The Philippine Clinical Practice Guidelines for the Diagnosis and Management of Hepatocellular Carcinoma 2021

Commissioned by the

RIZAL MEDICAL CENTER
DEPARTMENT OF HEALTH

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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.

**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, 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, and 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 is well-established and will unlikely be changed by new research findings. 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

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Panel Recommendation</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1. We recommend semi-annual screening of patients at risk of developing hepatocellular carcinoma.</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>1.2. We suggest the use of ultrasound, with or without alpha-fetoprotein test, for screening patients at risk of developing hepatocellular carcinoma.</td>
<td>Conditional</td>
<td>Very Low</td>
</tr>
<tr>
<td>2. We recommend the use of a multiphasic, contrast-enhanced CT scan or contrast-enhanced MRI in the diagnosis of hepatocellular carcinoma.</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>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.</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>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.</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td>4. There is insufficient evidence to recommend liver transplantation over liver resection among patients with early-stage hepatocellular carcinoma (BCLC 0-A).</td>
<td>None</td>
<td>Very Low</td>
</tr>
<tr>
<td>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).</td>
<td>None</td>
<td>Low</td>
</tr>
</tbody>
</table>
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
In the Philippines, there is a paucity of local data on 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. 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. 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. Other risk factors include exposure to aflatoxin, tobacco, obesity, diabetes, birth control pills, insulin resistance, hypothyroidism, and hyperlipidemia. 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. 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.

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.

References
3. Estimated number of cases in 2020, Philippines, both sexes, all ages. World Health Organization International
4. Agency for Research on Cancer. at https://gco.iarc.fr/today/online-analystable?v=2020&mode=cancer&mode_population=countries&population=900&population=608&key=asr&sex=0&cancer=39&type=0&statistic=5&population_group=11&ages_group%5B%5D=0&ages_group%5B%5D=1&group_cancer=1&include_nmsc=1&include_nmsc_other=1&collapse-group=0-3

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. 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 for setting the scope of the CPG by identifying and prioritizing clinical questions and formulating these questions, with a specific population, intervention, comparator, and outcomes of interest (PICO), before sending them 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. The key stakeholders who joined the series of online en banc meetings were general and hepatobiliary surgeons, medical and surgical oncologists, liver pathologists, interventional radiologists, family physician, infectious disease specialists, 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 the 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, quasirandomized 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 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 the 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 alphafetoprotein (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 an intermediate stage (BCLC B) hepatocellular carcinoma, should we do liver resection versus ablation (microwave ablation or radiofrequency ablation) to improve progression-free and overall survival, morbidity, and mortality?

9. Among hepatocellular carcinoma patients with an 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. Bases for assessing the certainty of evidence using GRADE approach

<table>
<thead>
<tr>
<th>Observational studies</th>
<th>Certainty of Evidence</th>
<th>Randomized trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely strong association and no major threats to validity</td>
<td>High (Further research unlikely to change our confidence in the estimate of effect)</td>
<td>No serious flaws in study quality</td>
</tr>
<tr>
<td>Strong consistent association and no plausible confounders</td>
<td>Moderate (Further research is likely to have an important impact)</td>
<td>Serious flaws in design or execution or quasi-experimental design</td>
</tr>
<tr>
<td>No serious flaws in study quality</td>
<td>Low (Further research is very likely to have an important impact)</td>
<td>Very serious flaws in design or execution</td>
</tr>
<tr>
<td>Serious flaws in design and execution</td>
<td>Very low (The estimate of effect is very uncertain)</td>
<td>Very serious flaws and at least one other serious threat to validity</td>
</tr>
</tbody>
</table>

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 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.

References

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 ALPHAtoFETOPROTEIN 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 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 sound waves 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 RCT3, the reported sensitivity estimates of US alone, AFP alone, and US + AFP were 84%, 69%, and 92%, respectively. 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. The overall certainty of the evidence for the first recommendation was deemed to be low because of the serious risk of bias and indirectness.2

1.2. The overall certainty of the evidence for the second recommendation was very low due to the 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 the use of AFP due to 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.

