bias and indirectness. All studies were retrospective and the performance of definitive surgery was largely dependent on the biopsy result that may overestimate accuracy. There was indirectness because the population of interest had liver masses seen on imaging but were not all suspected to have liver cancer.

Other Considerations

Cost

There is no study on cost-effectiveness.

Recommendations from Other Groups

2018 ESMO: Pathological diagnosis of HCC is based on a biopsy or a surgical specimen of the tumour.[6]

2021 NCCN: A biopsy is recommended when a lesion is highly suspicious for malignancy at multiphasic CT or MRI but does not meet imaging criteria for HCC.[7]

These guidelines, however, do not recommend a particular biopsy.

Consensus Issues

The discussions centered on accuracy in diagnosis, harm, cost, feasibility, equity, and patient preferences. CNB was preferred because of the following reasons: (1) It completely shows features of the liver architecture that may not always be possible with FNAB. (2) It provides more tissue specimen, sufficient for immunohistochemistry (IHC) staining should this be needed. (3) It is the first-line procedure in obtaining histological diagnosis in most countries. (4) The procedure can be performed by interventional radiologists or by surgeons (both general or liver specialists) and the tissue analyzed by a cytopathologist or a general or liver pathologist. (5) Its cost does not differ much from FNAB. (6) FNAB frequently gives inconclusive results and this may lead to higher costs due to repeated tests. (7) The risk of bleeding post-CNB may be offset by using hemostatic matrix.

FNAB was preferred by other panelists because (1) of consistently good experience in obtaining a diagnosis as long as it is imaging guided and the adequacy of the specimen is immediately checked, (2) patients favor it over CNB due to its less invasive nature, less risk of bleeding, and less cost, (3) accessible to more patients and its use will be more feasible and equitable.

Some panelists did not want to recommend one procedure over the other because of the low certainty of evidence, variation in institutional practices, and lack of experienced specialists in certain areas of the country. Some surgeons proceed with resection of a suspicious but small lesion on imaging and obtain the definitive tissue diagnosis post-operatively.

The final recommendations allow room for discussion between the patient and practitioner with regards individual preferences prior to making the choice between CNB and FNAB.

GRADE Evidence Profile

P *patients with suspected HCC*
I *FNAB*
C *CNB*
O *diagnosing hepatocellular carcinoma*

Table 8. Summary of findings on FNAB vs. CNB in diagnosis of hepatocellular carcinoma

Fine needle aspiration biopsy		Core needle biopsy	
Sensitivity	0.74 to 0.81	Sensitivity	0.73 to 0.84
Specificity	0.98 to 0.99	Specificity	0.98 to 0.99

Outcome	Importance	Basis	Effect per 1,000 patients tested Pretest probability of 7.8%		Interpretation	Certainty of Evidence
			FNAB	CNB		
True positives	Critical	2 Cross-sectional studies (cohort type accuracy study) n = 534	59 to 65	58 to 67	1 more to 2 fewer TP in FNAB	Low
False negatives	Critical		15 to 21	13 to 22	10 more FN in multiphasic CT scan	
True negative	Critical	2 Cross-sectional studies (cohort type accuracy study) n = 534	902 to 911	902 to 911	0 fewer to 0 fewer TN in FNAB	Low
False positives	Critical		9 to 18	9 to 18	0 fewer to 0 fewer FP in FNAB	

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LIVER TRANSPLANTATION vs. LIVER RESECTION *for early stage hepatocellular carcinoma (BCLC 0-A)*

Recommendation

4. There is insufficient evidence to recommend liver transplantation over liver resection among patients with early stage hepatocellular carcinoma (BCLC 0-A). ***(no recommendation, very low certainty of evidence)***

Liver resection (LR) is the treatment of choice for patients with HCC without cirrhosis, while liver transplantation (LT) is considered for those with decompensated cirrhosis.[1] Because of its ability to offer radical resection of the primary tumor/s, treat underlying liver disease and portal hypertension, and minimize the risk of tumor recurrence, liver transplantation is believed to be superior to resection. However, liver transplantation is not always feasible due to cost, scarcity of organs, and the risks associated with immunosuppression.

Evidence to Decision

Benefits and Harms

Sixteen observational studies[2-17] compared the outcomes of early-stage HCC who received LT or LR. Both surgical interventions were comparable in survival at 1- 3-, and 5 years and associated postoperative morbidity and mortality. However, LT was associated with better disease-free survival at 3 years (OR 0.26, 95% CI 0.12 to 0.56)[2-4,7,10,13,15-17] and 5 years (OR 0.20, 95% CI 0.11 to 0.36)[2-4,6-8,10,11,13,15-17].

Certainty of Evidence

The overall certainty of evidence is very low due to the risk of bias, inconsistency, and imprecision.

Other Considerations

Cost

LR was considered more cost-effective than cadaveric LT.[18] The incremental cost-effectiveness ratios (ICERs) of LT versus LR ranged from $111,821/QALY in Singapore to $156,300/QALY in Switzerland. All ICERs were all below the threshold for cost-effectiveness when the 5-year cumulative survival of LT exceeded 84.9%. In addition, the one-time cost of transplant and the 5-year cumulative HCC recurrence rates associated with LR were identified as sensitive parameters dictating cost-effectiveness.[18]

Recommendations from Other Groups

Across all guidelines from relevant organizations[18-23], LR is strongly recommended for early-stage HCC cases that were characterized by solitary tumors, well-preserved liver function, without portal

hypertension or hyperbilirubinemia. LT is strongly recommended for patients who fail to meet the criteria for resection or patients who satisfy certain clinical criteria (Milan, Hangzhou, UCSF).

Consensus Issues

The majority agreed that both interventions are acceptable since they are already treatment procedures for hepatocellular carcinoma (HCC) in the country. However, BCLC 0 is too early cancer stage for LT. The need to analyze prognosis and outcomes for patients with or without portal hypertension or with different Child-Pugh's classes was pointed out as a research gap. Liver resection was favored because of good outcomes and minor complications from clinical experience. It is more cost-effective, more accessible, feasible, and less complicated than LT.

