



Special Contribution

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Expert survey on systemic therapy indications for hepatocellular carcinoma in Korea: bridging clinical practice and reimbursement criteria

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This survey aimed to collect expert opinions from multidisciplinary specialists involved in the management of hepatocellular carcinoma (HCC) in Korea regarding real-world criteria for systemic therapy indications. In response to discrepancies between national reimbursement policies and clinical decision-making, members of the Korean Liver Cancer Association and Korean Association for the Study of the Liver participated in a web-based survey from February 4 to 14, 2025. A total of 89 respondents, primarily experienced clinicians, provided their views on major clinical scenarios including infiltrative HCC, bilobar multifocal disease, huge tumors, vascular invasion, extrahepatic metastasis, and transarterial chemoembolization (TACE) refractoriness. There was high agreement for including infiltrative HCC (69.7%), suspected portal vein invasion (70.8%), and TACE refractoriness (82.0%) as systemic therapy indications. TACE refractoriness, in particular, aligns with current guideline definitions. Additionally, over half of respondents (51.7%) supported extrahepatic metastasis under similar conditions. Notably, multidisciplinary discussion was emphasized across

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scenarios, but many respondents also favored allowing primary physician discretion in select cases. This report provides consolidated expert input to inform future updates to reimbursement policies and promote alignment with real-world clinical practice. These findings may help bridge the gap between national coverage criteria and clinical decision in systemic therapy for HCC. (*J Liver Cancer* 2025;25:160-168)

Keywords: Carcinoma, hepatocellular; Systemic therapy; Reimbursement mechanisms; TACE refractoriness; Portal vein invasion

INTRODUCTION

Systemic therapy plays a central role in the treatment of patients with advanced hepatocellular carcinoma (HCC), and the use of systemic chemotherapy has been steadily increasing in Korea.¹ However, discrepancies between national reimbursement criteria and real-world clinical practice have repeatedly resulted in claim rejections and prompted requests from clinicians and academic societies for updates to the reimbursement policies administered by the Health Insurance Review and Assessment Service (HIRA).^{2,3}

In August 2024, three academic societies –the Korean Liver Cancer Association (KLCA), the Korean Association for the Study of the Liver (KASL), and the Korean Society of Medical Oncology (KSMO)– convened a joint expert panel to clarify and propose criteria for systemic therapy indications. This panel reached consensus on representative clinical scenarios in which HCC may be considered unresectable or unsuitable for locoregional treatment, including 1) infiltrative HCC, 2) multiple bilobar HCCs, 3) huge tumors, 4) portal vein thrombosis, 5) extrahepatic metastasis, and 6) transarterial chemoembolization (TACE) refractoriness. These opinions were formally submitted to HIRA in November 2024. However, given the limited clinical evidence supporting each scenario, variations in interpretation are inevitable. To better understand expert perspectives on these cases, we conducted an expert survey targeting members of KLCA and KASL. The survey was conducted anonymously and on a voluntary basis, without incentives or external pressure, to ensure the authenticity and independence of responses. While not intended to generate high-level scientific evidence, the survey aimed to gather practical insights from specialists involved in real-world HCC management and to support future consensus development.

METHODS

An expert survey was conducted to assess real-world perspectives on systemic therapy indications in HCC. The survey was

distributed via Google Forms (Google, Mountain View, CA, USA) and remained open from February 4 to 14, 2025. It was distributed by email to 2,366 registered addresses from the KLCA and the KASL and a total of 89 responses were received. Participation was entirely voluntary and anonymous. No incentives or compensation were provided to respondents. The questionnaire included multiple-choice and multiple-response items focusing on clinical scenarios previously defined through expert consensus. The survey questions and response options were developed based on a review of current clinical guidelines, published literature, and prior expert consensus statements.³⁻⁶ Descriptive statistics were used to summarize the responses. All responses were complete, and no missing data were observed for the analyzed items.

