THE 7TH YONSEI LIVER SUMMIT

Honoring the Past, Empowering the Next

In Honor of Professors Jin Sub Choi and Myeong-Jin Kim's Retirement

2026년 2월 7일 (토)
연세의료원 에비슨 의생명연구센터(ABMRC), 유일한홀

주최 | YONSEI UNIVERSITY HEALTH SYSTEM
세브란스병원 간센터 • 연세암병원 간암센터 • 연세간암연구회

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08:50-09:00	Opening Remarks	김도영 (세브란스병원 간센터장)	
	Congratulatory Remarks	이강영 (세브란스병원장)	
09:00-10:00	**Session 1 From Chronic Liver Disease to HCC: Recent Update**	윤정환 (서울의대), 안상훈 (연세의대)	
09:00-09:20	From Steatosis to Carcinogenesis: Mechanistic Understanding in the Era of MASLD	유수종 (서울의대)	04
09:20-09:40	Updates of Non-Invasive Tests in Liver Disease	김승업 (연세의대)	11
09:40-10:00	Changing Epidemiology of HCC in South Korea and Its Implication	전영은 (차의과학대)	14
10:00-10:10	Coffee Break		
10:10-12:00	**Session 2 International Session**	한광협 (차의과학대), 유희철 (전북의대)	
10:10-10:35	Treatment Strategies for Liver Cirrhosis: From Mesenchymal Stromal Cell Therapy to Realizing Treatment Using Extracellular Vesicles	Shuji Terai (Niigata Univ., Japan)	17
10:35-11:00	Immunotherapy for HCC: Biomarker Development and Unmet Treatment Needs	Yi-Hsiang Huang (National Yang Ming Chiao Tung Univ., Taiwan)	29
11:00-11:25	Trends and Challenges in MRI for HCC Management	Tan Cher Heng (Tan Tock Seng Hospital, Singapore)	40
11:25-11:50	Image-Guided Anatomic Liver Resection	Xiaoying Wang (Fudan Univ., China)	42
11:50-12:00	Discussion		
12:00-13:00	Lunch		
13:00-13:40	**Special Lecture 1**	김순일 (인제의대)	
13:00-13:40	Evolution of Surgical Treatment for HCC during the Last Three Decades in Yonsei Liver Cancer Center	최진섭 (연세의대)	45
13:40-14:20	**Special Lecture 2**	박영년 (연세의대)	
13:40-14:20	Reflections on My Experience with the Evolution of Liver Imaging	김명진 (연세의대)	48
14:20-14:30	Coffee Break		
14:30-15:50	**Session 3 Evolving Imaging and Interventions in HCC**	김기황 (서울의료원), 원종윤 (연세의대)	
14:30-14:50	Prognostic Imaging Findings of HCC	윤자경 (연세의대)	60
14:50-15:10	Recent Update of AI Application in Liver Imaging	신재승 (성균관의대)	65
15:10-15:30	HCC Surveillance: The Cutting-Edge	이형진 (연세의대)	67
15:30-15:50	Recent Update of Radioembolization	현동호 (성균관의대)	78
15:50-16:00	Coffee Break		
16:00-17:20	**Session 4 Updated Multidisciplinary Approach for HCC**	성진실 (연세의대), 김경식 (연세의대)	
16:00-16:20	Tailored Curative Treatments for Early HCC Based on the Preoperative Tumor Characteristics	김나름 (연세의대)	90
16:20-16:40	Regional and Systemic Treatments Focusing on Conversion Surgery in Patients with Locally Advanced HCC	이혜원 (연세의대)	95
16:40-17:00	Downstaging with Immune Checkpoint Inhibitors or TARE in Advanced HCC: Post-Liver Transplantation Outcomes at Severance	김덕기 (연세의대)	98
17:00-17:20	Carbon-Ion Radiation Therapy: Curative and Combined Approaches for HCC	이익재 (연세의대)	103
17:20-17:30	Closing Remarks	최기홍 (연세암병원 간암센터장)	

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Session 1

From Chronic Liver Disease to HCC: Recent Update

좌장: 윤정환 (서울의대), 안상훈 (연세의대)

1. From Steatosis to Carcinogenesis: Mechanistic Understanding in the Era of MASLD
   유수종 (서울의대)
2. Updates of Non-Invasive Tests in Liver Disease
   김승업 (연세의대)
3. Changing Epidemiology of HCC in South Korea and Its Implication
   전영은 (차의과학대)

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From Steatosis to Carcinogenesis: Mechanistic Understanding in the Era of MASLD

유수종
(서울의대)

Su Jong Yu

Department of Internal Medicine and Liver Research Institute,

Seoul National University College of Medicine

The global epidemiology of hepatocellular carcinoma (HCC) has shifted substantially over the past decade, with metabolic dysfunction–associated steatotic liver disease (MASLD) emerging as a dominant underlying etiology alongside the worldwide increase in obesity, type 2 diabetes, and metabolic syndrome, as well as the declining burden of virus-related liver disease.[1,2] A recent multi-society Delphi consensus redefining fatty liver disease according to the presence of metabolic dysfunction has reframed MASLD as a systemic metabolic disorder rather than a diagnosis of

exclusion, placing metabolic injury, chronic inflammation, and immune dysregulation at the center of disease pathogenesis.[1] Within this framework, MASLD is recognized as a heterogeneous disease spectrum ranging from isolated steatosis to metabolic dysfunction–associated steatohepatitis (MASH), progressive fibrosis, cirrhosis, and HCC. MASLD-associated HCC frequently arises in the absence of cirrhosis, indicating that fibrotic burden alone does not adequately explain cancer risk.[2] Clinical and epidemiological evidence further suggests that metabolic derangements, inflammatory activity, and host susceptibility independently contribute to malignant transformation, thereby challenging surveillance paradigms that rely predominantly on advanced fibrosis.[2]

At the cellular level, HCC development in MASLD arises from sustained hepatocyte stress driven by lipid overload and lipotoxicity rather than triglyceride accumulation per se.[3] Excess delivery of free fatty acids from insulin-resistant adipose tissue, increased de novo lipogenesis, and impaired mitochondrial β-oxidation promote the accumulation of toxic lipid intermediates, including saturated fatty acids, ceramides, and diacylglycerols. These lipid species disrupt endoplasmic reticulum homeostasis, enhance oxidative stress, and impair mitochondrial function, leading to hepatocyte injury, cell death, and the release of damage-associated molecular patterns. Prolonged exposure to these insults promotes DNA damage, replication stress, and genomic instability, thereby creating a cellular environment permissive to HCC development.[3]

In the context of MASLD, sustained inflammatory signaling provides a mechanistic bridge between metabolic injury and HCC development.[4] Unlike pathogen-driven

inflammation, metabolic inflammation arises from chronic nutrient excess and altered inter-organ communication. Hepatic macrophages undergo phenotypic reprogramming toward pro-inflammatory and pro-fibrogenic states, producing cytokines such as tumor necrosis factor–α, interleukin-6, and transforming growth factor–β. These mediators perpetuate hepatocyte injury, activate hepatic stellate cells, and promote extracellular matrix deposition. Additional inflammatory amplifiers include inflammasome activation, oxidative stress–derived antigens, and dysregulated gut–liver axis signaling. Together, these processes generate a self-reinforcing inflammatory milieu that facilitates progression from steatosis to steatohepatitis, advances fibrotic remodeling, and supports the development of a tumor-permissive hepatic microenvironment conducive to HCC.[4]

MASLD-associated HCC is accompanied by substantial remodeling of the hepatic immune microenvironment. Single-cell and spatial profiling studies indicate that, during the transition from MASH to HCC, the liver progressively evolves from a predominantly inflammatory state toward an immunologically constrained milieu characterized by dysfunctional effector lymphocytes and expansion of immunosuppressive programs.[5] Experimental studies in steatohepatitis further suggest that $CD8^+$ T cells may acquire metabolically impaired, exhaustion-like phenotypes that promote tissue injury while failing to sustain effective anti-tumor surveillance, providing a mechanistic rationale for concern that immune checkpoint inhibition could be less effective in MASH-driven disease.[6] Clinical evidence, however, does not uniformly support a markedly reduced benefit of immune checkpoint inhibitors (ICIs) in MASLD-associated HCC. Post-hoc analyses of pivotal

immunotherapy trials and subsequent real-world studies indicate that outcomes with contemporary ICI-based regimens, including atezolizumab plus bevacizumab, are not consistently inferior in metabolic or non-viral etiologies compared with other causes of HCC.[7,8] Several factors may account for this apparent discrepancy, including heterogeneity within the MASLD–HCC population, imprecision of etiologic classification in clinical datasets, and the capacity of combination strategies incorporating anti-angiogenic agents to modulate the immunosuppressive tumor microenvironment. Collectively, these observations suggest that while immune dysfunction contributes to HCC development in MASLD, the clinical efficacy of ICIs may be more closely determined by specific immune-metabolic phenotypes and disease context than by etiology alone.[5-8]

Recent mechanistic studies have further refined this paradigm by identifying hepatocyte senescence as a critical, yet reversible, checkpoint in MASLD progression toward HCC.[9] Metabolic stress and DNA damage initially induce a p53-dependent senescence program that constrains hepatocyte proliferation and suppresses tumor initiation. Subsequent activation of oncogenic metabolic and pro-survival signaling pathways can dismantle this barrier. Loss of key metabolic regulators permits senescence reversal, enabling previously damaged hepatocytes or progenitor-like cells to re-enter the cell cycle, propagate accumulated mutations, and ultimately give rise to HCC. Through its close association with metabolic reprogramming and renewed proliferative capacity, senescence escape appears to mark a critical step in the progression from MASH to HCC.[9]

Fibrotic remodeling further consolidates the carcinogenic niche. Beyond serving as

a marker of cumulative injury, fibrosis actively reshapes the mechanical, vascular, and immunological landscape of the liver. Increased tissue stiffness, hypoxia, and altered mechano-transduction influence hepatocyte behavior and immune cell localization, promoting the survival and expansion of transformed clones. These changes reinforce the permissive microenvironment established by chronic inflammation and immune dysfunction, thereby facilitating HCC initiation and progression.[3]

Inter-individual variability in MASLD progression and HCC risk is strongly influenced by genetic susceptibility. Variants affecting hepatic lipid handling, mitochondrial function, and inflammatory signaling—in particular PNPLA3 and TM6SF2—modulate the severity of steatosis, the rate of fibrosis progression, and the likelihood of malignant transformation. Combined genetic risk appears additive, with specific variant constellations conferring substantial increases in the probability of cirrhosis and HCC, whereas loss-of-function variants in select metabolic genes such as HSD17B13 confer protection against disease progression.[10-12] These observations support the integration of genetic risk with metabolic and inflammatory phenotyping to refine surveillance and prevention strategies.

Taken together, current evidence indicates that HCC development in the era of MASLD arises from the combined effects of lipotoxic hepatocyte injury, chronic metabolic inflammation, immune microenvironment reprogramming, reversible senescence escape, and fibrotic remodeling. The conceptual shift introduced by the recent Delphi consensus has sharpened mechanistic focus on metabolic dysfunction as a primary driver of disease progression and HCC risk. Future advances in prevention and therapy will depend on integrated approaches combining genetic

susceptibility, noninvasive assessment of fibrosis, metabolic profiling, and immune characterization to enable precision surveillance and etiology-informed intervention strategies.

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Updates of Non-Invasive Tests in Liver Disease

김승업
(연세의대)

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Yonsei University College of Medicine

Non-invasive tests (NITs) have become an essential component of the diagnostic and prognostic strategy for chronic liver disease (CLD), offering accurate fibrosis assessment, longitudinal disease monitoring, and risk stratification without the limitations of liver biopsy. During the past several years—particularly with the publication of updated guidelines from EASL, AASLD, and KASL—there has been remarkable evolution in both conventional and emerging NIT modalities. This lecture summarizes the most important conceptual and practical updates that have reshaped

clinical pathways in 2024–2025.

First, serum-based algorithms remain the backbone of initial fibrosis screening, especially in metabolic dysfunction–associated steatotic liver disease (MASLD). The use of FIB-4 with age-adjusted thresholds has been standardized across societies, and a two-step strategy combining FIB-4 and vibration-controlled transient elastography (VCTE) is now strongly endorsed for primary care and endocrine clinics. Novel biomarkers—including ADAPT, NIS4, ELF-low-cutoff strategies, and FAST (FibroScan-AST)—are increasingly recognized for intermediate-risk resolution, although cost and availability still limit their widespread adoption. Recent data suggest that integrating traditional biomarkers with metabolic parameters or machine-learning–derived dynamic trajectories can markedly improve prognostic accuracy, especially for long-term liver-related events.

Second, imaging-based elastography has advanced both technically and clinically. VCTE remains the most validated tool globally, with refined cutoffs for MASLD (CAP $\geq$ 250 dB/m for steatosis; LSM > 8–10 kPa for advanced fibrosis) supported by large cohorts including VCTE-Prognosis and V-LINK. New SLD-specific composite algorithms—Agile 3+ and Agile 4—now provide improved specificity for advanced fibrosis and cirrhosis, outperforming LSM alone. Ultrasound 2D-shear wave elastography (2D-SWE) has matured into an equally reliable alternative, with standardized quality metrics and meta-analytic validation across etiologies. Magnetic resonance elastography (MRE) remains the most accurate fibrosis tool, with emerging

applications in portal hypertension, hepatic congestion, multi-organ metabolic phenotyping, and AI-enhanced risk prediction.