GRADE Evidence Profile

P *patients with early stage hepatocellular carcinoma (BCLC 0-A)*
I *liver transplantation*
C *liver resection*
O *progression-free and overall survival, morbidity and mortality*

Table 9. Summary of findings: liver transplantation vs. liver resection for early-stage hepatocellular carcinoma

Outcome	Importance	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
1-yr Overall Survival	Critical	8 observational studies (n = 1,288)	OR 0.97	0.63 - 1.50	Inconclusive	Very Low
3-yr Overall Survival	Critical	8 observational studies (n = 1,266)	OR 0.68	0.41 - 1.11	Inconclusive	Very Low
3-yr Disease-Free Survival	Critical	10 observational studies (n = 1,629)	OR 0.26	0.12 - 0.56	Net benefit with LT	Very Low
5-yr Overall Survival	Critical	14 observational studies (n = 2,245)	OR 0.68	0.46 - 1.01	Inconclusive	Very Low
5-yr Disease-Free Survival	Critical	13 observational studies (n = 2,274)	OR 0.20	0.11 - 0.36	Net benefit with LT	Very Low
Post-op Mortality	Critical	7 observational studies (n = 1,070)	OR 0.51	0.08 - 3.20	Inconclusive	Very Low
Post-op Complications	Critical	3 observational studies (n = 414)	OR 0.52	0.12 - 2.19	Inconclusive	Very Low

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LIVER TRANSPLANTATION vs. ABLATION *for early stage hepatocellular carcinoma (BCLC 0-A)*

Recommendation

5. There is insufficient evidence to recommend liver transplantation over radiofrequency ablation or microwave ablation among patients with early stage hepatocellular carcinoma (BCLC 0-A). **(*no recommendation, low certainty of evidence*)**

Liver transplantation (LT) is a procedure for tumors that are cannot be surgically resected because of severe liver dysfunction.[1] Radiofrequency ablation (RFA) is the local application of radiofrequency thermal energy to the lesion, while microwave ablation (MWA) involves an implanted electrode delivering high-frequency microwave into the tumor tissue. These ablative procedures are usually done for patients with liver-only disease but do not meet resectability criteria for HCC. In practice, it is done in Child-Pugh A or B patients with a single tumor <4 cm in diameter.[1]

Evidence to Decision

Benefits and Harms

One cohort study[2] (n = 1894) directly showed that first-line LT is associated with an increase in overall survival compared with ablation (HR 4.19, 95% CI 2.2 to 8.01) among newly diagnosed adult patients with hepatocellular carcinoma BCLC 0-A .

There is no study that directly compares adverse events between LT and ablation. Adverse events from RCTs comparing ablation and liver resection (LR), a more limited surgical procedure than LT, are presented. One RCT[3] (n = 120) reported that the number of patients with serious adverse events is higher in LR than ablation (OR 17.96, 95% CI 2.28 to 141.60). Two other RCTs[4,5] (n = 391) reported that the number of serious adverse events is also higher in LR (RR 7.02, 95% CI 2.29 to 21.46; I^2 = 0%).

Certainty of Evidence

The overall certainty of evidence is low because of risk of bias and indirectness. There was high risk of bias due to issues on random allocation and blinding that may affect outcome measurements. There was serious indirectness as the studies compared liver resection, not transplantation, to ablation.

Other Considerations

Cost

The PhilHealth case rate for liver transplantation is PHP 55,000.[6] In private hospitals in Metro Manila, the cost for liver transplantation is estimated to range from PHP 6 million to 9 million.[7] On

the other hand, the Philhealth case rates are PHP 18,000 and PHP 9,700, for laparoscopic and open or percutaneous ablation, respectively.[6] In private hospitals in Metro Manila, the cost ranges from PHP 112,000 to 190,700.[8]

Recommendations from Other Groups

The Barcelona Clinic Liver Cancer (BCLC) staging algorithm and most other algorithms suggest liver transplantation only for unresectable disease[9], and selection of recipients is done chiefly according to the Milan Criteria.[1]

In Korea, where the modified Union for International Cancer Control (mUICC) Staging System is used, liver transplantation is the first treatment choice for patients with single tumor <5 cm or those with small multinodular tumors (≤3 nodules ≤3 cm) and advanced liver dysfunction, who are not candidates for resection.[10]

In the 2018 EASL guidelines, radiofrequency is the standard care for patients with BCLC 0 to A tumors not suitable for surgery (*strong recommendation, high quality evidence*).[11] It is considered first-line treatment for tumors ≤2 cm because of at least equal cost-effectiveness and minimal adverse effects on liver function compared to surgical procedure such as LR. Radiofrequency ablation is strongly recommended as first-line therapy among patients with very early stage HCC (BCLC 0) as long as tumors are located in favorable locations (deep/central location) (*moderate quality evidence*).[11]

Consensus Issues

Ablation was preferred because (1) evidence favoring LT from one retrospective cohort study and indirect evidence on safety (i.e. study on liver resection versus ablation) are inadequate; (2) the complications of LT are of concern, not only from the surgery but also from prolonged immunosuppression; and (3) the cost of LT is much higher and donors are scarce.

Both procedures are expensive and there is concern about equity. Those in the high-income group can avail of these interventions more easily. The equity gap can be narrowed if the government would provide comprehensive reimbursement coverage for those who cannot afford LT or ablation.

GRADE Evidence Profile

P *patients with early stage hepatocellular carcinoma (BCLC 0-A)*
I *liver transplantation*
C *Ablation*
O *mortality, adverse events, serious adverse events*

Table 10. Summary of findings: liver transplantation vs. ablation for early stage hepatocellular carcinoma

Outcome	Importance	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Serious adverse events	Critical	1 RCT (n =120)	OR 17.96	2.28 - 141.60	Net harm with LR	Low

Outcome	Importance	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Serious adverse events	Critical	2 RCTs (n = 391)	RR 7.02	2.29 - 21.46	Net harm with LR	Low
Death (tumors 31-50 mm)	Critical	1 observational study (n = 709)	HR 4.191	2.192 - 8.013	Net benefit with LT	Low
Death (tumors 31-35mm)	Critical	1 observational study (n = 236)	HR 3.433	2.353 - 5.011	Net benefit with LT	Low
Death (tumors 21-30 mm)	Critical	1 observational study (n = 637)	HR 2.440	1.648 - 3.614	Net benefit with LT	Low
Death (tumors ≤ 20mm)	Critical	1 observational study (n = 548)	HR 2.627	1.544 - 4.467	Net benefit with LT	Low

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LIVER RESECTION vs. ABLATION *for early stage hepatocellular carcinoma (BCLC 0-A)*

Recommendation

6. We suggest liver resection over ablation, primarily radiofrequency ablation, for patients with hepatocellular carcinoma BCLC 0-A and compensated liver function. ***(conditional recommendation, very low certainty of evidence)***

Liver resection (LR) is a surgical modality that removes cancerous tissue but maintains preserved functional liver volume for early stage HCC.[1] LR is able to create tumor-free margins under direct vision and resect satellite nodules not identified on preoperative imaging.[2] These are notable advantages of LR over ablation.

Thermal ablation is an imaging-guided procedure wherein heat is generated to destroy tumor cells. It is an alternative treatment option to LR and transplantation for tumors BCLC 0-A.[1] It can minimize iatrogenic injury to surrounding parenchyma, especially in a cirrhotic liver.