Statistical analysis was performed using R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were summarized as frequencies and percentages. The chi-square test or Fisher's exact test was used to evaluate associations between response options. A two-sided *P*-value <0.05 was considered statistically significant.

RESULTS

Respondent characteristics

The baseline characteristics of the 89 respondents are summarized in Table 1. Most respondents were gastroenterologists (71.9%), and 67.0% reported ≥10 years of clinical experience in treating HCC. In terms of systemic therapy experience, 71.9% reported having prescribed atezolizumab plus bevacizumab at least once. These baseline characteristics suggest that the responses reflect insights from clinicians with substantial experience in the real-world management of HCC.

Expert opinions on infiltrative HCC

Regarding infiltrative HCC, respondents were allowed to select multiple applicable criteria for determining systemic therapy eli-

gibility. The most frequently supported criterion was modified Union for International Cancer Control (UICC) stage III or higher with computed tomography (CT)/magnetic resonance

Table 1. Baseline characteristics of survey respondents

	Total (n=89)	P-value
Specialty		<0.001
Gastroenterology	64 (71.9)	
Hepatobiliary surgery	8 (9.0)	
Radiology	10 (11.2)	
Radiation oncology	7 (7.9)	
Clinical experience in HCC treatment		<0.001
≤3 years	6 (6.8)	
4-5 years	8 (9.1)	
6-9 years	15 (17.0)	
≥10 years	59 (67.0)	
Experience prescribing atezolizumab+bevacizumab		<0.001
Yes	64 (71.9)	
No	25 (28.1)	

Data are presented as number (%).

HCC, hepatocellular carcinoma.

imaging (MRI) explicitly stating infiltrative HCC or suspicious for infiltrative HCC, which was selected by 69.7% of participants (Fig. 1). Additionally, 47.2% supported recognizing infiltrative disease even in the absence of direct radiologic description, if the tumor margin showed more than 50% irregular peripheral infiltration based on the clinician's judgment. Only 20.2% agreed that a multidisciplinary discussion or consultation with a relevant specialist should be mandatory to define the case as unsuitable for surgery or locoregional treatment.

Expert opinions on multiple bilobar HCCs

For multiple bilobar HCCs, the most commonly selected criterion (41.6%) was modified UICC stage III or higher, with ≥2 tumors across both lobes and the sum of tumor number and longest diameter >7 cm. Meanwhile, 31.5% of respondents agreed that bilobar HCCs should only be recognized as unsuitable for surgery or locoregional treatment when determined through multidisciplinary discussion or consultation with relevant specialists (Fig. 2).