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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Importance</th>
<th>Basis</th>
<th>Effect Estimate</th>
<th>95% CI</th>
<th>Interpretation</th>
<th>Overall CoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Critical</td>
<td>1 RCT (n=18,816)</td>
<td>RR 0.60</td>
<td>0.39 - 0.92</td>
<td>Benefit</td>
<td>Very Low</td>
</tr>
<tr>
<td>Proportion of resectable tumors</td>
<td>Critical</td>
<td>1 RCT (n=18,816)</td>
<td>RR 8.06</td>
<td>3.18 - 20.41</td>
<td>Benefit</td>
<td>Very Low</td>
</tr>
<tr>
<td>Detected Stage 1 HCC</td>
<td>Critical</td>
<td>1 RCT (n=8,816)</td>
<td>RR 82.07</td>
<td>5.16 - 1305.59</td>
<td>Benefit</td>
<td>Very Low</td>
</tr>
<tr>
<td>Sn (US)</td>
<td>Critical</td>
<td>1 CS</td>
<td>84.3%</td>
<td>71.4 - 93.0%</td>
<td>-</td>
<td>Low</td>
</tr>
<tr>
<td>Sp (US)</td>
<td>Critical</td>
<td>1 CS</td>
<td>97.0%</td>
<td>96.8 - 97.2%</td>
<td>-</td>
<td>Low</td>
</tr>
<tr>
<td>PPV (US)</td>
<td>Critical</td>
<td>1 CS</td>
<td>6.6%</td>
<td>5.8 - 7.6%</td>
<td>-</td>
<td>Low</td>
</tr>
<tr>
<td>False positive rate (US)</td>
<td>Critical</td>
<td>1 CS</td>
<td>2.98%</td>
<td>2.75 - 3.23%</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Sn (US + AFP)</td>
<td>Critical</td>
<td>1 CS</td>
<td>92.2%</td>
<td>81.1 - 97.8%</td>
<td>-</td>
<td>Low</td>
</tr>
<tr>
<td>Sp (US + AFP)</td>
<td>Critical</td>
<td>1 CS</td>
<td>92.5%</td>
<td>92.1 - 92.9%</td>
<td>-</td>
<td>Low</td>
</tr>
<tr>
<td>PPV (US + AFP)</td>
<td>Critical</td>
<td>1 CS</td>
<td>3%</td>
<td>2.7 - 3.3%</td>
<td>-</td>
<td>Low</td>
</tr>
<tr>
<td>False positive rate (US + AFP)</td>
<td>Critical</td>
<td>1 CS</td>
<td>7.5%</td>
<td>7.1 - 7.9%</td>
<td>-</td>
<td>Low</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Importance</th>
<th>Basis</th>
<th>Screened Group (n=9,373)</th>
<th>Usual Care Group (n=9,443)</th>
<th>Overall CoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year survival</td>
<td>Critical</td>
<td>1 RCT</td>
<td>65.9%</td>
<td>31.2%</td>
<td>Very Low</td>
</tr>
<tr>
<td>3-year survival</td>
<td>Critical</td>
<td>1 RCT</td>
<td>52.6%</td>
<td>7.2%</td>
<td>Very Low</td>
</tr>
<tr>
<td>5-year survival</td>
<td>Critical</td>
<td>1 RCT</td>
<td>48.4%</td>
<td>0</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

References
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 a multiphasic CT scan or MRI with extracellular contrast. 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. 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. 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.

Certainty of Evidence

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

Other Considerations

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

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

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

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

References

of double contrast agents in MR imaging vs. multidetector-row CT. Radiol Med 2009;114.

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 (CBN) 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 CBN 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 CBN had a 79% sensitivity (95% CI 76%, 83%). Specificity for both FNAB and CBN 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 CBN when tissue diagnosis is needed in the definitive diagnosis of HCC. However, there may be a need for multiple passes, with a higher risk of seeding and bile leak if the patient has portal hypertension.3 Core needle biopsy (CBN), 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 the 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 tumor.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 specimens, sufficient for immunohistochemistry (IHC) staining should this be needed. (3) It is the first-line procedure in obtaining a 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 a 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 the 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 regard to individual preferences prior to choosing 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 the diagnosis of hepatocellular carcinoma

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

References

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. 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 studies2-17 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 - 0.56)2,4,7,10,13,15-17 and 5 years (OR 0.20, 95% CI 0.11 - 0.36)2,4,6-8,10,11,13,15-17.