Third, portal hypertension assessment is undergoing a major paradigm shift. Non-invasive surrogates of clinically significant portal hypertension (CSPH), particularly LSM–platelet models (Baveno VII criteria and expanded Baveno), now guide variceal screening and beta-blocker initiation. Recent 2025 data highlight the prognostic superiority of spleen stiffness measurement (SSM) via SWE and MRE-derived portal hypertension markers, paving the way for more personalized surveillance.

Finally, NITs are increasingly incorporated into treatment decision pathways. Semaglutide, tirzepatide, and next-generation incretins demonstrate significant reductions in steatosis and stiffness, emphasizing the need for dynamic rather than static fibrosis assessment. Serial NIT-based trajectories—rather than single thresholds—are emerging as validated endpoints in MASLD drug trials and real-world management, enabling earlier intervention and precise risk stratification.

In summary, the landscape of NITs in CLD is rapidly evolving toward a multi-modal, dynamic, and algorithm-driven approach. Integrating serum biomarkers, elastography, portal pressure surrogates, and AI-augmented prediction tools will be central to optimizing patient care across the entire spectrum of chronic liver disease.

Changing Epidemiology of HCC in South Korea and Its Implication

전영은
(차의과학대)

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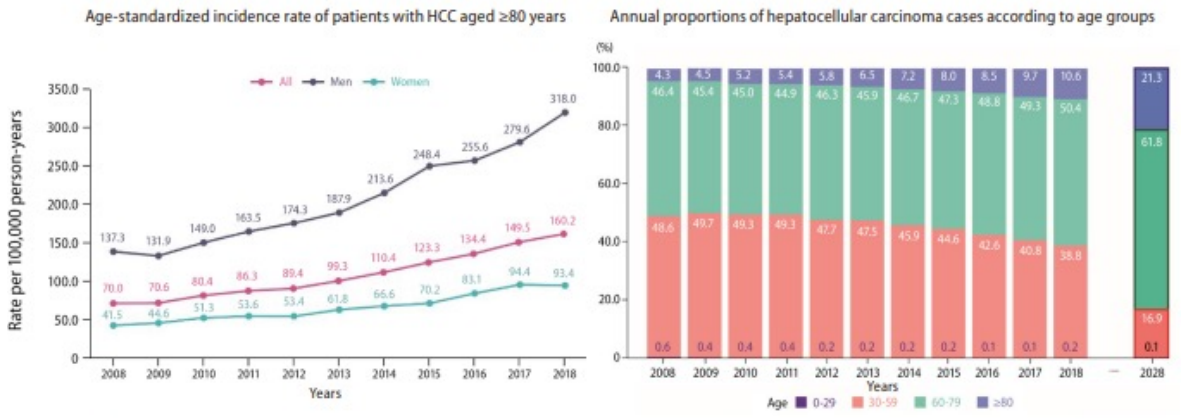
CHA Bundang Medical Center, CHA University

Using National Health Insurance Service (NHIS) data from 2008 to 2018, we investigated changes in the epidemiology of hepatocellular carcinoma (HCC) in South Korea, focusing on incidence rates, underlying etiologies, and treatment patterns. Several notable trends emerged.

First, although the overall incidence of HCC gradually declined during the study period, the incidence among elderly patients aged 80 years or older increased significantly, with an age-standardized incidence rate rising by 0.96% per year.

Second, HCC related to hepatitis B and hepatitis C viruses decreased, whereas HCC attributable to alcohol consumption and metabolic dysfunction–associated steatotic liver disease increased. In parallel, the prevalence of metabolic and systemic comorbidities among patients with HCC—including type 2 diabetes mellitus, chronic kidney disease, hypertension, cardiovascular disease, and cerebrovascular disease—also increased over time. Regarding primary treatment modalities, the use of transarterial therapy decreased, while the proportions of surgical resection, local ablation, and systemic therapy increased. Overall, understanding these evolving epidemiologic trends in HCC is crucial for anticipating future changes in disease burden, diagnosis, and treatment strategies, and for developing effective interventions for vulnerable populations at increased risk.



Session 2

International Session

좌장: 한광협 (차의과학대), 유희철 (전북의대)

1. **Treatment Strategies for Liver Cirrhosis: From Mesenchymal Stromal Cell Therapy to Realizing Treatment Using Extracellular Vesicles**
   Shuji Terai (Niigata Univ., Japan)
2. **Immunotherapy for HCC: Biomarker Development and Unmet Treatment Needs**
   Yi-Hsiang Huang (National Yang Ming Chiao Tung Univ., Taiwan)
3. **Trends and Challenges in MRI for HCC Management**
   Tan Cher Heng (Tan Tock Seng Hospital, Singapore)
4. **Image-Guided Anatomic Liver Resection**
   Xiaoying Wang (Fudan Univ., China)

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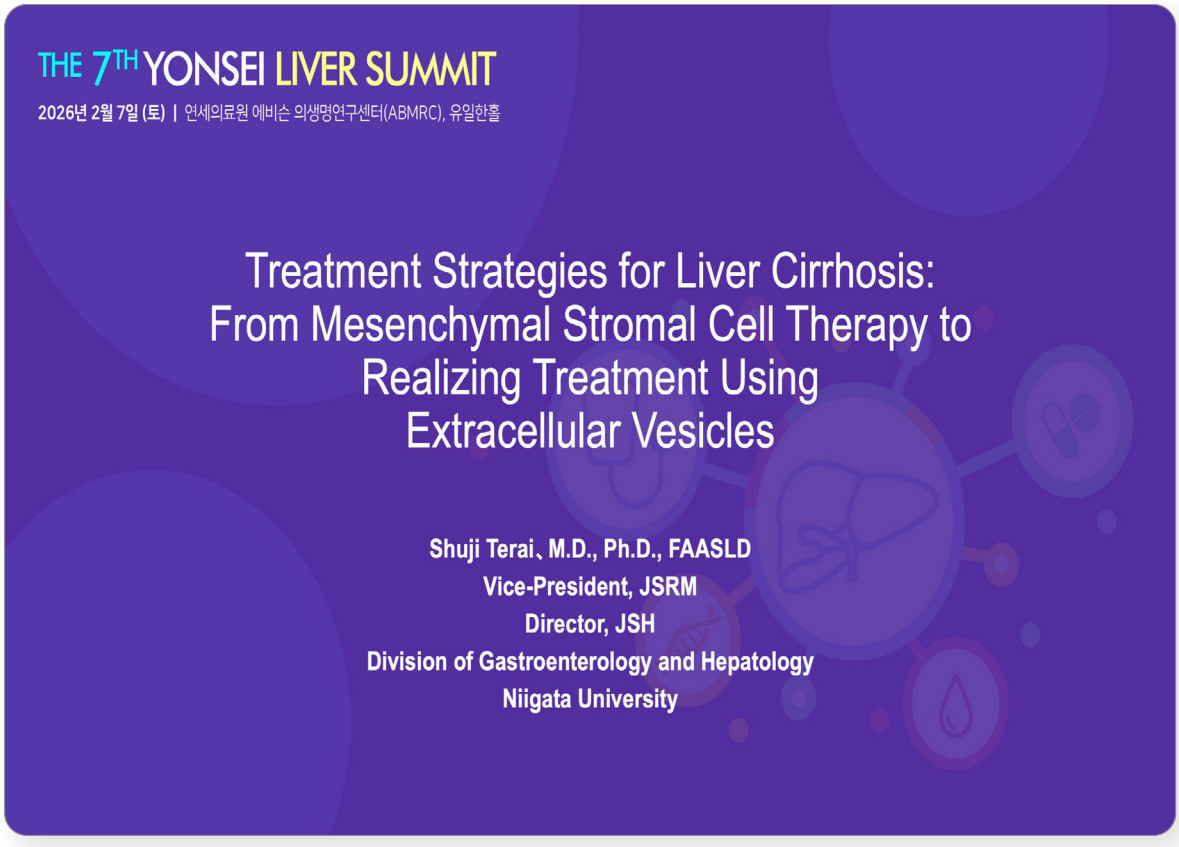
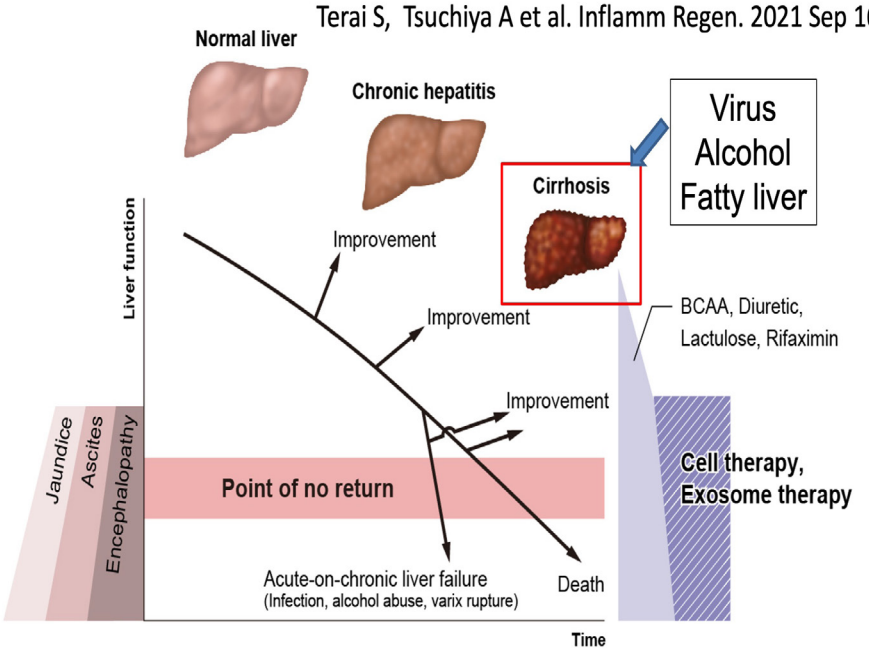
Treatment Strategies for Liver Cirrhosis: From Mesenchymal Stromal Cell Therapy to Realizing Treatment Using Extracellular Vesicles

Shuji Terai
(Niigata Univ., Japan)



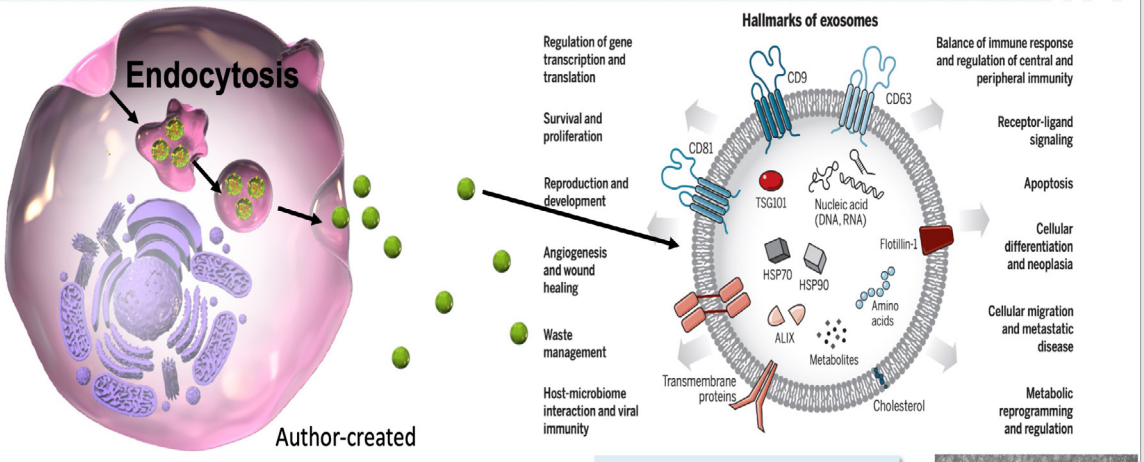
Need for a New Therapy for Cirrhosis

Terai S, Tsuchiya A et al. Inflamm Regen. 2021 Sep 16;41(1):27.