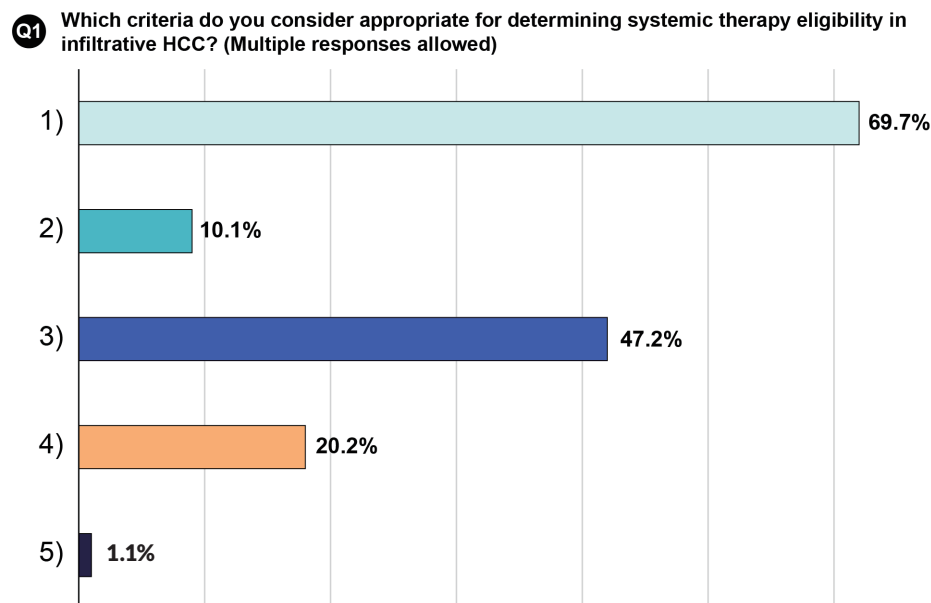


Figure 1. Expert responses on criteria for determining systemic therapy eligibility for infiltrative HCC. These criteria reflect real-world perspectives on initiating systemic therapy. Survey questions: Which criteria do you consider appropriate for determining systemic therapy eligibility in infiltrative HCC? (multiple responses allowed) Response options: 1) Modified UICC stage III or higher with CT/MRI explicitly stating infiltrative HCC or suspicious for infiltrative HCC. 2) Modified UICC stage III or higher with CT/MRI stating only infiltrative HCC; cases labeled suspicious not recognized. 3) Not mentioned in CT/MRI, but recognized if >50% of tumor margin shows irregular infiltration based on the clinician's judgment. 4) Recognize only if multidisciplinary discussion or specialist consultation deems the case unsuitable for surgery or locoregional treatment. 5) Other (please specify). HCC, hepatocellular carcinoma; UICC, Union for International Cancer Control; CT, computed tomography; MRI, magnetic resonance imaging.

Q2 Which criteria do you consider appropriate for determining systemic therapy eligibility in multiple bilobar HCCs? (Multiple responses allowed)

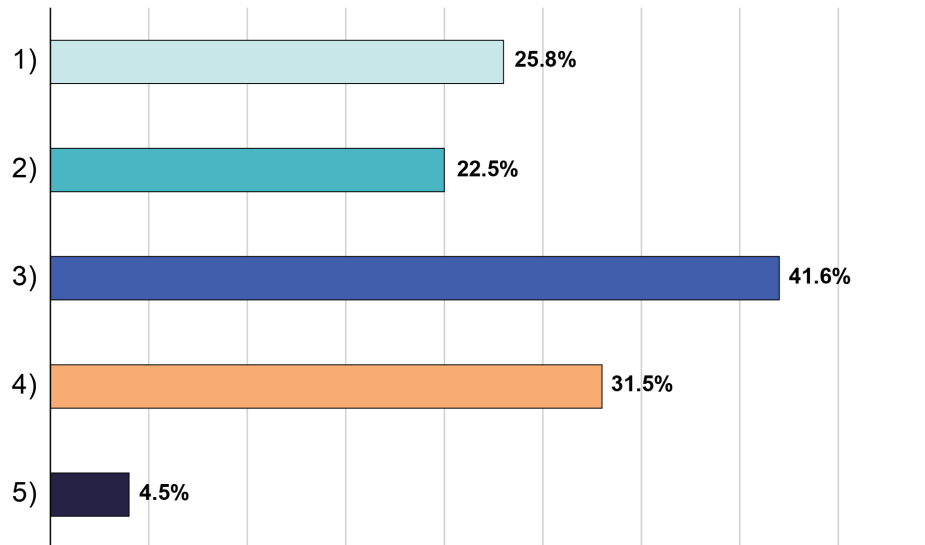


Figure 2. Expert responses on criteria for determining systemic therapy eligibility for multiple bilobar HCCs. Survey question: Which criteria do you consider appropriate for determining systemic therapy eligibility in multiple bilobar HCCs? (multiple responses allowed) Response options: 1) Modified UICC stage III or higher, with ≥ 2 tumors across both hepatic lobes on CT or MRI. 2) Modified UICC stage III or higher, with ≥ 3 tumors across both hepatic lobes on CT or MRI. 3) Modified UICC stage III or higher, with ≥ 2 tumors across both lobes and the sum of tumor number and longest diameter (cm) > 7 . 4) Recognize only if multidisciplinary discussion or specialist consultation deems the case unsuitable for surgery or locoregional treatment. 5) Other (please specify). HCC, hepatocellular carcinoma; UICC, Union for International Cancer Control; CT, computed tomography; MRI, magnetic resonance imaging.