Evidence to Decision

Benefits and Harms

Eight randomized controlled trials[3-10] compared liver resection (LR) versus ablation (radiofrequency or RFA, microwave or MWA) for early-stage hepatocellular carcinoma (BCLC 0-A). The overall survival (OS) did not differ between the two treatments. For solitary tumors ≤ 3cm, LR had significantly better OS at 5 years than RFA. The disease-free survival (DFS) was higher with LR.

Post-procedure adverse events were significantly higher in LR. Ablation causes fewer complications (including death, infections, pneumonia, blood loss, liver failure, and pain), has shorter hospital stays, and smaller costs. Early recurrence and intrahepatic recurrence were more common in ablation.

Certainty of Evidence

The overall certainty of evidence is very low due to very serious risk of bias and imprecision. Biases identified are selection bias and reporting bias.

Other Considerations

Cost

RFA is more cost-effective for very early HCC and in the presence of two to three tumors measuring ≤3 cm. Resection offers better survival outcomes at an acceptable cost for solitary early stage tumors >3 cm.[11]

LR and ablation are procedures available in highly specialized centers in the Philippines. The cost of LR or ablation ranges from PHP 150,000.00 to 300,000.00. Laparoscopic LR and MWA entail higher cost compared to RFA.

The Philhealth case rates updated in 2014 for these are as follows: laparoscopic RFA, PHP 18,000; open and percutaneous RFA, PHP 9,700; CT-guidance, additional PHP 8,020; and liver resection, PHP 53,000 to PHP 55,000.

Recommendations from Other Groups

The 2018 EASL[1] recommends both LR and RFA for early and very early HCC. Resection is recommended for HCC tumors on a non-cirrhotic liver (*strong recommendation, low quality evidence*) and solitary HCC of any size, especially for >2 cm with preserved hepatic function (*strong recommendation, moderate quality evidence*).[1]

Radiofrequency is the standard care for patients with BCLC 0 to A tumors not suitable for surgery (*strong recommendation, high quality evidence*).[1] It is the first-line treatment for tumors ≤ 2 cm because of at least equal cost-effectiveness and minimal adverse effects on liver function compared to LR. Patients with very early stage HCC (BCLC 0) can use RFA as first-line therapy as long as tumors are located in favorable locations (deep/central location) (*strong recommendation*, *moderate quality evidence*).[1]

The 2018 KLCA-NCC[12] recommends LR as first-line treatment for patients with solitary HCC (<3 cm) and well-preserved liver function with Child-Pugh A, and no portal hypertension, hyperbilirubinemia (A1).

Consensus Issues

Those favoring ablation did so because overall cost may be lower since the duration of hospital stay, which is longer in LR, can significantly add to the cost. Those favoring LR gave the following reasons: (1) LR is feasible in more hospitals (2) Ablation is more costly and fewer centers have the necessary equipment. (3) The studies that were reviewed had a wide range of ablation techniques and those may not be appropriate for the overall population of patients with HCC.

The panel raised the importance of proper patient selection, thorough evaluation of available resources (i.e., patient's finances, institution's resources, clinician's expertise), and discussion of patient's values and expectations before proceeding with any of these treatment procedures. Shared decision-making was raised as a practice that must be highly encouraged.

The important role of government in making the services available nationwide and help decrease the equity gap in access to these expensive life-saving procedures was highlighted.

GRADE Evidence Profile

P *patients with early stage hepatocellular carcinoma (BCLC 0-A)*
I *liver resection*
C *Ablation*

- *progression-free and overall survival, morbidity and mortality*

Table 11. Summary of findings: liver resection vs. ablation for early-stage hepatocellular carcinoma

Outcome	Importance	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
5-yr OS	Critical	3 RCTs (n =511)	RR 1.10	0.88 - 1.38	Inconclusive	Very Low
5-yr DFS	Critical	3 RCTs (n = 511)	RR 1.46	1.13 - 1.90	Net benefit with LR	Moderate
Overall recurrence	Critical	7 RCTs (n = 994)	RR 0.81	0.73 - 0.91	Net benefit with LR	Low
Treatment-related complications	Critical	7 RCTs (n = 994)	RR 2.97	1.79 - 4.94	Net harm with LR	Very Low
Liver failure	Critical	2 RCTs (n = 448)	RR 1.60	0.20 - 12.90	Inconclusive	Very Low
Physical performance	Critical	1 RCT (n = 48)	RR 0.47	0.30 - 0.75	Net benefit with ablation	Low
Early recurrence ≤3 years	Critical	3 RCTs (n = 616)	RR 0.75	0.60 - 0.93	Net benefit with LR	Moderate
10-yr DFS	Critical	1 RCT (n = 218)	RR 1.67	1.04 - 2.67	Net benefit with LR	Moderate
10-yr OS	Critical	1 RCT (n = 218)	RR 1.13	0.84 - 1.52	Inconclusive	Moderate
In-hospital mortality	Critical	5 RCTs (n = 799)	RR 3.31	0.34 - 32.41	Inconclusive	Very Low
1-yr DFS	Critical	6 RCTs (n = 931)	RR 1.01	0.95 - 1.06	Inconclusive	Low
3-yr DFS	Critical	7 RCTs (n = 994)	RR 1.16	0.92 - 1.48	Inconclusive	Very Low
3-yr OS	Critical	2 RCTs (n = 157)	RR 1.15	0.98 - 1.35	Inconclusive	Moderate
Overall infection	Critical	3 RCTs (n = 600)	RR 5.08	1.87 - 13.82	Net harm with LR	Very Low
Extrahepatic recurrence	Critical	6 RCTs (n = 918)	RR 1.10	0.62 - 1.97	Inconclusive	Very Low
2-yr DFS	Critical	5 RCTs (n = 713)	RR 1.03	0.80 - 1.32	Inconclusive	Very Low
Physical performance D7	Critical	1 RCT (n = 105)	RR 0.47	0.30 - 0.35	Net benefit with ablation	Very Low
1-yr OS	Critical	6 RCTs (n = 904)	RR 1.00	0.95 - 1.06	No effect	Very Low
4-yr OS	Critical	1 RCT (n = 230)	RR 1.25	1.07 - 1.46	Net benefit with LR	Moderate
Blood loss	Critical	6 RCTs (n = 931)	RR 3.61	1.27 - 10.25	Net harm with LR	Very Low
Local intrahepatic recurrence	Critical	6 RCTs (n = 888)	RR 0.34	0.13 - 0.94	Net benefit with LR	Very Low
4-yr DFS	Critical	1 RCT (n = 230)	RR 1.62	1.19 - 2.19	Net benefit with LR	Very Low
Distant intrahepatic recurrence	Critical	6 RCTs (n = 888)	RR 0.77	0.64 - 0.92	Net benefit with LR	Very Low
2-yr OS	Important	6 RCTs (n = 713)	RR 1.04	0.92 - 1.14	Inconclusive	Very Low
Pain	Important	2 RCTs (n = 350)	RR 31.61	16.86- 59.29	Net harm with LR	Low
Pneumonia	Important	2 RCTs (n = 368)	RR 6.32	1.14 - 34.96	Net harm with LR	Low