Urgent need for antifibrotic & regenerative therapies

Exosomes (Extracellular vesicle; EVs)



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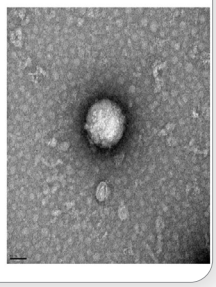
Size : about 100 nm

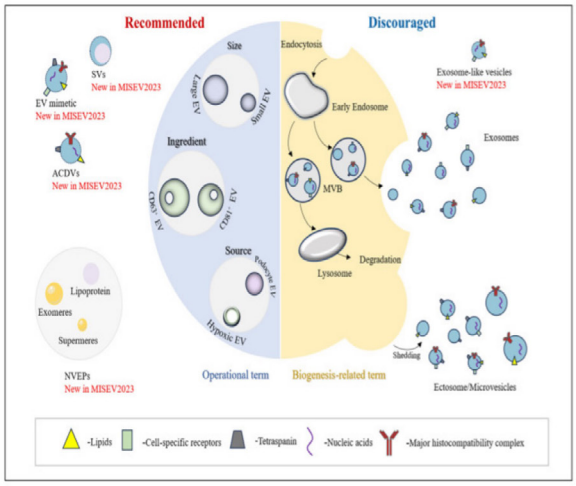
- Stable due to surrounding lipid bilayer
- Proteins and miRNAs are included

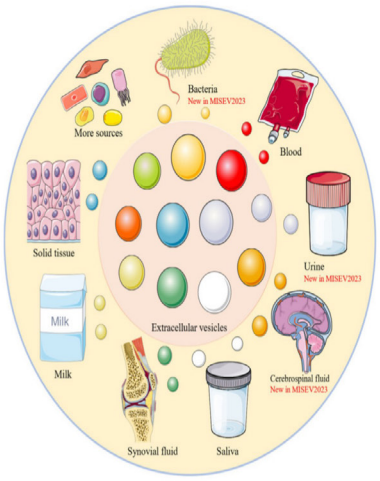


Electron microscope image

Multi-component drug-utilizing DDS

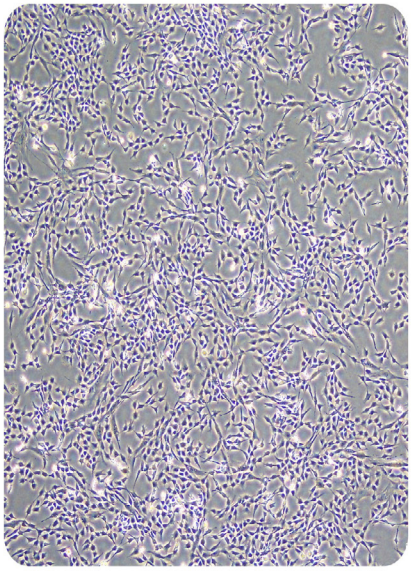
Minimal Information for Studies of Extracellular Vesicles (MISEV): Ten-Year Evolution (2014–2023)





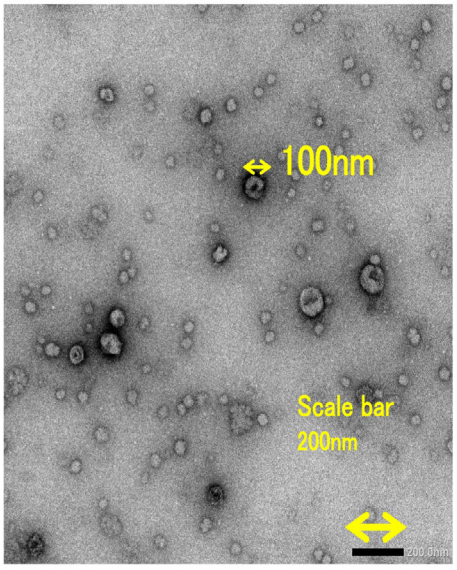
Zhang Y, Lan M, Chen Y. Minimal Information for Studies of Extracellular Vesicles (MISEV): Ten-Year Evolution (2014–2023). *Pharmaceutics*. 2024;16:1394. PMID: 39598518.

Mesenchymal Stromal Cell

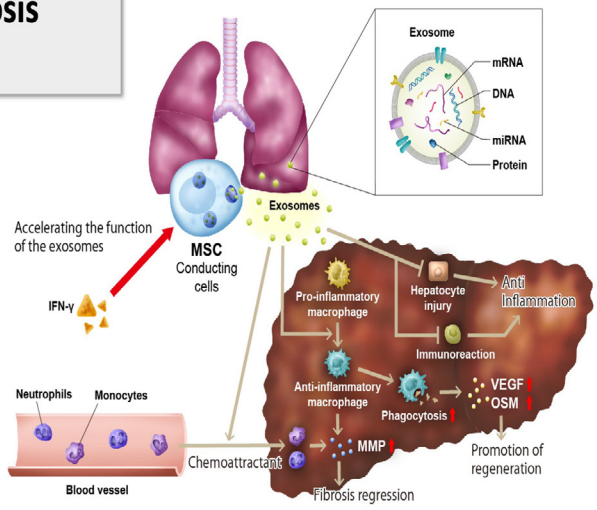


10 µm

Extracellular Vesicle

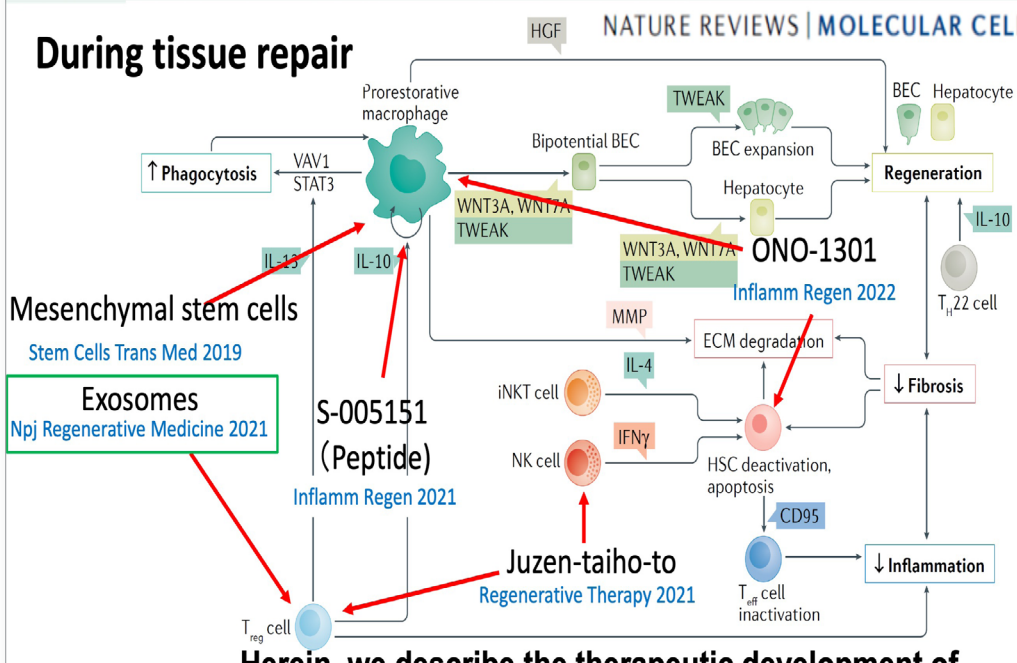


IFN-γ-induced mesenchymal stromal cell-derived extracellular vesicles improve fibrosis in liver cirrhosis and induce regeneration



Takeuchi S, Terai S et al. NPJ Regen Med. 2021 Mar 30;6(1):19.

Drugs and targets of our developing liver regenerative medicine therapies

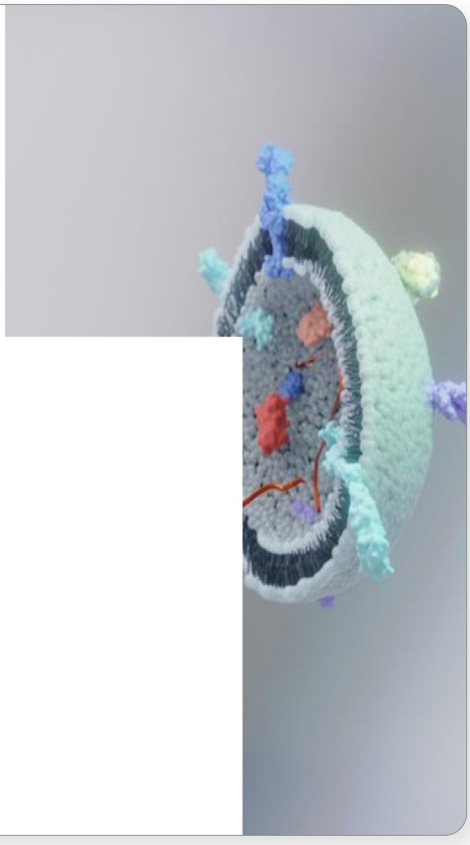


Herein, we describe the therapeutic development of mesenchymal stem cells (MSCs) and their exosomes

Clinical trials for liver cirrhosis conducted at Niigata University (Industry/Physician-Initiated)

	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Allogenic Mesenchymal Stromal Cell	Niigata Univ.		Decompensate liver cirrhosis				Compensate Liver cirrhosis			Complete Data Analysis Underway Next Phase Under Consideration
			Phase I		Phase II		Phase II			
			ROHTO				AMED			
HMGB1 Peptide			Niigata Univ. Basic Research				Compensate Liver cirrhosis			Trial Registration Complete Data Analysis Paper Submission in Progress
							Phase II			
							SHIONOGI			
Extarcellular vesicle (EVs)			Niigata Univ. Basic Research		Development of EV Therapy					
				AMED			AMED			

Latest Trends in the Exosome Market (2025–2032) Market Size Forecast and Clinical Trial Information/Outlook



Market Trends

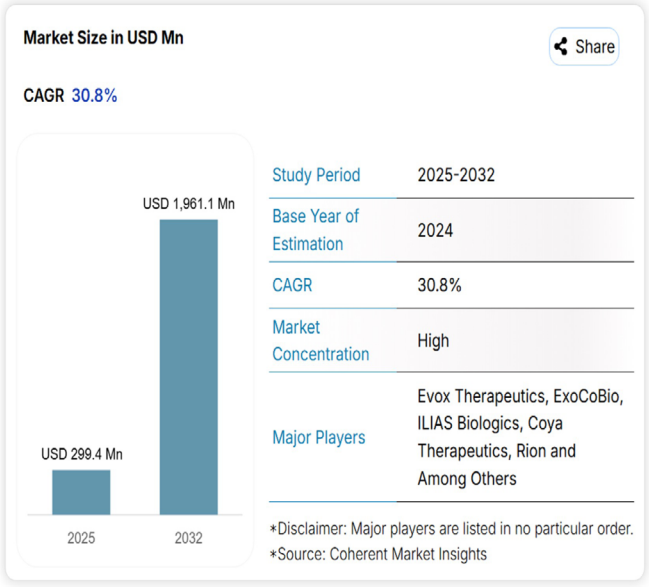
Expanding at an annual rate exceeding 30%

Clinical Trial Information

Currently, multiple trials have advanced to Phase II/III

Perspective

Engineered exosomes are a game changer

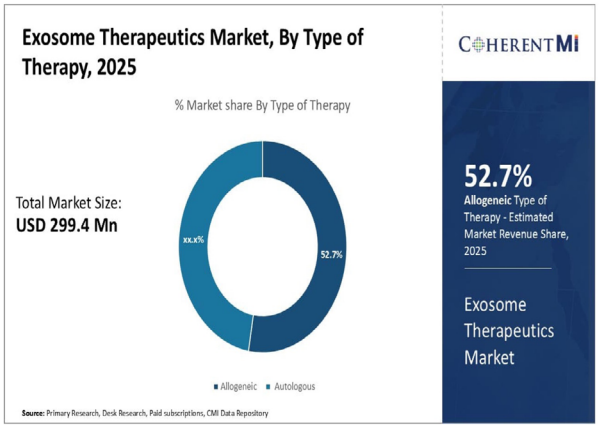


Coherent MI:
Exosome Therapeutics Market SIZE AND SHARE ANALYSIS - GROWTH TRENDS AND FORECASTS (2025-2032)

Market Overview

•Market Size:
Projected to reach USD 299.4 million in 2025 and USD 1.9611 billion (JPY 284.2 billion) by 2032
•CAGR (Compound Annual Growth Rate):
30.8% (2025–2032)
•Growth Factors:
Applications in targeted therapeutics and diagnostics, technological advancements, improved manufacturing efficiency, increased investment by pharmaceutical companies
•Market Drivers:
•Increased Demand for Targeted Therapies:
Enables direct delivery of immunomodulators and antitumor **RNA to tumors** in intractable diseases like cancer.
•Accelerated R&D:
Research underway on large-scale manufacturing, surface modification technologies, and safety/pharmacokinetic evaluations.

Segment Analysis

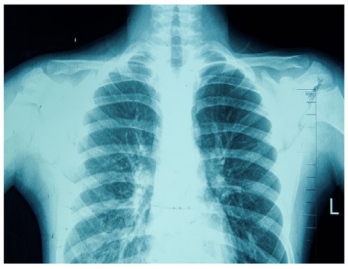


Coherent MI:
Exosome Therapeutics Market SIZE AND SHARE ANALYSIS - GROWTH TRENDS AND FORECASTS (2025-2032)

•By Treatment Type:
Allogeneic exosome therapy holds the largest share at 52.7%. Advantages include batch production from young donors, immediate administration, and reduced immune response. Safety confirmed in FIH clinical trials, attracting major pharmaceutical interest.

•By Target Disease:
Degenerative meniscus injury holds the largest share at **28.3%. This is a mass-market disease affecting over 1 million people annually in the US alone. Clinical evidence suggests exosomes promote tissue repair, anti-inflammation, and accelerated healing.**

•Regional Trends:
North America and Europe lead the market. Growth is anticipated in Asia-Pacific, Latin America, and Africa. Asia, Africa, and Latin America present significant growth potential due to high unmet needs in cancer, cardiovascular, neurological, and inflammatory diseases. Collaboration with local partners and governments offers opportunities for early commercialization.