Q3 Which criteria do you consider appropriate for determining systemic therapy eligibility in huge HCC? (Multiple responses allowed)

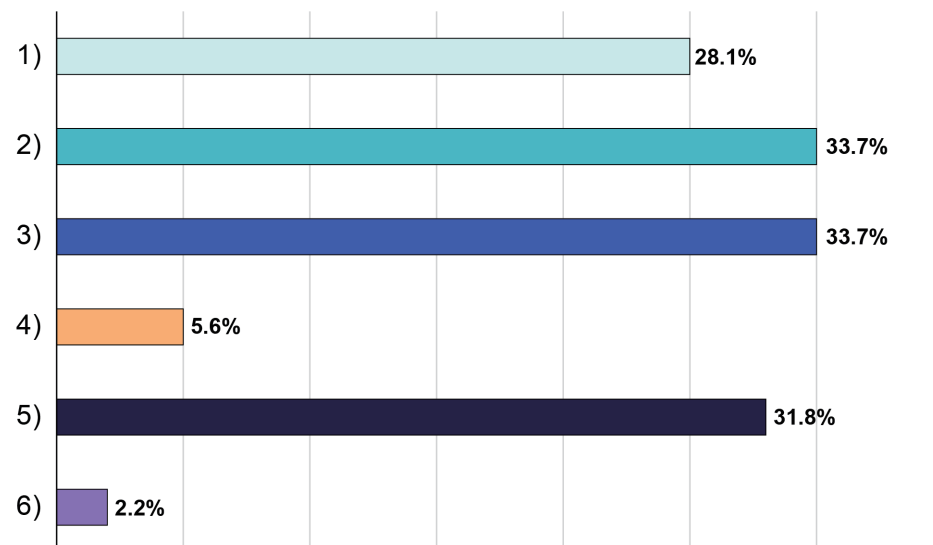


Figure 3. Expert responses on criteria for determining systemic therapy eligibility for huge HCC. Survey question: Which criteria do you consider appropriate for determining systemic therapy eligibility in huge HCC? (multiple responses allowed) Response options: 1) Modified UICC stage III or higher, with CT or MRI describing the tumor as huge HCC. 2) Modified UICC stage III or higher, with tumor diameter ≥ 8 cm on CT or MRI. 3) Modified UICC stage III or higher, with tumor diameter ≥ 10 cm on CT or MRI. 4) Modified UICC stage III or higher, with tumor diameter ≥ 15 cm on CT or MRI. 5) Recognize only if multidisciplinary discussion or specialist consultation deems the case unsuitable for surgery or locoregional treatment. 6) Other (please specify). HCC, hepatocellular carcinoma; UICC, Union for International Cancer Control; CT, computed tomography; MRI, magnetic resonance imaging.

Expert opinions on huge HCC

For huge HCCs, 33.7% of respondents agreed that tumors should be recognized as meeting the indication for systemic therapy when classified as modified UICC stage III or higher and the longest tumor diameter on CT or MRI is ≥ 8 cm, and an equal proportion supported a 10 cm threshold under the same staging condition. Meanwhile, 31.8% of experts stated that huge HCCs should only be recognized as unsuitable for surgery or locoregional treatment when determined through multidisciplinary discussion or consultation with relevant specialists. (Fig. 3).