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TRANSARTERIAL CHEMOEMBOLIZATION vs. SELECTIVE INTERNAL RADIATION THERAPY *for intermediate stage hepatocellular carcinoma*

Recommendation

7. We recommend transarterial chemoembolization over selective internal radiation therapy in intermediate stage (BCLC B) hepatocellular carcinoma. ***(strong recommendation, very low certainty of evidence)***

Most patients with HCC are diagnosed at the intermediate and advanced tumor stages with poor liver function, and less than 20% are eligible for surgery.[1] Conventional transarterial chemoembolization (TACE) or drug-eluting beads (DEB-TACE) and selective internal radiation therapy (SIRT, also called transarterial radioembolization or TARE) are alternative treatment strategies for unresectable hepatocellular carcinoma. The main advantages of radioembolization are the reduced number of treatments needed and the small size of the embolization particles with resultant preserved patency of the tumor feeding arteries. Since this maintains direct access to the tumor vessels, another local treatment, e.g., TACE, could still be performed as a second-line treatment in case of SIRT failure.[3]

Evidence to Decision

Benefits and Harms

We found three randomized control trials (PREMIERE[2], the Mainz trial[3], and SIRTACE[4]) comparing the use of SIRT to either conventional transarterial chemoembolization (cTACE) or DEB-TACE in treating hepatocellular carcinoma (HCC)-belonging to different BCLC stages.

There was no significant difference in the overall survival and one-year progression-free survival between SIRT and TACE. There was also no significant difference in the occurrence of adverse events between SIRT and cTACE. Adverse events include vascular complications, clinical and laboratory parameters.

Certainty of Evidence

The overall certainty of evidence is very low because of (1) serious risk of bias due to lack of blinding and selective reporting (2) indirectness because the population was a mixed group with various BCLC stages (3) inconsistency, and imprecision.

Other Considerations

Cost

Based on a cost comparison study[5] in UK, TACE costs slightly lower than that of Y-90 glass microspheres SIRT.

In 2011, the cost of SIRT in the Philippines was estimated to be at PHP 500,000 to 1,000,000.[6] In a personal communication with an expert in the field (April 2021), the current estimated procedure cost for conventional TACE is PHP 150,000 to 170,000, DEB-TACE is PHP

200,000/session and SIRT PHP 1,000,000 to 1,200,000. Other costs such as hospital and laboratory fees can increase the estimated cost of TACE can increase to PHP 350,000 and DEB-TACE to PHP 500,000, but this can greatly vary based on the specific needs of the patient and the rates of different institutions. However, final costing would greatly depend on the number of sessions needed by the patient, which depends on the size of the tumor.

Recommendations from Other Groups

2018 EASL: For BCLC B, TACE should be carried out selectively (e.g., patients with uni- or pauci-nodular disease without vascular invasion or metastases, no symptoms, and Child-Pugh stage of ≤ B7. (*evidence high; recommendation strong*).[7]

KLCA 2018: TACE for HCC patients with a good performance status without major vascular invasion or extrahepatic spread who are ineligible for surgical resection, liver transplantation, RFA, or PEIT (A1). TARE is an alternative treatment to TACE when patients have preserved liver function and reduction of post-embolization syndrome is required (B2).[8]

Brazilian Society of Hepatology: TACE as the treatment of choice for intermediate HCC (BCLC B) *(high level of evidence; strong recommendation*).[9]

Consensus Issues

The panel concurred that TACE is the standard of care for intermediate stage HCC, and evidence did not show the superiority of SIRT over TACE, in terms of efficacy and safety. It was also important that TACE is much less costly than SIRT and is found in more medical centers. The panelists recognized though that TACE can still be too expensive for the disadvantaged.

GRADE Evidence Profile

P *patients with intermediate stage hepatocellular carcinoma (BCLC B)*
I *transarterial chemoembolization*
C *selective internal radiation therapy*
O *overall survival, progression-free survival, adverse events*

Table 12. Summary of findings: TACE vs. SIRT for intermediate stage (BCLC B) hepatocellular carcinoma

Outcome	Importance	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
1-yr Overall Survival	Critical	3 RCTs (n = 97)	RR 0.83	0.49 - 1.41	Inconclusive	Very Low
1-yr Progression Free Survival	Critical	3 RCTs (n = 97)	RR 2.75	0.43 - 17.73	Inconclusive	Very Low
Adverse Events	Critical	3 RCTs (n = 73)	RR 0.74	0.51 - 1.07	Inconclusive	Very Low

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SELECTIVE INTERNAL RADIATION THERAPY vs. EXTERNAL BEAM RADIOTHERAPY *for intermediate stage hepatocellular carcinoma*

Recommendation

8. There is insufficient evidence to recommend treatment with either selective internal radiation therapy or external beam radiation therapy for hepatocellular carcinoma patients in the intermediate stage (BCLC B). ***(no recommendation, very low certainty evidence)***

Radiotherapy can offer local control of unresectable HCC, including cases with major vascular involvement, and can provide a modality to help bridge patients to potentially curative resection or transplantation.[1] Radiation may be from an internal or an external source.[1] Trans-arterial radioembolization (TARE) or selective internal radiation therapy (SIRT) involves injection of microspheres with β-emitting radioisotope, commonly 90Yttrium. It is usually done as a single therapy or sometimes in two-staged treatments, especially in bilobar HCC. Stereotactic body radiotherapy (SBRT) is a form of external beam radiation therapy (EBRT) that can accurately deliver high dose radiation in small fractions and in a shorter period of time to HCC with acceptable damage to the surrounding normal liver.[2]

Evidence to Decision

Benefits and Harms

There is no randomized controlled trial that directly answers the research question. However, two retrospective cohort studies taken from large nationwide databases directly compared SIRT (selective internal beam radiation) and EBRT (external beam radiation therapy).[3,4] There was no significant difference between the two treatments in terms of overall survival. However, EBRT/SBRT showed a longer mean overall survival by 3.8 months.

Specific adverse events, radiation-related complications, or morbidities were reported in single-arm studies, including fatigue (28% in EBRT vs. 43% in SIRT), lymphopenia (61%), gastritis (11.4%), abdominal pain (17.5%), thrombocytopenia (15.4%).