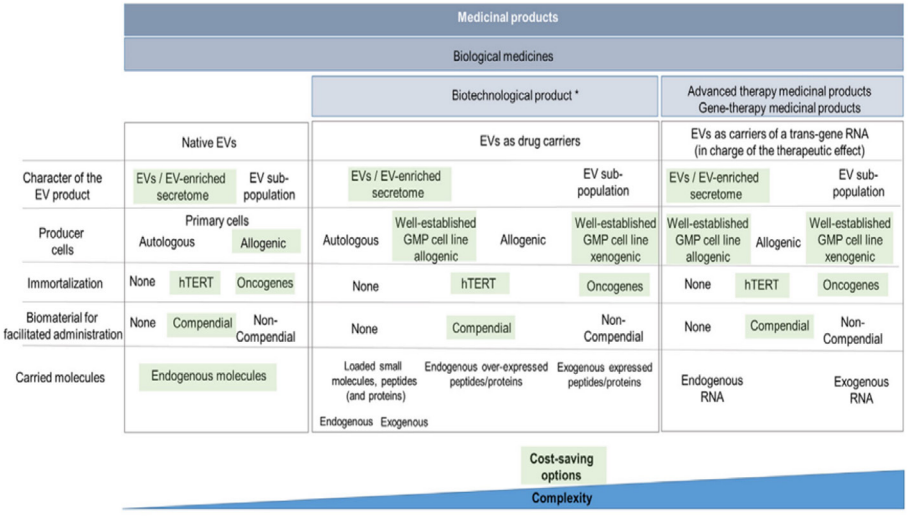


Phase III Clinical Trials List
As of June 8, 2025 / ClinicalTrials.gov

1. Exosome Treatment in Androgenetic Alopecia [NCT06539273]
2. Effect of Microvesicles and Exosomes Therapy on β-cell Mass in Type I Diabetes Mellitus (T1DM) [NCT02138331]
3. Efficacy and Safety of EXOSOME-MSC Therapy to Reduce Hyper-inflammation In Moderate COVID-19 Patients (EXOMSC-COV19) [NCT05216562]
4. The Effect of Stem Cells and Stem Cell Exosomes on Visual Functions in Patients With Retinitis Pigmentosa [NCT05413148]
5. Extracellular Vesicle Treatment for Acute Respiratory Distress Syndrome (ARDS) (EXTINGUISH ARDS) [NCT05354141]
6. Use of Autologous Plasma Rich in Platelets and Extracellular Vesicles in the Surgical Treatment of Chronic Middle Ear Infections [NCT04761562]

As technology advances
The scope and applications continue to expand

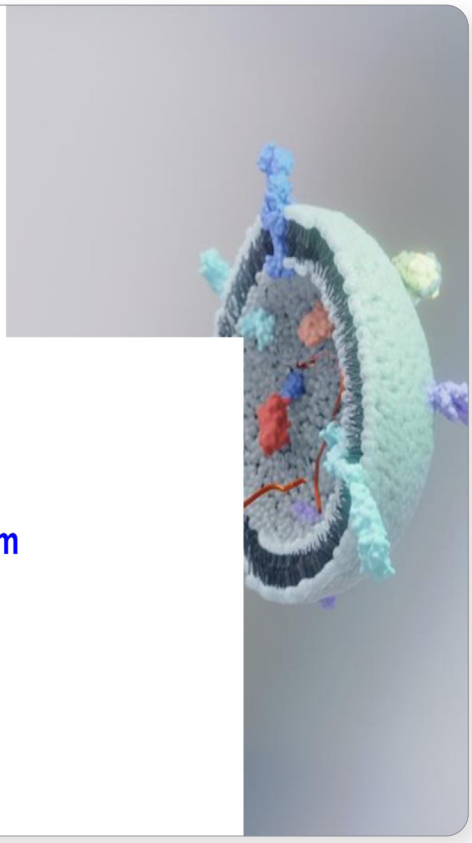
Alongside technological advances
Both fields and targets expand
Not only "natural-type" exosomes simply collected from cells,
but also "modified-type" exosomes undergoing various modifications, drug loading, nucleic acid loading, etc., are emerging.
The fields are also expected to expand beyond regeneration to include cancer, immune diseases, infectious diseases,
and a broader range of targets.



Amanda K.A. Silva, M. Morille, M. Piffoux et al. *Advanced Drug Delivery Reviews* 179 (2021) 114001

Activities Aiming for International Co-creation in the Development of MSC-Derived Extracellular Vesicles (EVs)

Quality, Manufacturing, Regulation, and Global Expansion



Consensu
ISCT · ISEV

Advance
Clinical
Guidance

Data platform (REAP)

May 4th, 2023

Globally Clinic-based unregulated administration is becoming a concern

Research | Open access | Published: 04 May 2023

Uncovering the gray zone: mapping the global landscape of direct-to-consumer businesses offering interventions based on secretomes, extracellular vesicles, and exosomes

Atiyeh Asadpour, Badrul Hisham Yahaya, Katrina Bicknell, Graeme S. Cottrell & Darius Widera

Stem Cell Research & Therapy **14**, Article number: 111 (2023) | Cite this article

4996 Accesses | **19** Citations | **216** Altmetric | Metrics

Abstract

Background

The last decade has seen a significant increase in media attention, industrial growth, and patient interest in stem cell-based interventions. This led to a rise in direct-to-consumer businesses offering stem cell "therapies" for multiple indications with little evidence of safety and efficacy. In parallel, the use of stem cell secretomes as a substitute for stem cell transplantation has become an increasing trend in regenerative medicine with multiple clinical trials currently assessing their efficacy and safety profile. As a result, multiple businesses and private clinics have now started to exploit this situation and are offering secretome-based interventions despite the lack of supporting data. This poses significant risks for the patients and could lead t

Methods

offering secretome-based interventions despite the lack of supporting data. This poses significant risks for the patients and could lead to a credibility crisis in the field.

such business activity requires tight regulations and monitoring by the respective national regulatory bodies to prevent patients from being conned and more importantly from being put at risk.

Approaches to Treatment by JSRM and Regulatory Authorities (PMDA)

Evidence-Based Appropriate Treatment Strategies

JSRM

Review > Regen Ther. 2022 May 19;21:19-24. doi: 10.1016/j.reth.2022.05.003. eCollection 2022 Dec.

Basic points to consider regarding the preparation of extracellular vesicles and their clinical applications in Japan

Atsunori Tsuchiya [1], Shuji Terai [1], Ikki Horiguchi [2], Yasuhiro Homma [3], Atsuhiro Saito [2], Norimasa Nakamura [4 5 6], Yoji Sato [7], Takahiro Ochiya [8], Masahiro Kino-Oka [2]; Working Group of Attitudes for Preparation and Treatment of Exosomes of Japanese Society of Regenerative Medicine

Affiliations + expand

PMID: 35619946 PMCID: PMC9127121 DOI: 10.1016/j.reth.2022.05.003

Abstract

In recent years, extracellular vesicles (EVs) have attracted attention as a new therapeutic tool. In Europe, the United States, and Asia, there is an accelerating trend of moving beyond basic research on clinical trials. However, treatment using EVs is still in the research and development stage, and the general public has insufficient awareness and understanding of the risks involved in ensuring safety and efficacy, the status of laws and regulations, and global research and development trends regarding their use. The Japanese Society for Regenerative Medicine, which has promoted the research and development of regenerative medicine, an innovative medical technology based on the principle of delivering it safely, effectively, and promptly, including the establishment of laws and regulations, would like to express two positions in light of the rapid development of therapies using EVs: 1) concern about treatments that are based solely on the discretion of medical practitioners, and 2) active promotion of treatments based on sound scientific evidence. Because EVs are released from cells, there are many similarities between EVs and processed cells in terms of manufacturing processes and safety hazards. As for efficacy, the mechanism of action of EVs is still unclear, as is the case with

PMDA

Report on Therapeutic Products Based on Extracellular Vesicles (EVs) Including Exosomes

Table of contents

Regenerative Therapy 29 (2025) 43–50

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Review

Guidance on the clinical application of extracellular vesicles*

Shuji Terai [a, m, *], Motohiro Asonuma [b, m], Ayuko Hoshino [c, d], Masahiro Kino-oka [e, f, m], Takahiro Ochiya [g, m, n], Kiyoshi Okada [h, m], Yoji Sato [i, m], Yuki Takahashi [j, n], Morikuni Tobita [k, m], Atsunori Tsuchiya [a, l, m, n]

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[g] Department of Molecular and Cellular Medicine, Center for Future Medical Research, Institute of Medical Science, Tokyo Medical University, Tokyo, Japan
[h] X-innovation Committee for Health and Medical, Osaka University Graduate School of Medicine, Osaka, Japan
[i] Division of Drugs, National Institute of Health Sciences, Kanagawa, Japan
[j] Department of Drug Delivery Research, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan
[k] Medical Technology Innovation Center, Juntendo University, Tokyo, Japan
[l] Department of Gastroenterology and Hepatology, Faculty of Medicine, University of Yamanashi, Shimokato, 1110 Chuo, Yamanashi, Japan
[m] The Japanese Society for Regenerative Medicine, Japan[1]
[n] The Japanese Society for Extracellular Vesicles, Japan[2]

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Guidance

ABSTRACT

Therapies using extracellular vesicles (EVs), exosomes, or cell culture supernatants containing EVs or exosomes (referred to as "EV therapies" in this Guidance) have garnered an increasing amount of interest. However, pharmaceutical products containing EVs as their main active ingredient are yet to receive regulatory approval.

The "Basic points to consider regarding the preparation of extracellular vesicles and their clinical applications in Japan," was announced by the Japanese Society for Regenerative Medicine (JSRM) on March 10, 2021, with a specific focus on exosomes among EVs to promote high safety standards in this evolving field and facilitate the application of EV clinically. The Scientific Committee of the Pharmaceuticals and Medical Devices Agency and the Japanese Society for Extracellular Vesicles have issued reports and statements regarding treatment, resulting in a growing momentum toward treatment in Japan.

This article summarized the basic items that should be recognized comprehensively for clinical practice in three categories: (1) risk profiling, (2) preparation (manufacturing) process and quality, and (3) verification of EVs checking items and effectiveness. This guideline will be revised in the future with technological innovations and new findings; nevertheless, it will serve as a guide for the development of treatments.

Abbreviations: EVs, extracellular vesicles; DDS, drug delivery system; ISEV, International Society for Extracellular Vesicles; JSRM, Japanese Society for Regenerative Medicine; JSEV, Japanese Society for Extracellular Vesicles; PMDA, Scientific Committee of the Pharmaceuticals and Medical Devices Agency; ASRM, The Act on the Safety of Regenerative Medicine; FCM, nano-flow cytometry; NTA, Nanoparticle Tracking Analysis; TRPS, Tunable Resistive Pulse Sensing; DLS, Dynamic Light Scattering; FFF, Field Flow Fractionation; FBS, fetal bovine serum; CQAs, critical quality attributes.

* This guidance was written by the Japanese Society for Regenerative Medicine in cooperation with the Japanese Society for Extracellular Vesicles.

* Corresponding author. Niigata University, 1-757 Asahimachi-dori, Chuo-ku, Niigata 951-8510, Japan.
E-mail address: terai@med.niigata-u.ac.jp (S. Terai).

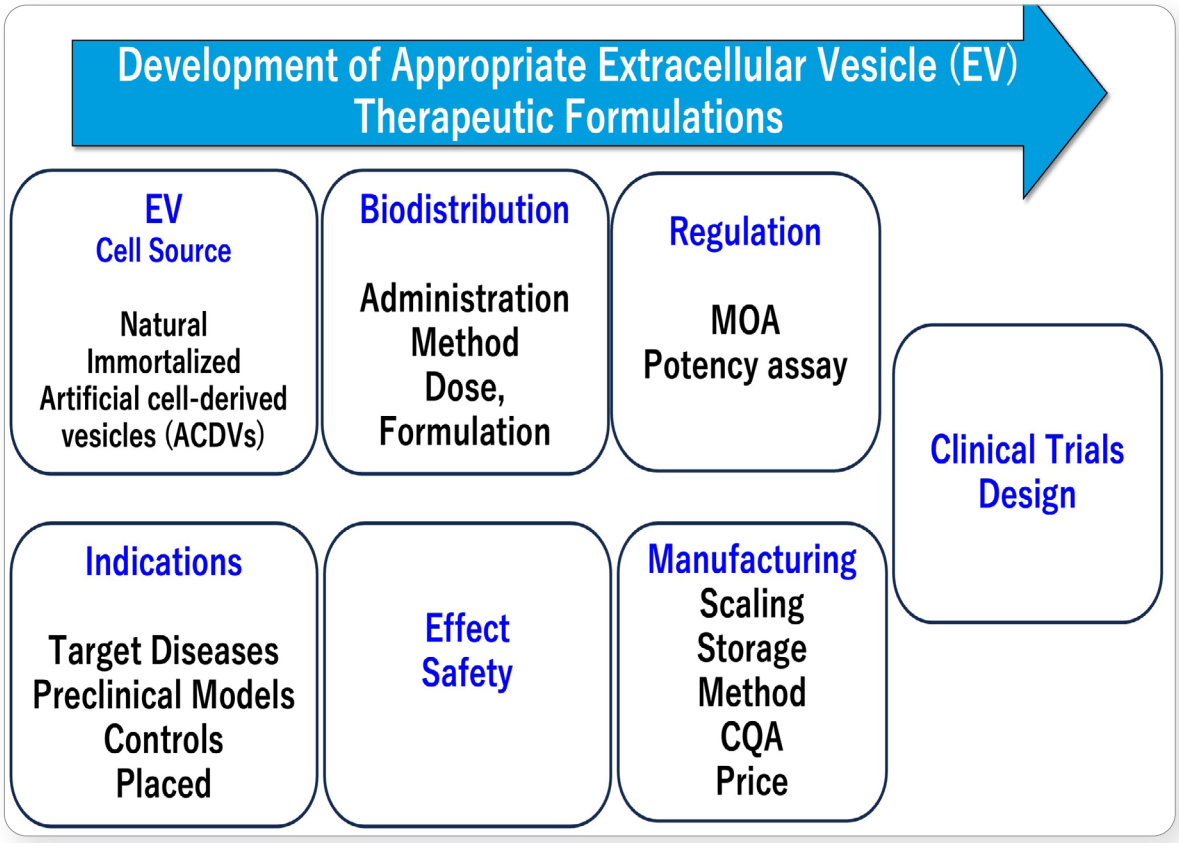
Peer review under responsibility of the Japanese Society for Regenerative Medicine.