Certainty of Evidence

The overall certainty of the 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. 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 organizations18-23, 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 a 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance</th>
<th>Basis</th>
<th>Effect Estimate</th>
<th>95% CI</th>
<th>Interpretation</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-yr Overall Survival</td>
<td>Critical</td>
<td>8 observational studies (n = 1,288)</td>
<td>OR 0.97</td>
<td>0.63 - 1.50</td>
<td>Inconclusive</td>
<td>Very Low</td>
</tr>
</tbody>
</table>
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 not 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 a 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 study2 (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 - 8.01) among newly diagnosed adult patients with hepatocellular carcinoma BCLC 0 to 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 RCT3 (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 RCTs4,5 (n = 391) reported that the number of serious adverse events is also higher in LR (RR 7.02, 95% CI 2.29 - 21.46; I² = 0%).

Certainty of Evidence

The overall certainty of the evidence is low because of the risk of bias and indirectness. There was a 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 - 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 - 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 - 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 a 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 themselves 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance</th>
<th>Basis</th>
<th>Effect Estimate</th>
<th>95% CI</th>
<th>Interpretation</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>Critical</td>
<td>1 RCT</td>
<td>OR 17.96</td>
<td>2.28 - 141.60</td>
<td>Net harm with LR</td>
<td>Low</td>
</tr>
</tbody>
</table>

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Liver resection (LR) is a surgical modality that removes cancerous tissue but maintains preserved functional liver volume 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 the evidence is very low due to the very serious risk of bias and imprecision. The 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 - 300,000.00. Laparoscopic LR and MWA entail higher costs 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 - 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 the 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, a 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 the government in making the services available nationwide and help decrease the equity gap in access to these expensive life-saving procedures were highlighted.