Certainty of Evidence

The overall certainty of evidence is very low due to (1) serious risk of bias (selection and detection bias) (2) indirectness due to difference in the population in the studies (AJCC 7th edition stages I to III) but the desired population is BCLC B (equivalent to AJCC Stage IIIA) and no direct comparison in morbidity, and (3) imprecision.

Other Considerations

Cost

There is no published cost-effectiveness study on SIRT and EBRT. The estimated cost of procedures in one private tertiary hospital in Manila was obtained: SIRT (one-time treatment, two

admissions) costs PHP 1.3 to 1.5 million; SBRT costs PHP 300,000 to 500,000; and intensity-modulated radiotherapy (IMRT, a form of EBRT) ranges from PHP 250,000 to 300,000.

Recommendation from Other Groups
2021 ESMO: TACE is the standard of care for BCLC B, with transplantation, resection, systemic therapy, and SIRT as alternative treatments.[5,6]

Consensus Issues

The following concerns were highlighted:

1. The need for more studies, especially on specific forms of beam radiation, since different modes of therapy can be categorized into one form of beam radiation but the techniques are different.
2. Performing radiation in large and multifocal lesions can be challenging.
3. The importance of proper patient selection for positive outcomes
4. Both procedures are costly and available in limited centers.

GRADE Evidence Profile

P *patients with intermediate stage hepatocellular carcinoma (BCLC B)*
I *selective internal beam radiation*
C *external beam radiation therapy*
O *progression-free and overall survival, morbidity and mortality*

Table 13. Summary of findings: SIRT vs. EBRT for intermediate stage (BCLC B) hepatocellular carcinoma

Outcome	Importance	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Overall survival	Critical	2 observational studies (n = 2,874)	HR 1.111	0.81 -1.51	Inconclusive	Very Low
Overall survival in months	Critical	2 observational studies (n = 2,874)	MD 4.74 months	1.73-7.75	Net benefit with SIRT	Low
Disease-specific survival	Critical	1 observational study (n = 189)	HR 0.70	0.46 - 1.01	Inconclusive	Low
Disease-specific survival in months	Critical	1 observational study (n = 189)	MD 0 month	11 – 21	SIRT = EBRT	Low

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TRANSARTERIAL CHEMOEMBOLIZATION alone or combined with TARGETED THERAPY *for intermediate stage hepatocellular carcinoma*

Recommendation

9. There is insufficient evidence to recommend the addition of targeted therapy to transarterial chemoembolization in BCLC B hepatocellular carcinoma. ***(no recommendation, low certainty of evidence)***

Transarterial chemoembolization (TACE) is considered standard treatment for intermediate stage HCC. This transcatheter procedure combines the embolization of the tumor-feeding arterial vessels and the infusion of chemotherapeutic agents (e.g., doxorubicin) to achieve both ischemic and cytotoxic effects.[1] Targeted therapy (e.g., sorafenib) modulate specific genes or proteins which affect cell cancer proliferation and are usually reserved for the advanced stage of the disease. It is hypothesized that the combination of targeted therapy and TACE can improve intermediate stage HCC cases that do not respond to TACE alone.[2]

Evidence to Decision

Benefits and Harms

Based on three RCTs, there were no significant differences between response rate, progression-free survival (PFS), overall survival (OS), and time to progression (TTP) for TACE compared with TACE and sorafenib in intermediate stage hepatocellular carcinoma (HCC).[3-5] Measures of patient-reported quality of life (QOL) were worse and adverse events, including treatment-related deaths (TRDs) were more common for the targeted therapy group.

Certainty of Evidence

The overall certainty of evidence is low due to serious risk of bias, inconsistency, and imprecision. The serious risk of bias was due to attrition[3-5], unclear randomization[3,5,] unclear allocation and pharmaceutical funding.[1]

Other Considerations

Cost

One cost-effectiveness analysis compared TACE monotherapy and TACE-sorafenib combination therapy in unresectable (intermediate-advanced stage) HCC. In China, TACE costing $26,951 yields 0.71 quality-adjusted life-years (QALYs), while TACE-sorafenib costing $44,542 yields 1.02 QALYs. The incremental cost-effectiveness ratio of the combination vs. TACE was $56,745 per QALY gained and it can be inferred that TACE monotherapy is more cost-effective.[6]

In the Philippines, one session of TACE is approximately PHP 70,000 to PHP 200,000 while the drug cost for a 21-day treatment with sorafenib (400mg tablet 2x a day) is PHP 208,600.[7]

Recommendations from Other Groups

Currently, there is no recommendation regarding the simultaneous use of targeted therapy and TACE.[2] Hepatology and oncology associations, including the EASL, recommend TACE recommended for intermediate stage HCC while targeted therapy is for advanced stage HCC.[8-11]

Consensus Issues

TACE was preferred because of higher net benefits and lower costs compared to the combination therapy The panel preferred to make no recommendation for now because of awaited results of ongoing trials on newer targeted therapy drugs (other than sorafenib) that may show less toxicities. Patients with residual illness or lesions that are not or poorly treated with TACE and are still classified intermediate stage, according to some experts, may benefit from targeted treatment.

GRADE Evidence Profile

P *patients with intermediate stage hepatocellular carcinoma (BCLC B)*
I *targeted therapy (e.g. sorafenib, Lenvatinib) plus TACE*
C *TACE alone*
O *response rate, progression-free and overall survival. preservation of liver function, and quality of life*

Table 14. Summary of findings: SIRT vs. EBRT for intermediate stage (BCLC B) hepatocellular carcinoma

Outcome	Importance	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Overall survival	Critical	2 RCTs (n = 620)	HR 0.91	0.71 - 1.15	Inconclusive	Low
Progression-Free Survival	Critical	1 RCT (n = 313)	HR 0.99	0.77 - 1.27	Inconclusive	Low
Time-to-Progression	Critical	3 RCTs (n = 700)	HR 0.67	0.44 - 1.03	Inconclusive	Low
Overall Response	Critical	2 RCTs (n = 620)	RR 1.11	0.91 - 1.34	Inconclusive	Very Low
Complete Response	Critical	2 RCTs (n = 620)	RR 1.22	0.89 - 1.68	Inconclusive	Very Low
Partial Response	Critical	2 RCTs (n = 620)	RR 1.05	0.68 - 1.61	Inconclusive	Very Low
Adverse Events	Critical	2 RCTs (n = 617)	RR 1.37	1.07 - 1.75	Net harm with targeted therapy	Moderate
Bleeding	Critical	3 RCTs (n = 697)	RR 1.68	1.12 - 2.52	Net harm with targeted therapy	Moderate
Treatment-Related Deaths	Critical	2 RCTs (n = 617)	RR 3.45	0.72 - 16.50	Inconclusive	Low

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SORAFENIB vs. COMBINATION of IMMUNUNOTHERAPY and BEVACIZUMAB *for advanced stage hepatocellular carcinoma*