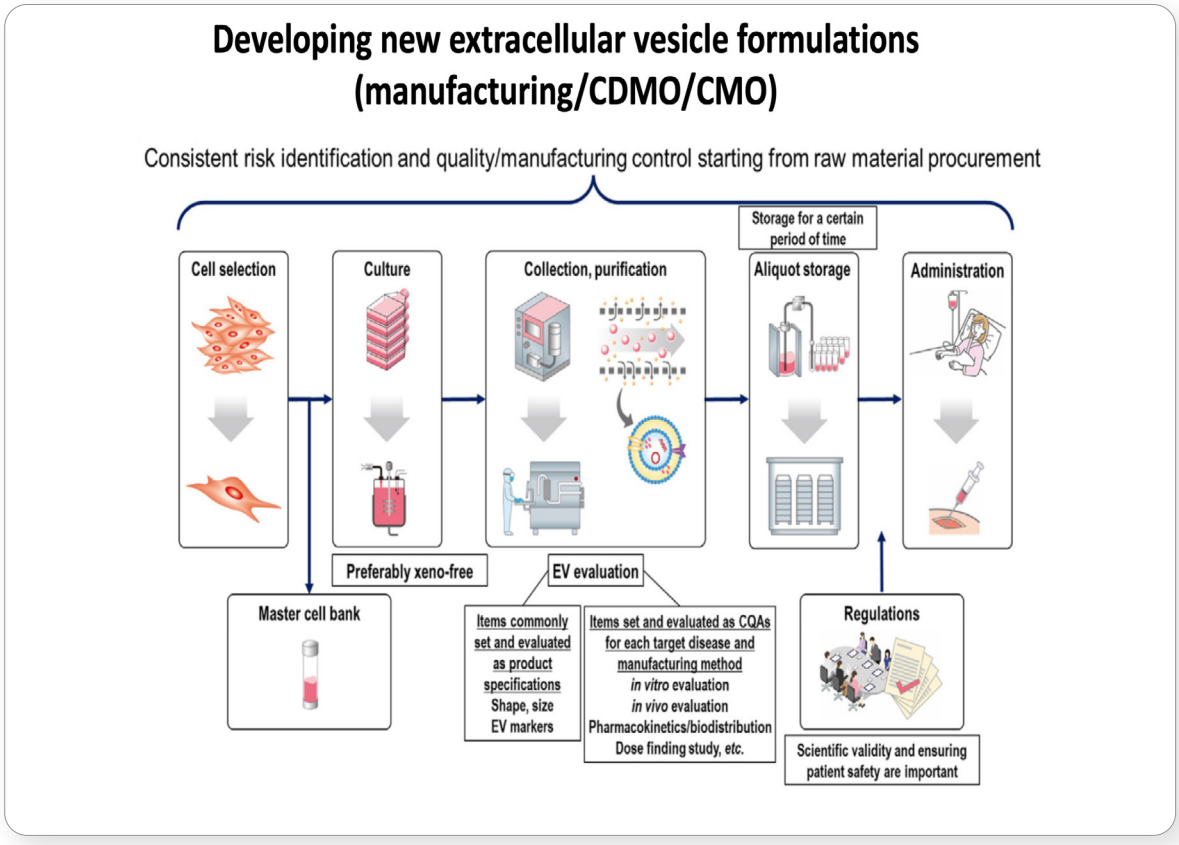
[1] https://www.jsrm.jp/
[2] https://jsev.jp/

https://doi.org/10.1016/j.reth.2025.02.008

Global rollout of the world's first reference document on the clinical application of extracellular vesicles

→ Apr 25 ISEV 2025 May 10 ISCT 2025


Development of Appropriate Extracellular Vesicle (EV) Therapeutic Formulations
EV
Cell Source
Natural
Immortalized
Artificial cell-derived vesicles (ACDVs)
Biodistribution
Administration
Method
Dose,
Formulation
Regulation
MOA
Potency assay
Clinical Trials Design
Indications
Target Diseases
Preclinical Models
Controls
Placed
Effect
Safety
Manufacturing
Scaling
Storage
Method
CQA
Price


Developing new extracellular vesicle formulations (manufacturing/CDMO/CMO)
Consistent risk identification and quality/manufacturing control starting from raw material procurement
Storage for a certain period of time
Cell selection
Culture
Collection, purification
Aliquot storage
Administration
Preferably xeno-free
EV evaluation
Master cell bank
Items commonly set and evaluated as product specifications
Shape, size
EV markers
Items set and evaluated as CQAs for each target disease and manufacturing method
in vitro evaluation
in vivo evaluation
Pharmacokinetics/biodistribution
Dose finding study, etc.
Regulations
Scientific validity and ensuring patient safety are important

NRMD and REAP: Features of the two databases

JSRM

Regenerative Medicine Patient Data Registration Systems Established and Operated by the Japanese Society for Regenerative Medicine

NRMD *(National Regenerative Medicine Database)*

NRMD/CR Platform for registering
non-commercial clinical research on specified processed cells,
certified advanced medical care using specified processed cells, and
commercial clinical trials of regenerative medical products (CTPs/GTPs)

NRMD/PMS Platform for registering
post-marketing surveillance of regenerative medical products

REAP *(Regenerative Medicine Evidence Accumulation Platform)*

Platform for registering
therapies based on physician's discretion using specified processed cells

There is no particular difference in the electronic data capture (EDC) system used.

20

Development of MSC-Derived Extracellular Vesicles Based on Experience with Mesenchymal stromal Cells (MSCs)

Experience with past mesenchymal stem cell culture and quality control methods is crucial for developing extracellular vesicles derived from mesenchymal stem cells(QbD: Quality by Design)
Developing safe and secure therapies is essential

Verification-based medical practice

REAP
Regenerative medicine Evidence Accumulation Platform

MISEV 2023

2024 JSRM EV Guidance

Safe and reliable quality extracellular vesicle preparations Based on functional assays using appropriate disease models
Clinical research and physician-initiated trials (data accumulation)

Appropriate clinical trials (company-sponsored trials) Large-scale clinical trials

Regulatory approval

Developing safe and secure therapies is essential
Extracellular vesicle medicine is becoming a reality

Thank you for your attention

Snow Ship

新潟大学地域医療教育センター
魚沼基幹病院 消化器内科学分野

Sun Ship

新潟大学大学院医歯学総合研究科
消化器内科学分野

Swan Ship

新潟大学医学部健康寿命延伸
消化器疾患先制医学講座

F-EDC

新潟大学未来医療
研究開発センター
(Exosome Designer Cell)

Sky Ship

新潟大学医学部消化器疾患
低侵襲予防医学開発講座

Soul Ship

新潟大学医学部消化器疾患
診療ネットワーク講座

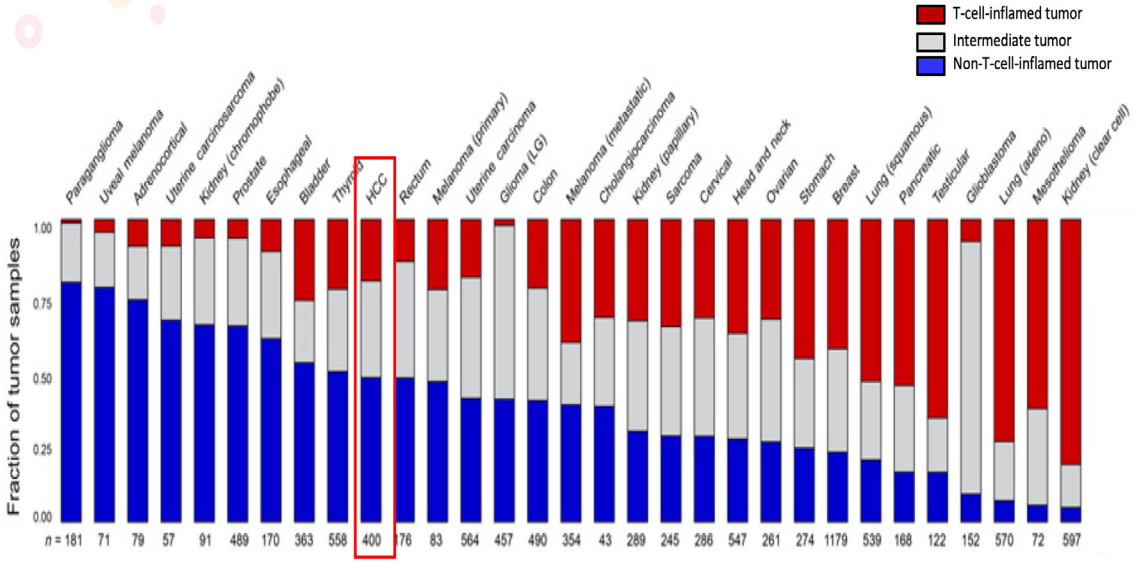
Sophistication Ship

新潟大学医歯学総合病院
肝疾患相談センター

Immunotherapy for HCC: Biomarker Development and Unmet Treatment Needs

Yi-Hsiang Huang
(National Yang Ming Chiao Tung Univ., Taiwan)

Tumor microenvironment differences between cancer types



➢ **HCC is indicated relatively higher ratio of "Non-T-cell- inflamed Tumor" compared to another cancers, which means HCC is classified as "Immune Cold Tumor"**

Luke JJ, et al; Clin Cancer Res 2019; 25(10):3074-3083

THE 7TH YONSEI LIVER SUMMIT

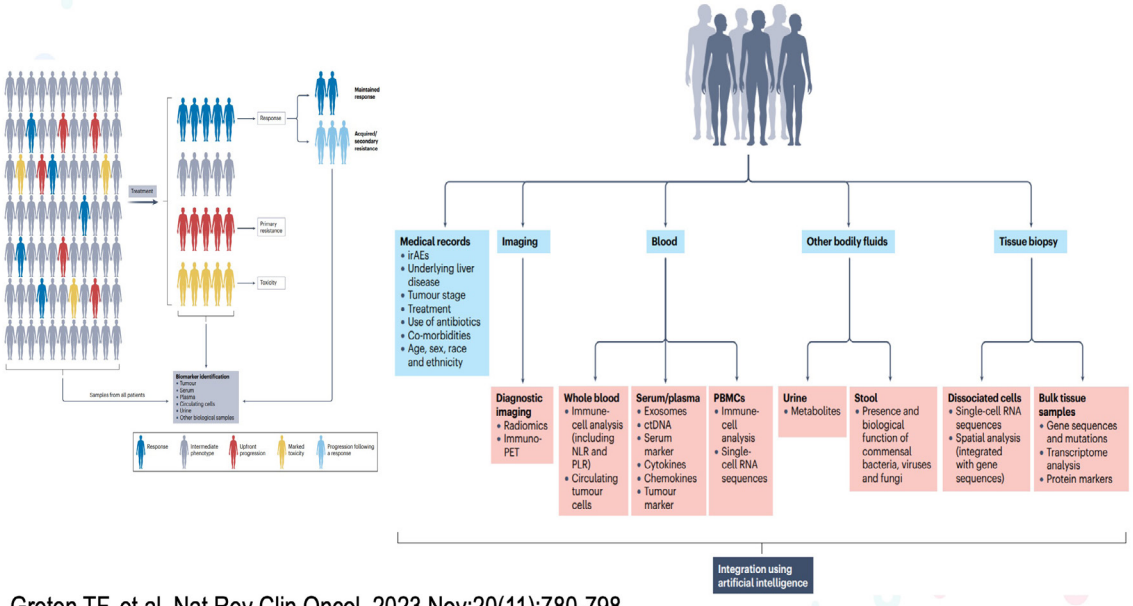
IO + anti-VEGF vs IO + IO for uHCC

	Imbrave 150	Cares 310	HIMALAYA	CM 9DW
mOS (HR)	19.2m (0.66)	22.1m (0.62)	16.4m (0.78) Asian 16.8m (0.68)	23.7m (0.79)
mPFS (HR)	6.9m (0.65)	5.6m (0.52)	3.78m (0.9)	9.1m (0.87)
ORR (CR) RECIST 1.1	30% (8%)	25.4% (1.1%)		
DCR	74%	78.3%	60.1% Asian 59.0%	68%
TRAE-related De ath	2.0%	0.4%	2.3%	**4.0%**

Finn R. NEJM. 2020;382:1894. Abou-Alfa G. NEJM Evid. 2022;1:EVIDoa2100070. Qin. Lancet. 2023;402:1133. Galle PR, ASCO 2024. Lau G. J Hepatol https://doi.org/10.1016/j.jhep.2024.07.017

THE 7TH YONSEI LIVER SUMMIT

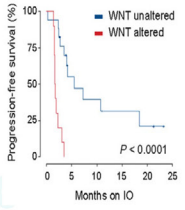
HCC immunotherapy: biomarker-deficient cancer



Greten TF, et al. Nat Rev Clin Oncol. 2023 Nov;20(11):780-798.