GRADE Evidence Profile

<table>
<thead>
<tr>
<th>P</th>
<th>patients with early-stage hepatocellular carcinoma (BCLC 0-A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>liver resection</td>
</tr>
<tr>
<td>C</td>
<td>Ablation</td>
</tr>
<tr>
<td>O</td>
<td>progression-free and overall survival, morbidity, and mortality</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance</th>
<th>Basis</th>
<th>Effect Estimate</th>
<th>95% CI</th>
<th>Interpretation</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr OS</td>
<td>Critical</td>
<td>3 RCTs (n = 511)</td>
<td>RR 1.10</td>
<td>0.88 - 1.38</td>
<td>Inconclusive</td>
<td>Very Low</td>
</tr>
<tr>
<td>5-yr DFS</td>
<td>Critical</td>
<td>3 RCTs (n = 511)</td>
<td>RR 1.46</td>
<td>1.13 - 1.90</td>
<td>Net benefit with LR</td>
<td>Moderate</td>
</tr>
<tr>
<td>Overall recurrence</td>
<td>Critical</td>
<td>7 RCTs (n = 994)</td>
<td>RR 0.81</td>
<td>0.73 - 0.91</td>
<td>Net benefit with LR</td>
<td>Low</td>
</tr>
<tr>
<td>Treatment-related complications</td>
<td>Critical</td>
<td>7 RCTs (n = 994)</td>
<td>RR 2.97</td>
<td>1.79 - 4.94</td>
<td>Net harm with LR</td>
<td>Very Low</td>
</tr>
<tr>
<td>Liver failure</td>
<td>Critical</td>
<td>2 RCTs (n = 440)</td>
<td>RR 1.60</td>
<td>-12.90 - -0.75</td>
<td>Inconclusive</td>
<td>Very Low</td>
</tr>
<tr>
<td>Physical performance</td>
<td>Critical</td>
<td>1 RCT (n = 48)</td>
<td>RR 0.47</td>
<td>0.20 - 0.30</td>
<td>Net benefit with ablation</td>
<td>Low</td>
</tr>
<tr>
<td>Early recurrence ≤3 years</td>
<td>Critical</td>
<td>3 RCTs (n = 616)</td>
<td>RR 0.75</td>
<td>0.60 - 0.93</td>
<td>Net benefit with LR</td>
<td>Moderate</td>
</tr>
<tr>
<td>10-yr DFS</td>
<td>Critical</td>
<td>1 RCT (n = 218)</td>
<td>RR 1.67</td>
<td>1.04 - 2.67</td>
<td>Net benefit with LR</td>
<td>Moderate</td>
</tr>
<tr>
<td>10-yr OS</td>
<td>Critical</td>
<td>1 RCT (n = 218)</td>
<td>RR 1.13</td>
<td>-1.52</td>
<td>Inconclusive</td>
<td>Moderate</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>Critical</td>
<td>5 RCTs (n = 799)</td>
<td>RR 3.31</td>
<td>-32.41</td>
<td>Inconclusive</td>
<td>Very Low</td>
</tr>
<tr>
<td>1-yr DFS</td>
<td>Critical</td>
<td>6 RCTs (n = 931)</td>
<td>RR 1.01</td>
<td>-1.06</td>
<td>Inconclusive</td>
<td>Low</td>
</tr>
<tr>
<td>3-yr DFS</td>
<td>Critical</td>
<td>7 RCTs (n = 994)</td>
<td>RR 1.16</td>
<td>0.92 - 1.48</td>
<td>Inconclusive</td>
<td>Very Low</td>
</tr>
<tr>
<td></td>
<td>Stage</td>
<td>RCTs</td>
<td>RR</td>
<td>95% Confidence Interval</td>
<td>Conclusion</td>
<td>Certainty</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------</td>
<td>------</td>
<td>----</td>
<td>-------------------------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>3-yr OS</td>
<td>Critical</td>
<td>2</td>
<td>1.15</td>
<td>0.98 - 1.35</td>
<td>Inconclusive</td>
<td>Moderate</td>
</tr>
<tr>
<td>Overall infection</td>
<td>Critical</td>
<td>3</td>
<td>5.08</td>
<td>1.87 - 13.82</td>
<td>Net harm with LR</td>
<td>Very Low</td>
</tr>
<tr>
<td>Extrahepatic recurrence</td>
<td>Critical</td>
<td>6</td>
<td>1.10</td>
<td>-1.97 - -1.32</td>
<td>Inconclusive</td>
<td>Very Low</td>
</tr>
<tr>
<td>2-yr DFS</td>
<td>Critical</td>
<td>5</td>
<td>1.03</td>
<td>0.62 - 0.80</td>
<td>Inconclusive</td>
<td>Very Low</td>
</tr>
<tr>
<td>Physical performance D7</td>
<td>Critical</td>
<td>1</td>
<td>0.47</td>
<td>0.30 - 0.35</td>
<td>Net benefit with ablation</td>
<td>Very Low</td>
</tr>
<tr>
<td>1-yr OS</td>
<td>Critical</td>
<td>6</td>
<td>1.00</td>
<td>0.95 - 1.06</td>
<td>No effect</td>
<td>Very Low</td>
</tr>
<tr>
<td>4-yr OS</td>
<td>Critical</td>
<td>1</td>
<td>1.25</td>
<td>1.07 - 1.46</td>
<td>Net benefit with LR</td>
<td>Moderate</td>
</tr>
<tr>
<td>Blood loss</td>
<td>Critical</td>
<td>6</td>
<td>3.61</td>
<td>1.27 - 10.25</td>
<td>Net harm with LR</td>
<td>Very Low</td>
</tr>
<tr>
<td>Local intrahepatic recurrence</td>
<td>Critical</td>
<td>6</td>
<td>0.34</td>
<td>0.13 - 0.94</td>
<td>Net benefit with LR</td>
<td>Very Low</td>
</tr>
<tr>
<td>4-yr DFS</td>
<td>Critical</td>
<td>1</td>
<td>1.62</td>
<td>1.19 - 2.19</td>
<td>Net benefit with LR</td>
<td>Very Low</td>
</tr>
<tr>
<td>Distant intrahepatic recurrence</td>
<td>Critical</td>
<td>6</td>
<td>0.77</td>
<td>0.64 - 0.92</td>
<td>Net benefit with LR</td>
<td>Very Low</td>
</tr>
<tr>
<td>2-yr OS</td>
<td>Important</td>
<td>6</td>
<td>1.04</td>
<td>0.92 - 1.14</td>
<td>Inconclusive</td>
<td>Very Low</td>
</tr>
<tr>
<td>Pain</td>
<td>Important</td>
<td>2</td>
<td>31.61</td>
<td>16.86 - 59.29</td>
<td>Net harm with LR</td>
<td>Low</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Important</td>
<td>2</td>
<td>6.32</td>
<td>1.14 - 34.96</td>
<td>Net harm with LR</td>
<td>Low</td>
</tr>
</tbody>
</table>