Expert opinions on portal vein invasion

For portal vein invasion (PVI), portal vein thrombosis or portal vein tumor thrombosis, 53.9% of respondents agreed that the same standard should apply to other vascular invasions including hepatic vein or inferior vena cava involvement and to bile duct invasion. Additionally, 44.9% of experts supported recognizing PVI as an indication for systemic therapy even when suspicious for Vp1 or higher. Another 44.9% agreed that, regardless of PVI level (Vp1-3), recognition could be guided by the outcome of

multidisciplinary discussion or consultation with relevant specialists.

In a subgroup analysis, 70.8% supported recognizing suspected PVI (e.g., suspicious PVI or suspicious portal vein thrombosis), while only 20.2% opposed it. Regarding the threshold level for PVI, 53.9% supported recognition from Vp1 or higher, followed by 32.6% for Vp2 or higher, and 30.3% for Vp3 or higher (Fig. 4).

Expert opinions on extrahepatic metastasis

For extrahepatic metastasis, 51.7% of respondents agreed that systemic therapy may be indicated when metastasis is either histologically confirmed or suspected based on imaging studies including CT, MRI, bone scan, or positron emission tomography-CT (PET-CT). In a subgroup analysis regarding the recognition of suspected lesions, the proportion of respondents who supported recognizing suspected extrahepatic metastasis was higher than those who did not (51.7% vs. 23.6%) (Fig. 5).

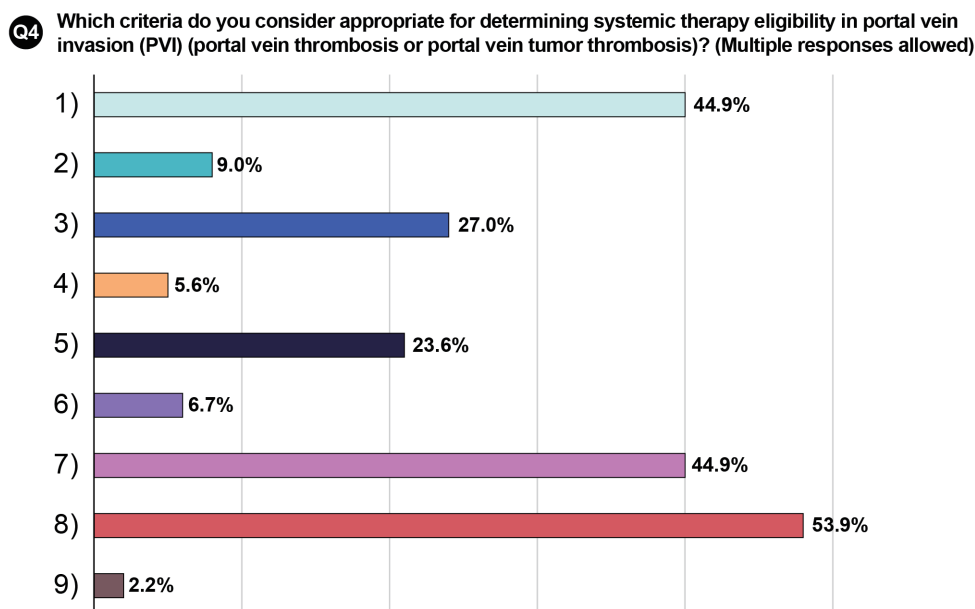


Figure 4. Expert responses on criteria for determining systemic therapy eligibility for PVI. Survey question: Which criteria do you consider appropriate for determining systemic therapy eligibility in PVI, portal vein thrombosis or portal vein tumor thrombosis? (multiple responses allowed) Response options: 1) Recognize Vp1 or higher, including suspected PVI. 2) Recognize Vp1 or higher, excluding suspected PVI. 3) Recognize Vp2 or higher, including suspected PVI. 4) Recognize Vp2 or higher, excluding suspected PVI. 5) Recognize Vp3 or higher, including suspected PVI. 6) Recognize Vp3 or higher, excluding suspected PVI. 7) Recognize if multidisciplinary discussion or specialist consultation deems the case unsuitable for surgery or locoregional treatment. 8) Apply the same standard to hepatic vein, inferior vena cava, or bile duct invasion. 9) Other (please specify). PVI, portal vein invasion.