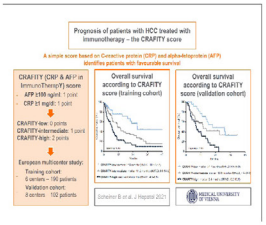
Potential biomarkers for HCC immunotherapy for Atezo/Beva

CTNNB1 mutation



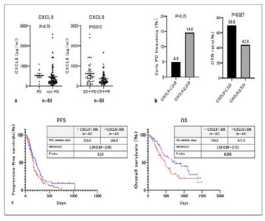
Harding JJ, et al. Clin Cancer Res. 2019 (25) (7) 2116-2126

CRAFITY score



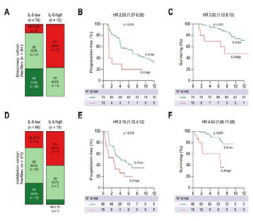
Scheiner B, et al. J Hepatol. 2022 Feb;76(2):353-363

Baseline CXCL9



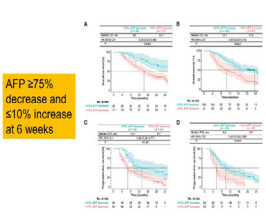
Hosoda S, et al. Liver Cancer. 2022 Oct 31;12(2):156-170

Baseline IL6



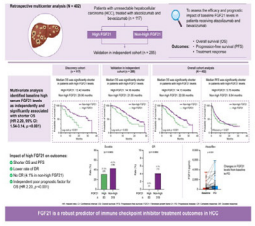
Yang H, et al. JHEP Rep. 2023 Jan 16;5(4):100672

AFP



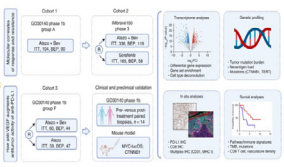
Zhu AX, et al. Clin Cancer Res. 2022 Aug 15;28(16):3537-3545.

FGF21



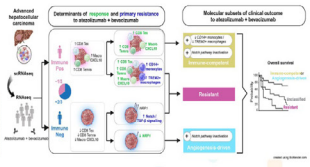
Kohya R, et al. JHEP Rep. 2025 Feb 19;7(5):101364

Pre-existing immunity Indicator, ABRS



Zhu AX, et al. Nat Med. 2022 Aug;28(8):1599-1611

Single-cell RNA seq-derived signatures

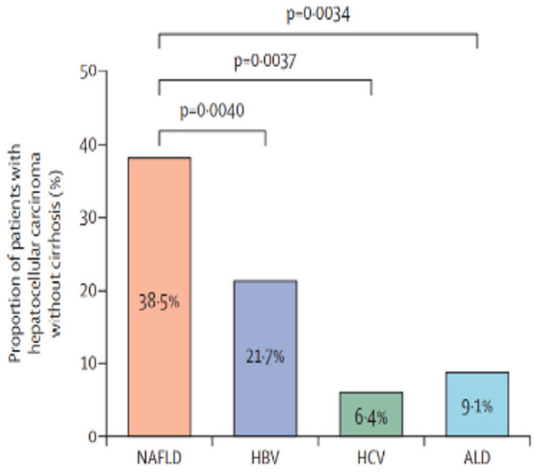


Cappuyns S, et al. J Hepatol. 2025 Jun;82(6):1036-1

Comparable or better outcomes in Asian subgroups compared to global populations in major HCC immunotherapy trials

Trial	Population	OS HR vs Sorafenib	Median OS (months)	ORR (%)
IMbrave150	Asian	0.44	NR vs 11.4	24.6 vs 6.7
	Global	0.58	19.2 vs 13.4	30 vs 12
HIMALAYA	Asian excl. Japan	0.68	16.8 vs 10.3*	28.2 vs 9.0
	Global	0.78	16.4 vs 13.8	20.1 vs 5.1
CM 9DW	Asian	0.75	34.0 vs 22.5	-
	Global	0.79	23.7 vs 20.6	-
CARES-310	Predominantly Asian	-	Improved	Improved

Proportion of patients with HCC without cirrhosis



Tan DJH, et al. Lancet Oncol . 2022 Apr;23(4):521-530.

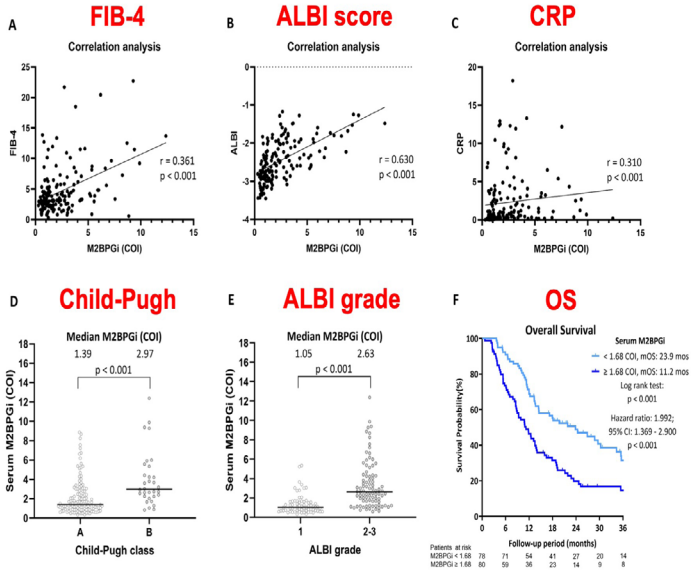
Serum M2BPGI highly correlates with FIB-4, ALBI score, and CRP

- Eligible patients with uHCC receiving immunotherapy was enrolled in a biomarker study from September 2017.
- Serum samples were collected before treatment.
- Serum M2BPGi was measured by CLEIA (Sysmex Corporation, Hyogo, Japan).
- Variables associated with overall survival (OS) were analyzed.

Training cohort
Sep 2017 – Sep 2022
(n = 158)
ICIs approved by TFDA:
Nivolumab
Pembrolizumab
Atezolizumab plus Bevacizumab

Validation cohort
From Oct 2022
(n = 60)
ICIs approved by TFDA:
Atezolizumab plus Bevacizumab
Tremelimumab plus Durvalumab

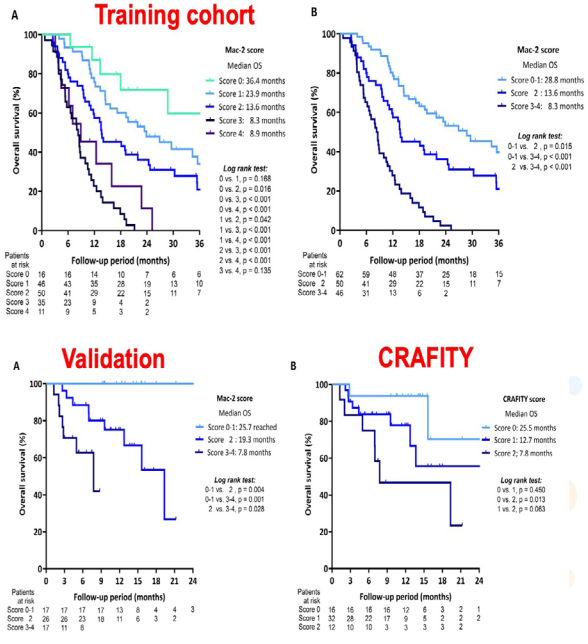
- Development and validation of a M2BPGi-based model to predict survival benefit of the patients.



Lee PC, Huang YH* JHEP Rep. 2025 Jun 26;7(9):101491. doi: 10.1016/j.jhepr.2025.101491

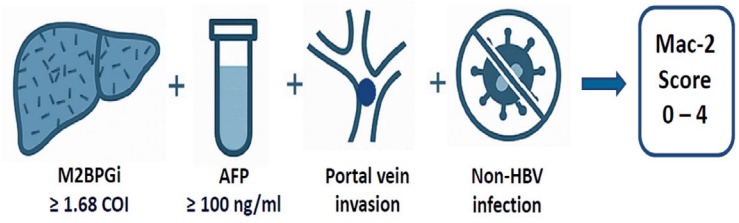
Mac-2 score based on factors associated with OS

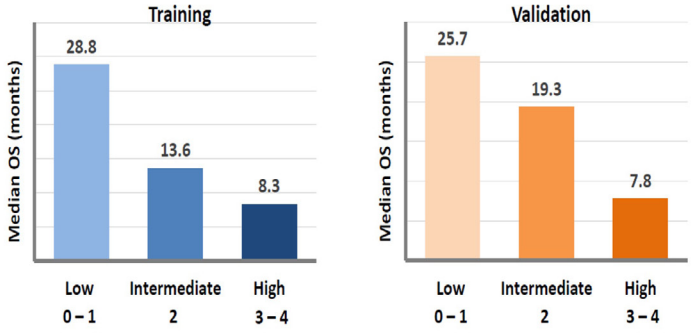
	HR	95% CI	P
HBsAg (+)	0.616	0.407 – 0.932	0.022
Portal vein invasion	1.629	1.050 – 2.699	0.030
AFP ≥ 100 ng/mL	1.605	1.061 – 2.428	0.025
M2BPGi ≥ 1.68 COI	1.684	1.050 – 2.699	0.030



Lee PC, Huang YH* JHEP Rep. 2025 Jun 26;7(9):101491. doi: 10.1016/j.jhepr.2025.101491

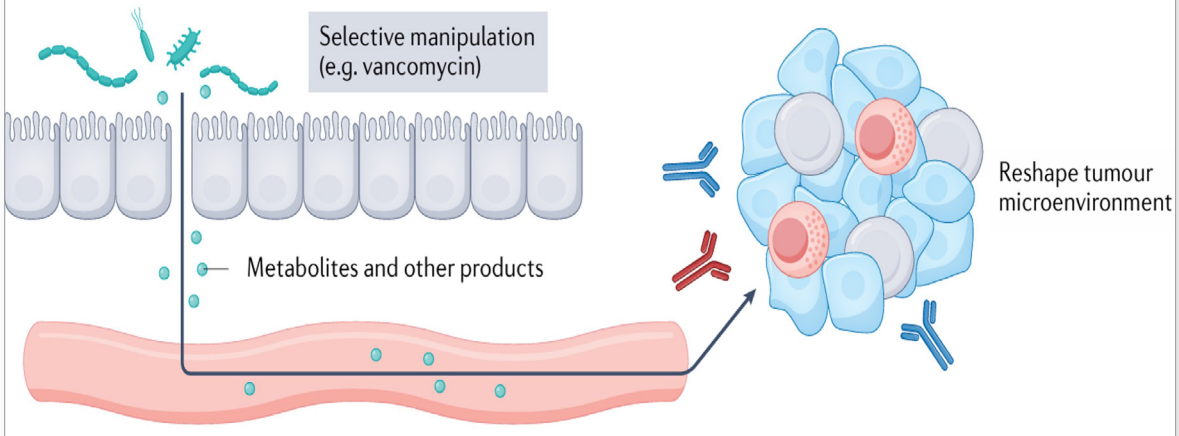
Mac-2 Score: A Serum Fibrosis Marker-Based Model Predicts Survival of uHCC under Immunotherapy





Lee PC, Huang YH* JHEP Rep. 2025 Jun 26;7(9):101491. doi: 10.1016/j.jhepr.2025.101491

Gut microbiota: Emerging immunotherapy-based strategies with therapeutic potential



Yang C, et al. Nat Rev Gastroenterol Hepatol. 2023 Apr;20(4):203-222

Gut microbiota compositions associate with tumor response

Patient selection

Development cohort: eligible patients from **May 2018 to Feb. 2020**.

Patients with uHCC who received ICI therapy (n = 41)

Healthy volunteers (n = 17)

Responders (n = 20)

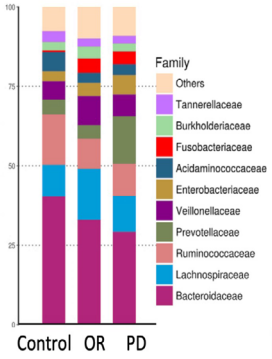
Non-responders (n = 21)

- Fecal samples were analyzed for microbiota and metabolites.
- Development of fecal signature predicting treatment response

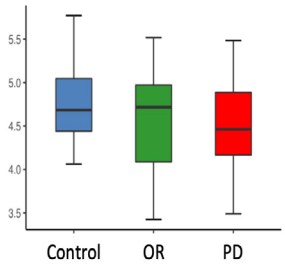
Validation cohort: consecutive Child–Pugh A, ICI-treated patients were investigated for validation of signature **(n = 33 since Mar. 2020)**

Patients who used **lactulose, PPi, NSAIDs, antibiotics, probiotics, prebiotics or ursodeoxycholic acids** within **4 weeks** prior to ICI treatment were excluded.