Recommendation

10. We suggest the use of combination therapy (atezolizumab plus bevacizumab) over sorafenib as first-line treatment for advanced stage hepatocellular carcinoma in selected patients. ***(conditional recommendation, low certainty of evidence)***

The standard of care for advanced hepatocellular carcinoma is sorafenib.[1-4] Sorafenib is an oral multikinase inhibitor of the Raf serine-threonine kinases and receptor tyrosine kinases implicated in tumorigenesis, tumor progression, and angiogenesis.[1-7]

Immunotherapy (e.g. atezolizumab, pembrolizumab, nivolumab, ipilimumab) with bevacizumab, on the other hand, is a novel systemic treatment for advanced HCC. Bevacizumab is a humanized monoclonal IgG_1 antibody that inhibits VEGF binding to cell surface receptors, and reducing microvascular growth of tumor blood vessels.[1,5-12] Atezolizumab reduces immunosuppressive signals found within the tumor microenvironment thereby increasing T-cell mediated immunity against the tumor by blocking the PD-L1/PD-1 immune checkpoint.[1,5-12] Both bevacizumab and atezolizumab are given intravenously.

Evidence to Decision

Benefits and Harms

One randomized controlled trial[6,13] shows better progression-free and overall survival outcomes and a delay in deterioration of the patient-reported quality of life in combination therapy compared to sorafenib in patients with advanced stage hepatocellular cancer (HCC). However, a greater predilection for bleeding complications is associated with bevacizumab, thus caution should be exercised when using it among patients with advanced liver disease and portal hypertension.

Certainty of Evidence

The overall certainty of evidence is low due to imprecision and serious risk of bias due to lack of blinding.

Other Considerations

Cost

Economic evaluation from the US and China showed that combination therapy had incremental benefits over sorafenib but it was not a cost-effective option.[14-16]

Based on informal surveys in the country, the drug cost for a 21-day treatment with sorafenib (400mg tablet 2x a day) is PHP 208,600.00. Combination therapy with atezolizumab 1200mg and bevacizumab 15mg/kg for a 60kg patient) is PHP 366,815.56. This is reduced to PHP 139,063.12 upon availing of the manufacturer's access program. Additional costs for pre-medications,

administration fees, and other expenses incurred in giving intravenous medications are applicable.

Recommendations from Other Groups

The international guidelines (ASCO[5], ESMO[17], NCCN[18]) state that the combination therapy may be offered as a first-line treatment among patients with advanced HCC. The NCCN particularly recommend the combination therapy for advanced or metastatic and/or unresectable HCC while sorafenib was in the other recommended regimens (Category 1).

Consensus Issues

Combination immunotherapy was favored because of the following reasons: (1) net benefit (2) acceptability (3) subsidy from health insurance is possible making it affordable. However, cost remains a barrier to implementation. Moreover, selection of patients who will benefit most from combined treatment (similar to those enrolled in the RCT) remains crucial.

GRADE Evidence Profile

P *locally advanced, metastatic, and/or unresectable HCC without prior systemic therapy*
I *combination therapy atezolizumab plus bevacizumab (CT)*
C *sorafenib (S)*
O *overall survival, progression-free survival, quality of life, adverse events*

Table 15. Summary of findings: combination therapy (atezolizumab plus bevacizumab) vs. sorafenib for advanced HCC

Outcome	Importance	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Overall Survival	Critical	1 RCT (n = 501)	HR 0.58	0.42 - 0.79	Net benefit with CT	Moderate
Progression-Free Survival	Critical	1 RCT (n = 501)	HR 0.59	0.47- 0.76	Net benefit with CT	Moderate
Quality of life (median time to deterioration)	Critical	1 RCT	HR 0.63	0.46 - 0.85	Net Benefit with CT	Moderate
Serious adverse events	Critical	1 RCT (n = 485)	RR 1.23	0.94 - 1.62	Inconclusive	Low
Discontinuation due to adverse events	Critical	1 RCT (n = 485	RR 1.51	0.89 – 2.56	Inconclusive	Low

CT- combination therapy, S-sorafenib, RCT-randomized controlled trial, HR- hazard ratio, RR-relative risk

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Chapter 4. RESEARCH GAPS

In the search for high-quality evidence for each clinical question and formulation of the recommendations, many queries remain unanswered. These clinical queries on diagnostic and therapeutic interventions provide fertile ground for further research.

Evidence from well-conducted and replicated randomized controlled trials serves as solid basis for clinical decision-making. Unfortunately, many of the surgical or radiotherapeutic modalities for HCC (LT, LR, ablation, SIRT, EBRT) did not have direct comparative studies. Some intervention studies which enrolled subjects with different stages of disease or liver function status (cirrhotics versus non-cirrhotics) did not segregate data for the different subgroups. Results of RCTs on new systemic treatments for advanced HCC are not yet available.

For diagnostic modalities of interest, there is no study comparing the diagnostic accuracy and safety of multiphasic CT scan and contrast-enhanced abdominal MRI in patients with comorbidities (i.e., ascites, renal disease, and pulmonary diseases); conditions wherein the choice of non-invasive imaging modality is critical. There is also no direct comparison between FNAB and CNB in a population suspected with HCC. Given the expertise and interest in HCC in the country, these studies are feasible and can reduce much of the uncertainty in the choice of the appropriate diagnostic pathway for individual patients.

Studies on disease prevalence, disease presentation, mapping of available diagnostic and treatment expertise, evaluation of manpower needs, cost, patients' values and preferences, response to treatment can provide much-needed information to further aid the decision-making process of the relevant stakeholders. These research projects would support holistic care for patients with hepatocellular carcinoma in the country.

Chapter 5. DISSEMINATION AND IMPLEMENTATION OF THE GUIDELINES

Dissemination to Industry Partners, Regulatory Agencies, and Payors

The Task Force will submit the full-text manuscript of this CPG to the Department of Health. The Disease Prevention and Control Bureau of DOH will transmit copies of this CPG to the Philippine Health Insurance Corporation, health maintenance organizations, and pharmaceutical industry partners. DOH will release a memorandum to notify all stakeholders of the publication.

Dissemination to Medical Societies and Training Institutions

This CPG will be presented during conferences and annual conventions of medical societies. Copies of this CPG with the endorsement of relevant medical institutions will be sent to medical schools and libraries to integrate the recommendations in their training curricula, with the support of the faculty members and heads of hospital-based departments, including but not limited to surgery, radiology, pathology, and internal medicine.

Dissemination to Patients and Public in General

The Taskforce, headed by the Steering Committee, will develop a simplified version of this CPG and make it available in a format ready for reproduction and dissemination to patients in clinics and hospitals.