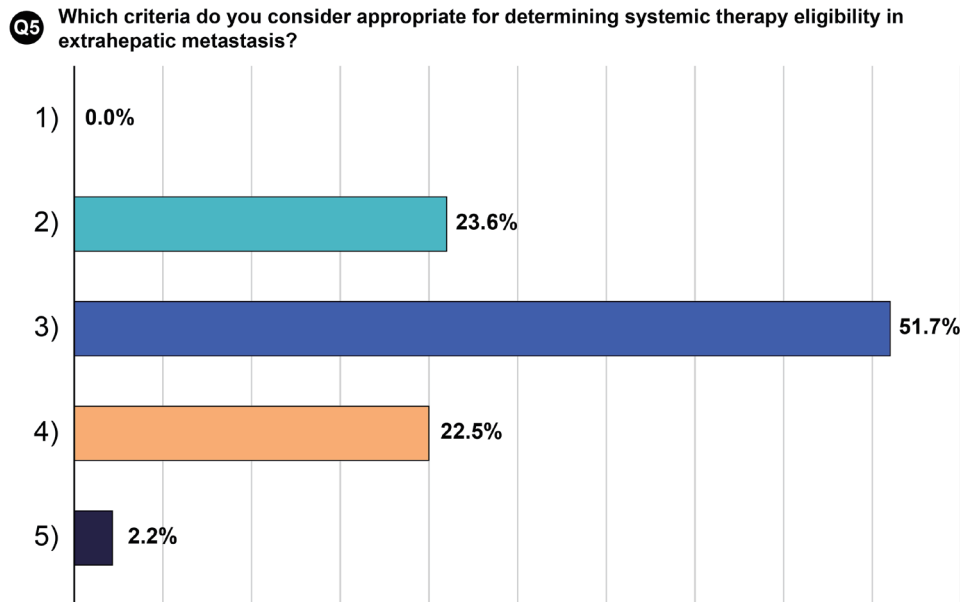


Figure 5. Expert responses on criteria for determining systemic therapy eligibility for extrahepatic metastasis. Survey question: Which criteria do you consider appropriate for determining systemic therapy eligibility in extrahepatic metastasis? Response options: 1) Recognize only when extrahepatic metastasis is histologically confirmed. 2) Recognize only when confirmed by histology or clearly identified on CT, MRI, bone scan, or PET-CT; suspected lesions not recognized. 3) Recognize when histologically confirmed or suspected on CT, MRI, bone scan, or PET-CT. 4) Recognize if histologically confirmed, or if suspected on CT, MRI, bone scan, or PET-CT and subsequently confirmed through multidisciplinary discussion or specialist consultation. 5) Other (please specify). CT, computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography.