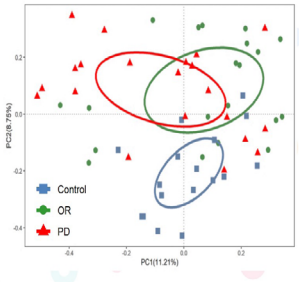
Relative abundance (%)



Shannon index



Bray-Curtis metrics

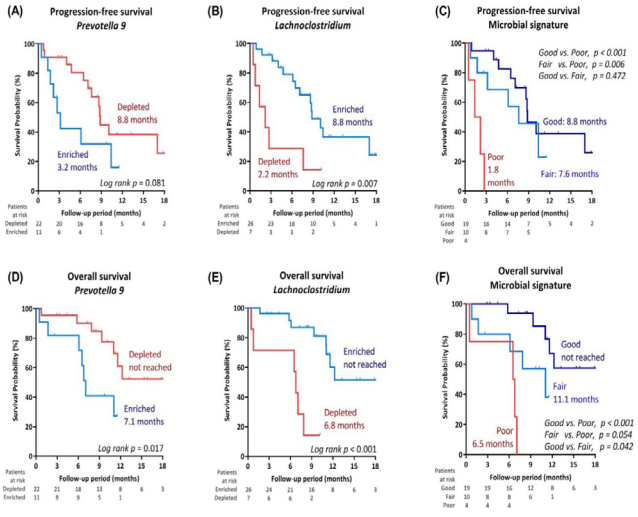


p value by PERMANOVA tests	
OR vs. PD	***p* = 0.019**
Healthy vs. OR	*p* < 0.001
Healthy vs. PD	*p* < 0.001

Lee PC, Wu CJ, Huang YH* Journal for ImmunoTherapy of Cancer 2022 Jun;10(6):e004779

Gut microbiota associated with tumor response, PFS, and OS

Gut microbial signature#		
Poor	Fair	**Good**
n = 4	n = 10	**n = 19**
0 (0)	2 (20.0)	**10 (52.6)**
0 (0)	7 (70.0)	**8 (42.1)**
4 (100.0)	1 (10.0)	**1 (5.3)**
0 (0)	2 (20.0)	**10 (52.6)**
	0.060	
0 (0)	9 (90.0)	**18 (94.7)**
	< 0.001	



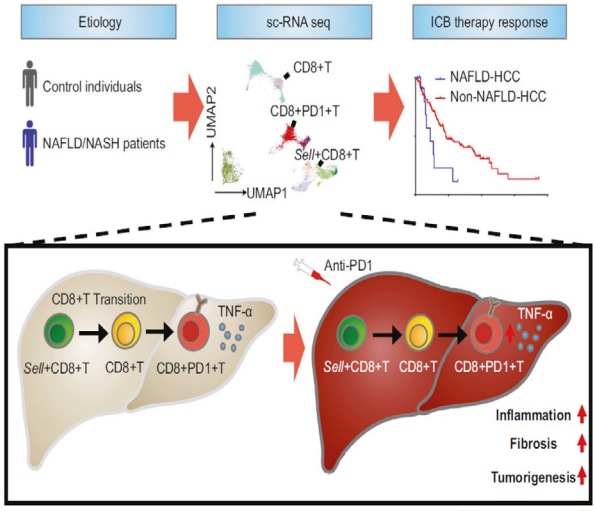
#Gut microbial signature
Good signature: coexistence of depleted *Prevotella 9* and enriched *Lachnoclostridium*
Poor signature: coexistence of enriched *Prevotella 9* and depleted *Lachnoclostridium*
Fair signature: coexistence of depleted both two bacteria or enriched both two bacteria

Lee PC, Wu CJ, Huang YH* Journal for ImmunoTherapy of Cancer 2022 Jun;10(6):e004779

Article

NASH limits anti-tumour surveillance in immunotherapy-treated HCC

Dominik Pfister[1,82], Nicolás Gonzalo Núñez[2], Roser Pinyol[3], Olivier Govaere[4], Matthias Pinter[5,6], Marta Szydlowska[1], Revant Gupta[7,8], Mengjie Qiu[9], Aleksandra Deczkowska[10], Assaf Weiner[10], Florian Müller[1], Ankit Sinha[11,12], Ekaterina Frie Thomas Engleitner[13,14,15], Daniela Lenggenhager[16], Anja Moncsek[17], Danijela Heide[1], Kristin Stirm[1], Jan Kosla[1], Eleni Kotsiliti[1], Valentina Leone[1,18], Michael Dudek[19], Suhail Yo Donato Inverso[20,21], Indrabahadur Singh[1,22], Ana Teijeiro[23], Florian Castet[3], Carla Montir Philipp K. Haber[24], Dina Tiniakos[4,25], Pierre Bedossa[4], Simon Cockell[26], Ramy Younes[4,27], Michele Vacca[28], Fabio Marra[29], Jörn M. Schattenberg[30], Michael Allison[31], Elisabetta Bugianesi[27], Vlad Ratziu[32], Tiziana Pressiani[33], Antonio D'Alessio[33], Nicola Personeni[33,34], Lorenza Rimassa[33,34], Ann K. Daly[4], Bernhard Scheiner[5,6], Katharina Pomej[5,6], Martha M. Kirstein[35,36], Arndt Vogel[35], Markus Peck-Radosavljevic[37], Florian Hucke[37], Fabian Finkelmeier[38], Oliver Waidmann[38], Jörg Trojan[38], Kornelius Schulze[39], Henning Wege[39], Sandra Koch[40], Arndt Weinmann[40], Marco Buete Fabian Rössler[41], Alexander Siebenhüner[42], Sara De Dosso[43], Jan-Philipp Mallm[44], Viktor Umansky[45,46], Manfred Jugold[47], Tom Luedde[48], Andrea Schietinger[49,50], Peter Schirmacher[51], Brinda Emu[1], Hellmut G. Augustin[20,21], Adrian Billeter[52], Beat Mülle Stich[52], Hiroto Kikuchi[53], Dan G. Duda[53], Fabian Kütting[54], Dirk-Thomas Waldschmidt[54], Matthias Philip Ebert[55], Nuh Rahbari[56], Henrik E. Mei[57], Axel Ronald Schulz[57], Marc Ringelhan[58,59,60], Nisar Malek[61], Stephan Spahn[61], Michael Bitzer[61], Marina Ruiz de Galarreta[24,62], Amaia Lujambio[24,62,63], Jean-Francois Dufour[64,65], Thomas U. Marron[24,66], Ahmed Kaseb[67], Masatoshi Kudo[68], Yi-Hsiang Huang[69,70], Nabil Djouder[23], Katharina Wolter[71,72], Lars Zender[71,72,73], Parice N. Marche[74,75], Thomas Decaens[74,75,76], David J. Pinato[77,78], Roland Rad[13,14,15], Joachim C. Mertens[17], Achim Weber[16,79], Kristian Unger[16], Felix Meissner[11], Susanne Roth[9], Zuzana Macek Jilkova[74,75,77], Manfred Claassen[7,8], Quentin M. Anstee[4,80], Ido Amit[10], Percy Knolle[19], Burkhard Becher Josep M. Llovet[3,24,81] ✉ & Mathias Heikenwalder[1] ✉



Pfister, D , et al. Nature. 2021 Apr;592(7854):450-456.

THE 7TH YONSEI LIVER SUMMIT

HEPATOLOGY

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ORIGINAL ARTICLE

Distinct gut microbiota but common metabolomic signatures between viral and MASLD HCC contribute to outcomes of combination immunotherapy

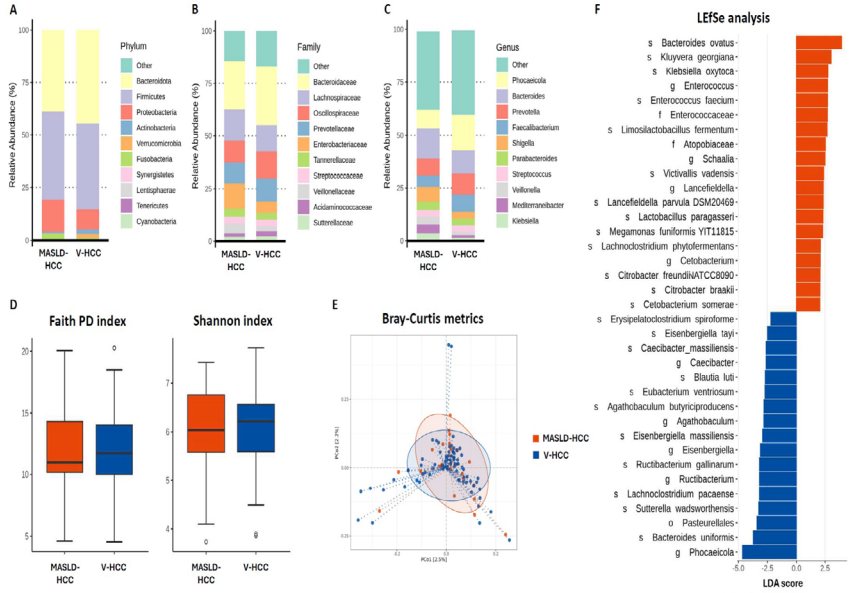
Lee, Pei-Chang[1,2]; Wu, Chi-Jung[1,2]; Hung, Ya-Wen[2,3]; Lee, Chieh-Ju[4,5]; Mon, Hsien-Chen[1]; Chi, Chen-Ta[1,2]; Lee, I-Cheng[1,2]; Kuo, Yu-Lun[6]; Chou, Shih-Hsuan[6]; Luo, Jiing-Chyuan[1,2]; Hou, Ming-Chih[1,2]; Huang, Yi-Hsiang[1,4,5]

Author Information

Hepatology ():10.1097/HEP.0000000000001446, June 30, 2025. | *DOI:* 10.1097/HEP.0000000000001446

THE 7TH YONSEI LIVER SUMMIT

The composition, diversities and predominant fecal bacteria in MASLD-HCC and V-HCC



Lee PC, Huang YH* Hepatology. 2025 Jun 30. doi: 10.1097/HEP.0000000000001446. Online ahead of print.

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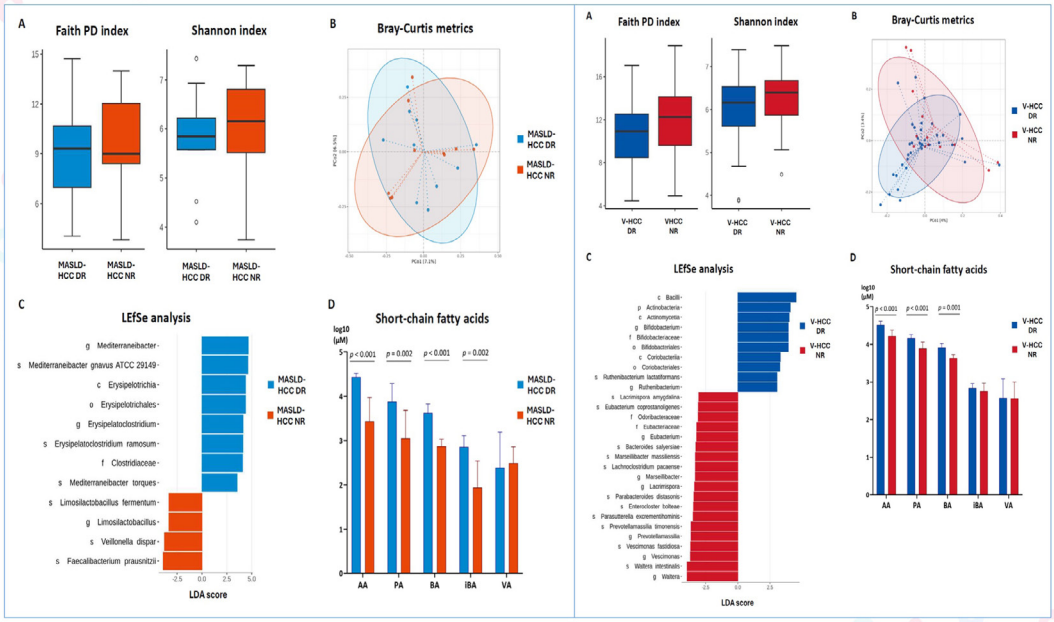
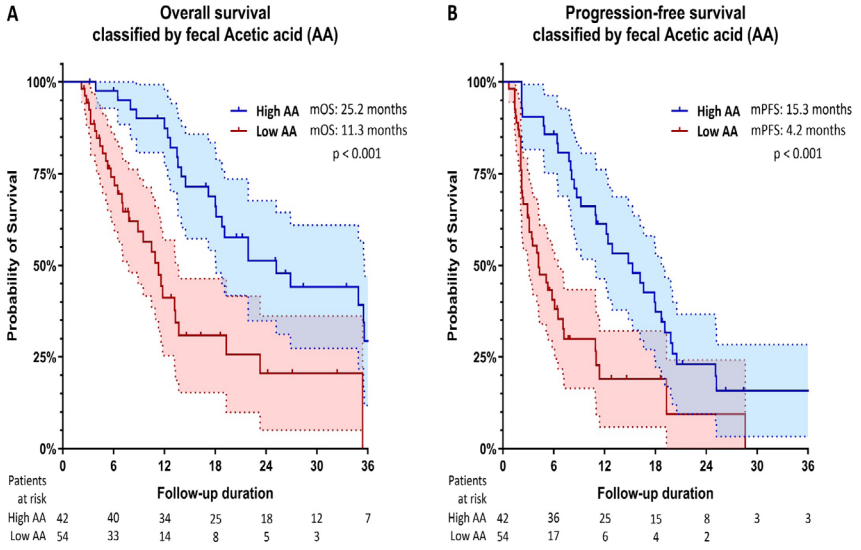
Gut microbiota, metabolomic signatures in Viral and MASLD HCC



Lee PC, Huang YH* Hepatology. 2025 Jun 30. doi: 10.1097/HEP.0000000000001446. Online ahead of print.