Implementation and Monitoring

The Taskforce will distribute a questionnaire annually, aiming to determine the best practices of relevant stakeholders in terms of diagnosis and management of hepatocellular carcinoma. Monitoring the use of this clinical practice guideline may also be a subject of research by interested parties.

Chapter 6. UPDATING OF THE GUIDELINES

The recommendations herein shall hold until such time that new evidence on screening strategies, diagnostic tests, medicines, and surgical interventions for hepatocellular cancer emerges or other contingencies compel the updating of this CPG.

The HCC Task Force intends to review this CPG no later than 2024.

Chapter 7. AUTHORSHIP, CONTRIBUTIONS, ACKNOWLEDGEMENT

This project would not have been possible without the initiative and funding from the Department of Health.

The DOH neither imposed any condition nor exerted any influence in formulating the final recommendations.

Steering Committee. The steering committee was indispensable in creating working groups and coordinating the preparatory work, evidence review, and formulation of the recommendations. It organized the consensus panel and facilitated the *en banc* meeting. The SC was responsible for the overall organization and management and is accountable for the overall quality of this clinical practice guideline.

Ryan Ruel T. Barroso, MD, FPCS (Hepatopancreatobiliary Surgery and Liver Transplantation, Lead of CPG), Avril P. David, MD, FPCS (Hepatopancreatobiliary Surgery); Irene F. Abisinia, MD, FPCS (Surgical Endoscopy and Minimally-invasive Surgery); Timothy Joseph S. Orillaza, MD, FPSVIR (Vascular and Interventional Radiology); Bernadette Semilla-Lim, MD, FPSG (Gastroenterology); Jonathan C. Nolasco, MD, FPCS (Hepatopancreatobiliary Surgery); Kitchie C. Antipuesto, MD, FPSMO (Medical Oncology); Jennielyn C. Agcaoili-Conde, MD, FPSG (General and Transplant Hepatology); and Glenda Lyn Y. Pua, MD, DPSP (Gastrointestinal and Hepatobiliary Pathology).

Technical Working Group. Asia-Pacific Center for Evidence Based Healthcare, Inc. undertook extensive technical work in (1) searching and summarizing the evidence while ensuring objectivity in each stage of the process, (2) presenting the evidence in the panel meeting, and (3) documenting and writing the final output.

Evelyn O. Salido, MD, MSc (Lead); Maria Vanessa C. Villaruz-Sulit, RN, MSc (Technical Coordinator); Howell Henrian G. Bayona, MSc; Fides Roxanne M. Castor, MD; Eunice Victoria M. Co, RMT, MD, FPCP; Louie F. Dy, MD (cand.); Emmanuel P. Estrella, MD, MSc; Aldrin B. Loyola, MD, MBAH, FPCP; Corinna M. Puyat, MD (cand.); Marvin Jonne L. Mendoza, MD, Beatrice J. Tiangco, MD, MSc, Grazielle S. Verzosa, MD, DPPS, Marc Andrew O. Perez, MD, DPPS, DPSN, DPNSP (Evidence Reviewers); Myzelle Anne J. Infantado, PTRP, MSc (cand.) (Technical Writer); and Leonila F. Dans, MD, MSc (Technical Adviser).

Consensus Panel. This CPG is invaluable because of the involvement and active participation of the panelists from various sectors of healthcare who dedicated their time and effort to share their expertise, experience, and knowledge in scrutinizing the scientific evidence with consideration of other critical factors such as patient values and preferences and current healthcare system in the Philippines. The Panel is composed of the following:

Samuel D. Ang, MD, FPCS (Surgical Oncology); Clarito U. Cairo Jr. MD, FPCOM (Public Health); Ramon L. De Vera, MD, FPCS (Hepatopancreaticobiliary Surgery); Maria Vanessa H. De Villa, MD, FPCS (Hepatopancreaticobiliary Surgery and Liver Transplantation); Jade D. Jamias, MD, FPSG (General and

Transplant Hepatology); Paulo Giovanni L. Mendoza, MD, FPSP (Liver Pathology); Janus P. Ong, MD, FPSG (General and Transplant Hepatology); Teresa T. Sy Ortin, MD, FPROS (Radiation Oncology); Evangeline Santiago, MD, FPAFP (Family Medicine); Ray Sarmiento, MD, FASGE (Surgical Endoscopy, Minimally-invasive Surgery and Upper GI Surgery); Marvin Tamaña, MD, FPSVIR (Vascular and Interventional Radiology); Ernesto C. Tan, MD, FPCS (Hepatopancreatobiliary Surgery); Catherine SC Teh, MD, FPCS (Hepatopancreaticobiliary Surgery and Liver Transplantation); Maria Luisa A. Tiambeng, MD, FPSMO (Medical Oncology); Edhel S. Tripon, MD, FPSG (General and Transplant Hepatology); Billie James G. Uy, MD, FPCS (Hepatopancreatobiliary Surgery); Primo B. Valenzuela, MD, FPCP (Internal Medicine); Ronald G. Yebes, MD, FPCR (Diagnostic Radiology); and Pelagio C. Baldovino, MD, MPH (General Medicine and patient representative).

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Sharlene Marie L. Lao, MD, DPBS; Paul Michael Vincent Lugtu, MD, DPBS; Wesley Wendell B. Cruz, MD, FPCS; Raymond Joseph De Vera, MD DPBS; Onofree O'Connor, MD, DPBS; Lauren Victoria Rellora, MD; Jared Trent Matthew Chua, MD; Xandra Regina Martinez, MD; and Dr. Arlyn Canones, MD, FPCS.

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APPENDIX A. Declaration of Conflicts of Interest