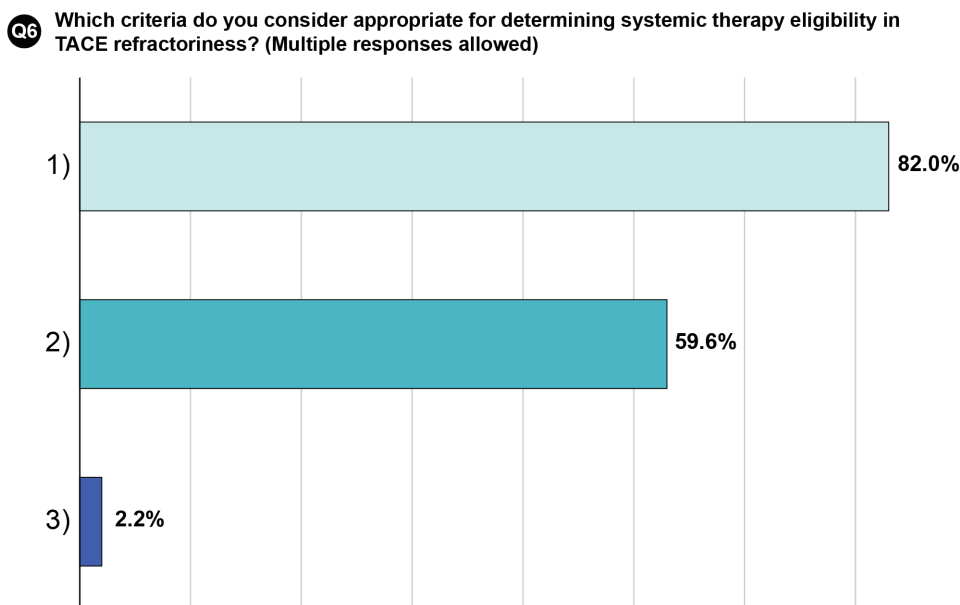


Figure 6. Expert responses on criteria for determining systemic therapy eligibility for TACE refractoriness. Survey question: Which criteria do you consider appropriate for determining systemic therapy eligibility in TACE refractoriness? (multiple responses allowed) Response options: 1) Recognize when, despite at least two on-demand conventional TACE sessions within six months, there is no objective response (complete or partial response), or new vascular invasion or extrahepatic metastasis occurs, based on the 2022 KLCA-NCC Korea practice guidelines for the management of HCC. 2) Recognize when multidisciplinary discussion or specialist consultation determines that, in addition to TACE, other locoregional treatments such as radiotherapy or radiofrequency ablation are also unsuitable. 3) Other (please specify). TACE, transarterial chemoembolization; KLCA, Korean Liver Cancer Association; NCC, National Cancer Center; HCC, hepatocellular carcinoma.

Expert opinions on TACE refractoriness

For TACE refractoriness, 82.0% of respondents agreed that systemic therapy may be indicated when, despite at least two on-demand conventional TACE sessions within 6 months, there is no objective response (complete or partial response) or the development of new vascular invasion or extrahepatic metastasis.^{3,4} Additionally, 59.6% of respondents supported recognizing TACE refractoriness when multidisciplinary discussion or specialist consultation determines that, in addition to TACE, other locoregional treatments such as radiotherapy or radiofrequency ablation are also unsuitable (Fig. 6).

Summary of additional comments

Several additional expert comments were noted. Some respondents suggested that specifying situations where multidisciplinary discussion is unnecessary could improve clarity. Regarding TACE refractoriness, there were opinions that systemic therapy should be permitted even if only TACE, without other locoregional treatments, is deemed unsuitable. Others emphasized that even when systemic therapy is initiated based on a judgment of unsuitability for locoregional treatment, supplementary locoregional therapy should be allowed if certain lesions could benefit from it.

Comments also proposed that, for PVI, systemic therapy reimbursement should be granted regardless of the feasibility of radiotherapy or surgery. Some experts suggested that systemic therapy should also be considered when locoregional treatments are technically feasible but clinically ineffective.

Additionally, concerns were raised that it may be difficult to uniformly define resectability based solely on tumor size, and that current evidence is insufficient to set specific size thresholds.

Another comment suggested that HCC with associated shunts identified on angiography should be considered unsuitable for TACE and eligible for systemic therapy coverage.

DISCUSSION

Through this expert survey, we were able to capture real-world perspectives from frontline clinicians regarding systemic therapy indications for HCC. A high level of agreement was observed regarding the inclusion of infiltrative HCC (69.7%), suspected PVI (70.8%), and TACE refractoriness (82.0%) as indications for systemic therapy. This particularly high agreement on TACE

refractoriness aligns with current guideline definitions.^{3,4} Many responses also highlighted a disconnect between current reimbursement criteria and clinical decision-making in real-world practice. While multidisciplinary discussion was considered important across most scenarios, a substantial proportion of respondents emphasized the need to respect individual physician discretion in selected cases.