References


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)
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 - 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 unio or paucinodular 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 stage 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**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance</th>
<th>Basis</th>
<th>Effect Estimate</th>
<th>95% CI</th>
<th>Interpretation</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-yr Overall Survival</td>
<td>Critical</td>
<td>3 RCTs (n = 97)</td>
<td>RR 0.83</td>
<td>0.49 - 1.41</td>
<td>Inconclusive</td>
<td>Very Low</td>
</tr>
<tr>
<td>1-yr PFS</td>
<td>Critical</td>
<td>3 RCTs (n = 97)</td>
<td>RR 2.75</td>
<td>0.43 - 17.73</td>
<td>Inconclusive</td>
<td>Very Low</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>Critical</td>
<td>3 RCTs (n = 73)</td>
<td>RR 0.74</td>
<td>0.51 - 1.07</td>
<td>Inconclusive</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

**References**


Radiotherapy can offer local control of unresectable HCC. 

**Recommendation**

There is no randomized controlled trial that directly provides a modality to help bridge patients to potentially curative resection or transplantation. Radiation may be from an internal or an external source. 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 - HCC with acceptable damage to the surrounding normal liver.

**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). 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 singlearm studies, including fatigue (28% in EBRT vs. 43% in SIRT), lymphopenia (61%), gastritis (11.4%), abdominal pain (17.5%), thrombocytopenia (15.4%).

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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. Radiation may be from an internal or an external source. 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 - HCC with acceptable damage to the surrounding normal liver.

---

**Certainy 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 - 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.

**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

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

References


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**

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

**References**

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.\(^1\)\(^-\)\(^12\) 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.\(^1\)\(^-\)\(^12\) 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.
Table 15. Summary of findings: combination therapy (atezolizumab plus bevacizumab) vs. sorafenib for advanced HCC

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

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

References


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.

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 Henrigan 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, FPSP (General and Transplant Hepatology); Paulo Giovanni L. Mendoza, MD, FPSP (Liver Pathology); Janus P. Ong, MD, FPSP (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 (Hepatopancreaticobiliary Surgery); Catherine SC Teh, MD, FPCS (Hepatopancreaticobiliary Surgery and Liver Transplantation); Maria Luisa A. Tiambeng, MD, FPSMO (Medical Oncology); Edhel S. Tripon, MD, FPSP (General and Transplant Hepatology); Billie James G. Uy, MD, FPCS (Hepatopancreaticobiliary 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).

The developers of this guideline would like to express gratitude to the following physicians:

Dr. Arlyn Canones, MD, FPCS for her participation during the consensus panel meetings as a resource expert in the field of advanced therapeutic endoscopy; Drs. 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; and Xandra Regina Martinez, MD for their invaluable contribution in the formulation of the clinical questions.

This project would not have been successful without the leadership and guidance of Dr. Evelyn O. Salido, Dr. Leonila F. Dans, and Dr. Maria Rica Lumague.