Table 1. COIs of the Consensus Panel members

Name	Expertise/Representation	Affiliation	Summary of Disclosure or other relevant interest
Samuel D. Ang, MD, FPCS	Surgical oncology	Chinese General Hospital & Medical Center	None declared
Pelagio C. Baldovino, MD, MPH	General medicine/ Patient advocate	Baldovino Medical Family Clinic	None declared
Clarito U. Cairo, Jr., MD	Public health	Department of Health	Non-financial interest: Medical Officer IV of Department of Health – Program Manager of Cancer Control
Ramon L. De Vera, MD, FPCS	Hepatopancreatobiliary surgery	Philippine General Hospital	None declared
Maria Vanessa H. De Villa, MD, FPCS	Hepatopancreatobiliary surgery, Liver transplantation	The Medical City	Received study research support from Planet-NCCS Emerald- AstraZeneca (2017-present), participated in SIRveNIB/SARAH Advisory Board Meeting -SIRTEX (makers of SIR Spheres for SIRT) with paid travel and accommodations (August 2017) Co-author, Current role of SIRT in liver tumor
Jade D. Jamias, MD, FPSG	General and transplant hepatology	National Kidney & Transplant Institute	Participated in round table discussion with drug companies (Systemic treatment and tyrosine kinase inhibitor for HCCA), with at least two lectures (2020)
Paulo Giovanni L. Mendoza, MD, FPSP	Liver pathology	Cardinal Santos Medical Center	None declared
Janus P. Ong, MD, FPSG	General and transplant hepatology	The Medical City	Received money and honoraria from clinical trial (Exelixis in 2020 and Hi-Eisai in 2020); Received research support from AstraZeneca (2017), SCRI (2021) Non-financial interest: Member, Hepatology Society of the Philippines
Teresa T. Sy Ortin, MD, FPCR	Radiation oncology	Benavides Cancer Institute, University of Santo Tomas Hospital	None declared
Evangeline P. Santiago, MD, FPAFP	Family medicine	Rizal Medical Center	None declared
Ray I. Sarmiento, MD, FASGE	Surgical endoscopy, MIS and upper GI surgery	Rizal Medical Center, St. Luke's Medical Center, Asian Medical Center	Non-financial interest: Board of Director.

Name	Expertise/Representation	Affiliation	Summary of Disclosure or other relevant interest
			Philippine Association of Laparoscopic and Endoscopic Surgeons (PALES), Philippine Association of Hepatopancreatobiliary Surgeons (PAHPBS)
Marvin T. Tamaña, MD, FPSVIR	Vascular and interventional radiology	Philippine Heart Center, Philippine Society of Vascular and Interventional Radiology	None declared
Ernesto C. Tan, MD, FPCS	Hepatopancreatobiliary surgery	Rizal Medical Center	Non-financial interest: Independent Director, Davao Doctors Hospital
Catherine S.C. Teh, MD, FPCS	Hepatopancreatobiliary surgery and liver transplantation	National Kidney and Transplant Institute	Non-financial Interest: President, PAHPBS Director, Philippine College of Surgeons Cancer Commission
Maria Luisa A. Tiambeng, MD, FPSMO	Medical oncology	Rizal Medical Center	Consultant – Advisory board member (Hi-Eisei, Roche), 2020-2021 Received monetary compensation as Principal investigator of Roche (2010-2017), paid travel to meetings from Hi-eisai and Roche (2010-2019) and speaker's honoraria from Hi-eisai and Roche (2005-2021)
Edhel S. Tripon, MD, FPSG	General and transplant hepatology	Hepatology Society of the Philippines	Technical consultant – HP Diagnostics (2012-present) Investment interests (stocks) – Amihan Corp. The Medical City (2012-present) Received honoraria from SIRTEX, Abbott (2017-2018) with continuous exposure to companies with commercial interest in HCC diagnostics, medications, interventions because of work as present board member of HSP Board
Billie James G. Uy, MD, FPCS	Hepatopancreatobiliary surgery	Rizal Medical Center	Non-financial interest. Board Member, Philippine Society of General Surgeons, Metro Manila Chapter, Philippine Association of Hepato-Pancreato-Biliary Surgeons
Primo B. Valenzuela, MD, FPCP	Internal medicine	Rizal Medical Center	None declared
Ronald G. Yebes, MD, FPCR	Diagnostic radiology	The Medical City	None declared

Table 2. COIs of the Lead CPG Developers/Steering Committee

Name	Expertise/Representation	Affiliation	Summary of Disclosure or other relevant interest
Ryan Ruel T. Barroso, MD, FPCS	Hepatopancreatobiliary surgery and liver transplantation	Rizal Medical Center, Cardinal Santos Medical Center, Chinese General Hospital	Board member of Philippine Association of Hepatopancreatobiliary Surgeons, Inc.
Irene F. Abisinia, MD, FPCS	Surgical endoscopy and MIS	Rizal Medical Center	None declared
Jennielyn C. Agcaoili-Conde, MD, FPSG	General and transplant hepatology	Hepatology Society of the Philippines	None declared
Kitchie C. Antipuesto, MD, FPSMO	Medical oncology	Cardinal Santos Medical Center	None declared
Avril P. David, MD, FPCS	Hepatopancreatobiliary surgery	Rizal Medical Center	None declared
Jonathan C. Nolasco, MD, FPCS	Hepatopancreatobiliary surgery	Rizal Medical Center	None declared
Timothy Joseph S. Orillaza, MD, FPSVIR	Vascular and interventional radiology	Rizal Medical Center	None declared
Glenda Lyn Yu Pua, MD, DPSP	Gastrointestinal and hepatobiliary pathology	Rizal Medical Center	None declared
Bernadette Semilla-Lim, MD, FPSG	Gastroenterology	Rizal Medical Center	None declared

Table 3. COIs of the Evidence Review Experts

Name	Affiliation	Summary of Disclosure or other relevant interest
Evelyn O. Salido, MD, MSc, FPCP, FPRA	UP Manila	None declared
Maria Vanessa V. Sulit, MSc, RN	Asia-Pacific Center for Evidence-Based Healthcare, Inc.	Non-financial interest: Coordinator, Asia-Pacific Center for Evidence-Based Healthcare, Inc. Engage in CPG and EBM work and trainings
Howell Henrian G. Bayona, MSc	University of the Philippines Manila (UP Manila), St. Luke's Medical Center Global City, The Medical City	None declared
Fides Roxanne M. Castor, MD	Philippine General Hospital	None declared
Eunice Victoria M. Co, RMT, MD, FPCP	None	None declared
Louie F. Dy, MD	UP College of Medicine	None declared
Emmanuel P. Estrella, MD, MSc	UP Manila	None declared
Aldrin B. Loyola, MD, MBAH, FPCP	UP College of Medicine	Received funding for clinical trial Bayer AG (2013-2018); Cadila (2012-2021); Astra Zeneca (2009-2016) Non-financial interest: Chair, Committee on CME of the Philippine College of Physicians (FY 2020-2021) Director, Happy to be 10B Inc. Director, Adult Medicine Research Unit
Corinna M. Puyat, MD (cand.)	UP College of Medicine	None declared

Marvin Jonne L. Mendoza, MD	Philippine General Hospital Cancer Institute	Non-financial interest: Chief fellow, PGH Division of Medical Oncology (until March 31, 2021)
Marc Andrew O. Perez, MD, DPPS, DPSN, DPNSP	The Medical City Pangasinan	None declared
Beatrice J. Tiangco, MD, MSc	The Medical City	Received monetary compensation for CANDLE study (5 years) from Philippine Council for Health Research and Development (PCHRD); non-financial support from PCHRD in Early cancer diagnosis in the liver of the Filipinos with chronic hepatitis B infection
Grazielle S. Verzosa, MD, DPPS	East Avenue Medical Center	None declared