While more than half of respondents supported initiating systemic therapy in cases of suspected extrahepatic metastasis, this approach is often constrained by restrictive reimbursement criteria in Korea. Notably, many experts recognized the diagnostic and staging utility of PET-CT in this context. A recent study evaluating dual-tracer PET-CT demonstrated improved accuracy in staging and in identifying HCC in patients with indeterminate lesions or unexplained alpha-fetoprotein elevations.⁷ These findings suggest that broader use of PET-CT could facilitate earlier and more appropriate treatment decisions in advanced HCC.

Bile duct invasion also emerged as a clinically relevant scenario beyond traditional vascular criteria. The demand to expand systemic therapy indications beyond vascular invasion to include bile duct invasion may reflect emerging evidence supporting systemic therapy in such cases. Although bile duct invasion is less common than PVI, it is associated with similarly poor prognosis and often precludes surgical intervention.^{8,9} Growing clinical evidence suggests that systemic therapy may offer benefit in patients with bile duct invasion, particularly when surgical resection is not feasible.⁹

The respondents' support for systemic therapy in TACE refractoriness likely reflects an unmet clinical need in practice, especially where guideline-based treatment is not supported by reimbursement policies. For instance, while the guidelines do not limit systemic therapy for TACE refractoriness based on HCC stage, Korea's reimbursement criteria currently restrict its use in patients with modified UICC stage II TACE refractoriness.

In contrast, for multiple bilobar lesions and huge tumors, expert opinions were more diverse, suggesting variability in clinical practice regarding these scenarios. This lack of consensus may reflect the complexity of clinical decision-making in such cases, where the assessment of tumor burden, liver function, and treatment eligibility can vary significantly across patients. These findings underscore the importance of a multidisciplinary approach, which may facilitate individualized decision-making tailored to each clinical context.

Although the importance of multidisciplinary care has been emphasized in several guidelines and studies,^{3,5,10} our survey re-

vealed that across all items, the opinion that decisions should rely solely on multidisciplinary discussion or specialist consultation did not reach majority agreement. A substantial proportion of clinicians favored allowing primary physician discretion in certain scenarios, highlighting that rigid requirements for mandatory consultation may not align with clinical realities. These findings suggest the need for more flexible and practical criteria that better reflect the complexity and urgency of real-world clinical practice.

This study has several limitations. First, because responses were self-reported by voluntary participants, selection bias cannot be excluded. Although the survey was distributed to a large number of clinicians, the response rate was limited, which reflects a general limitation of voluntary, email-based surveys. Second, the respondents were limited to members of Korean academic societies, and the results were based on a single-round survey, which may affect the generalizability of the findings. Third, data on institutional characteristics (e.g., availability of diagnostic or treatment equipment) were not collected, which may limit interpretation of variations in clinical opinions that could stem from differences in facility readiness. These limitations should be considered when interpreting the results.

Overall, the findings of this survey clearly demonstrate a significant gap between the current reimbursement criteria and clinical realities. There is a strong demand for broader recognition of systemic therapy indications in cases such as infiltrative lesions, vascular invasion, and extrahepatic metastasis, and for TACE refractoriness to be judged solely based on established definitions. We hope that the results of this survey will contribute to shaping reimbursement policies and guiding coverage assessment criteria that acknowledge clinical complexity and support individual physician discretion in real-world clinical practice.

Acknowledgement

We thank all the clinicians who participated in the survey for their valuable time and insights.

Conflicts of Interests

Jeong-Ju Yoo is an editorial board member of Journal of Liver Cancer and was not involved in the review process of this article. Otherwise, the authors have no conflicts of interest to disclose.

Ethics Statement

The requirement for written informed consent was waived. Participation was voluntary, and completing the survey was consid-

ered to imply consent after being informed of the survey's purpose.

Funding Statement

This study received no external funding.

Data Availability

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

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