The developers of this guideline would also like to give special thanks to Dr. Bernadette Heizel Manapat-Reyes for facilitating the consensus panel meeting and to Ms. Myzelle Anne Infantado for collating the evidence base and writing the CPG manuscript.
## APPENDIX A. Declaration of Conflicts of Interest

### COIs of the Consensus Panel members

<table>
<thead>
<tr>
<th>Name</th>
<th>Expertise/Representation</th>
<th>Affiliation</th>
<th>Summary of Disclosure or other relevant interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samuel D. Ang, MD, FPCS</td>
<td>Surgical oncology</td>
<td>Chinese General Hospital &amp; Medical Center</td>
<td>None declared</td>
</tr>
<tr>
<td>Pelagio C. Baldovino, MD, MPH</td>
<td>General medicine/ Patient advocate</td>
<td>Baldovino Medical Family Clinic</td>
<td>None declared</td>
</tr>
<tr>
<td>Clarito U. Cairo, Jr., MD</td>
<td>Public health</td>
<td>Department of Health</td>
<td>Non-financial interest: Medical Officer IV of Department of Health – Program Manager of Cancer Control</td>
</tr>
<tr>
<td>Ramon L. De Vera, MD, FPCS</td>
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<td>None declared</td>
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<td>Maria Vanessa H. De Villa, MD, FPCS</td>
<td>Hepatopancreatobiliary surgery, Liver transplantation</td>
<td>The Medical City</td>
<td>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</td>
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<tr>
<td>Jade D. Jamias, MD, FPSG</td>
<td>General and transplant hepatology</td>
<td>National Kidney &amp; Transplant Institute</td>
<td>Participated in round table discussion with drug companies (Systemic treatment and tyrosine kinase inhibitor for HCCA), with at least two lectures (2020)</td>
</tr>
<tr>
<td>Paulo Giovanni L. Mendoza, MD, FPSP</td>
<td>Liver pathology</td>
<td>Cardinal Santos Medical Center</td>
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<td>Janus P. Ong, MD, FPSG</td>
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<td>The Medical City</td>
<td>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</td>
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<td>None declared</td>
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<td>Family medicine</td>
<td>Rizal Medical Center</td>
<td>None declared</td>
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<tr>
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<td>Rizal Medical Center, St. Luke’s Medical Center, Asian Medical Center</td>
<td>Non-financial interest: Board of Director, Philippine Association of Laparoscopic and Endoscopic Surgeons (PALES), Philippine Association of Hepatopancreatobiliary Surgeons (PAHPBS)</td>
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<tr>
<td>Marvin T. Tamaña, MD, FPSVIR</td>
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<td>Non-financial interest: Independent Director, Davao Doctors Hospital</td>
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<tr>
<td>Catherine S.C. Teh, MD, FPCS</td>
<td>Hepatopancreatobiliary surgery and liver transplantation</td>
<td>National Kidney and Transplant Institute St. Luke’s Medical Center, Makati Medical Center</td>
<td>Non-financial Interest: President, PAHPBS Director, Philippine College of Surgeons Cancer Commission</td>
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### COIs of the Lead CPG Developers/Steering Committee

<table>
<thead>
<tr>
<th>Name</th>
<th>Expertise/Representation</th>
<th>Affiliation</th>
<th>Summary of Disclosure or other relevant interest</th>
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<td>None declared</td>
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### COIs of the Evidence Review Experts

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Summary of Disclosure or other relevant interest</th>
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<tbody>
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<td>Asia-Pacific Center for Evidence-Based Healthcare, Inc.</td>
<td>Non-financial interest; Coordinator, Asia-Pacific Center for Evidence-Based Healthcare, Inc. Engage in CPG and EBM work and trainings</td>
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<tr>
<td>Louie F. Dy, MD</td>
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<tr>
<td>Name</td>
<td>Institution</td>
<td>Financial Interest/Non-financial Interest</td>
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<tr>
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<tr>
<td>Aldrin B. Loyola, MD, MBAH, FPCP</td>
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<td>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</td>
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<td>Non-financial interest: Chief fellow, PGH Division of Medical Oncology (until March 31, 2021)</td>
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