THE 7TH YONSEI LIVER SUMMIT

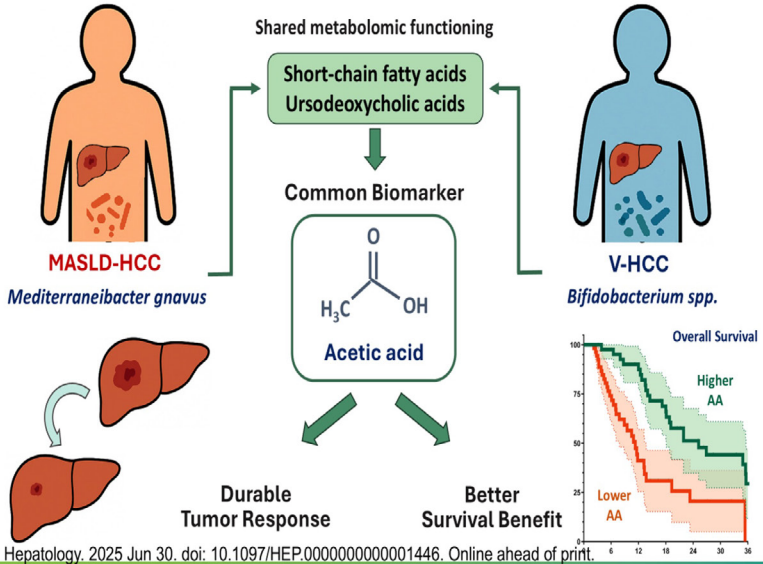
Fecal acetic acid level highly associated with OS and PFS



Lee PC, Huang YH* Hepatology. 2025 Jun 30. doi: 10.1097/HEP.0000000000001446. Online ahead of print.

THE 7TH YONSEI LIVER SUMMIT

Distinct gut microbiota but common metabolomic signatures between Viral and MASLD HCC contribute to outcomes of combination immunotherapy

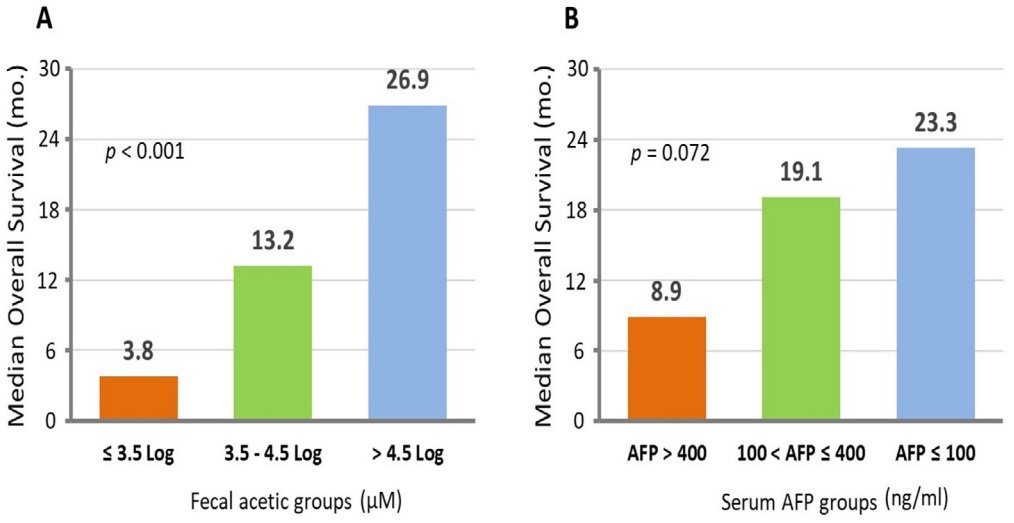


Lee PC, Huang YH* Hepatology. 2025 Jun 30. doi: 10.1097/HEP.0000000000001446. Online ahead of print.

AASLD Lee, et al | HEPATOLOGY. 2025. HEPATOLOGY

THE 7TH YONSEI LIVER SUMMIT

Fecal acetate vs AFP levels in relating to OS in uHCC patients undergoing ICIs



Lee PC, Huang YH* Hepatology July 29, 2025. DOI: 10.1097/HEP.0000000000001482

THE 7TH YONSEI LIVER SUMMIT

Trends and Challenges in MRI for HCC Management

Tan Cher Heng
(Tan Tock Seng Hospital, Singapore)

MEMO

MEMO

Image-Guided Anatomic Liver Resection

Xiaoying Wang
(Fudan Univ., China)

MEMO

MEMO

Special Lecture 1

좌장: 김순일 (인제의대)

Evolution of Surgical Treatment for HCC during the Last Three Decades in Yonsei Liver Cancer Center
최진섭 (연세의대)

주최
YONSEI UNIVERSITY HEALTH SYSTEM
세브란스병원 간센터 • 연세암병원 간암센터 • 연세간암연구회

Evolution of Surgical Treatment for HCC during the Last Three Decades in Yonsei Liver Cancer Center

최 진 섭
(연세의대)

MEMO

MEMO

Special Lecture 2

좌장: 박영년 (연세의대)

Reflections on My Experience with the Evolution of Liver Imaging
김명진 (연세의대)

주최 YONSEI UNIVERSITY HEALTH SYSTEM
세브란스병원 간센터 • 연세암병원 간암센터 • 연세간암연구회

Reflections on My Experience with the Evolution of Liver Imaging

김명진
(연세의대)

Radiology. 1997 Feb;202(2):383-8. doi: 10.1148/radiology.202.2.9015062.

Nodular hepatocellular carcinomas: detection with arterial-, portal-, and delayed-phase images at spiral CT

G J Hwang [1], M J Kim, H S Yoo, J T Lee

Affiliations + expand

PMID: 9015062 DOI: 10.1148/radiology.202.2.9015062

Abstract

Purpose: To evaluate the effectiveness of three-phase spiral computed tomography (CT) for the evaluation of nodular hepatocellular carcinoma (HCC).

Materials and methods: Images obtained at three-phase spiral CT in 45 patients with 81 nodular HCCs were reviewed. Images were obtained with 10-mm collimation and 10 mm/sec table speed during intravenous administration of 2 mL/kg 68% nonionic contrast material at a rate of 3 mL/sec. Hepatic arterial-phase (AP), portal-phase (PP), and delayed-phase (DP) images were obtained 25-30 seconds, 60-70 seconds, and 300 seconds, respectively, after injection of the contrast material. Lesion detectability and conspicuity were compared among these three protocols by two readers.

A CENTURY OF 1906 2006 AJR MEDICAL IMAGING

Optimal Scan Window for Detection of Hypervascular Hepatocellular Carcinomas During MDCT Examination

Myeong-Jin Kim[1,2,3]
Jin Young Choi[1,3]
Joon Seok Lim[3]
Jin Yong Kim[1,3]
Joo Hee Kim[3]
Young Taik Oh[1,3]
Eun Hye Yoo[1,3]
Jae Joon Chung[1]
Ki Whang Kim[1]

OBJECTIVE. The purpose of this study was to define the optimal scan window for acquiring arterial phase images in the detection of hypervascular hepatocellular carcinomas (HCCs).

MATERIALS AND METHODS. Biphasic arterial phase CT examinations were performed using a 16-MDCT scanner on 198 patients (159 men and 39 women; mean age, 59 years; age range, 25–82 years) with nodular HCC. All examinations were performed after administering 120–150 mL of a nonionic contrast media (370 mg I/mL) at a rate of 3–4 mL/s. The scan delay—the interval between when the bolus-tracking program detected the threshold enhancement of 100 H in the abdominal aorta and the start of the first arterial scan—was progressively lengthened by 2-second intervals, from 10 seconds in group 1 to 20 seconds in group 6. The second arterial phase scan was started 6 seconds after the end of the early scan. A tube col-

Kim, M. J., et al. (2006). AJR Am J Roentgenol 187(1): 198-206.

Abdom Imaging 26:149–156 (2001)
DOI: 10.1007/s002610000121

Abdominal Imaging

Hepatic iron deposition on MR imaging in patients with chronic liver disease: correlation with serial serum ferritin concentration

M.-J. Kim,[1]* D. G. Mitchell,[1] K. Ito,[1] H.-W. L. Hann,[2] Y. N. Park,[3] P. N. Kim[1]

[1]Department of Radiology, Thomas Jefferson University Hospital, 1096 Main Building, 132 S 10th Street, Philadelphia, PA 19107, USA
[2]Department of Medicine, Jefferson Medical College, 1025 Walnut Street, Philadelphia, PA 19107, USA
[3]Department of Anatomic Pathology, Yonsei University College of Medicine, Seodaemun-ku Shinchon-dong 134, Seoul, Republic of Korea, 120-752

Received: 9 May 2000/Accepted: 28 June 2000

Journal of Computer Assisted Tomography
26(6):988–993

Hepatic Iron Deposition on Magnetic Resonance Imaging: Correlation with Inflammatory Activity

Myeong-Jin Kim, Donald G. Mitchell, Katsuyoshi Ito, Joo Hee Kim, Denise Pasqualin, and Raphael Rubin

Abdom Imaging 26:269–276 (2001)
DOI: 10.1007/s002610000177

Abdominal Imaging

Hepatic MR imaging: comparison of 2D and 3D gradient echo techniques

M.-J. Kim,* D. G. Mitchell, K. Ito,† P. N. Kim‡

Department of Radiology, Thomas Jefferson University Hospital, 132 South 10th Street, 1096 Main Building, Philadelphia, PA 19107-5244, USA

Received: 11 May 2000/Revision accepted: 6 September 2000

Abdom Imaging 25:462–470 (2000)
DOI: 10.1007/s002610000014

Abdominal Imaging

Portosystemic collaterals of the upper abdomen: review of anatomy and demonstration on MR imaging

M.-J. Kim,* D. G. Mitchell, K. Ito

Department of Radiology, The Thomas Jefferson University Hospital, 1096 Main Building, 132 South 10th Street, Philadelphia, PA 19107, USA

Radiology

Myeong-Jin Kim, MD
Joo Hee Kim, MD
Jae-Joon Chung, MD
Mi Suk Park, MD
Joon Seok Lim, MD
Young Taik Oh, MD

Index terms:
Contrast media, comparative studies
Gadolinium
Iron
Liver neoplasms, diagnosis, 761.3121, 761.3199, 761.323, 761.33
Liver neoplasms, MR, 761.12143
Magnetic resonance (MR), contrast media

Published online before print
10.1148/radiol.2283020735
Radiology 2003; 228:719–726

Focal Hepatic Lesions: Detection and Characterization with Combination Gadolinium- and Superparamagnetic Iron Oxide–enhanced MR Imaging[1]

PURPOSE: To compare gadolinium- and superparamagnetic iron oxide (SPIO)–enhanced magnetic resonance (MR) imaging for detection and characterization of focal hepatic lesions when different contrast agent administration sequences are used.

MATERIALS AND METHODS: Unenhanced, dynamic gadolinium-enhanced, and

JOURNAL OF MAGNETIC RESONANCE IMAGING 20:612–621 (2004)

Original Research

Detection and Characterization of Focal Hepatic Lesions: Mangafodipir vs. Superparamagnetic Iron Oxide-enhanced Magnetic Resonance Imaging

Myeong-Jin Kim, MD,[1,2,3,6*] Joo Hee Kim, MD,[1,2] Joon Seok Lim, MD,[1,2] Young Taik Oh, MD,[1,2] Jae-Joon Chung, MD,[1,2,5] Jin Sup Choi, MD,[4] Woo Jung Lee, MD,[4] and Ki Whang Kim, MD[1,2]

A CENTURY OF 1906 2006 AJR MEDICAL IMAGING

Optimal TE for SPIO-Enhanced Gradient-Recalled Echo MRI for the Detection of Focal Hepatic Lesions

Myeong-Jin Kim[1,2,3]
Joo Hee Kim[1,3]
Jin Young Choi[1]
Sung Ho Park[1]
Jae-Joon Chung[1,4]
Ki Whang Kim[1,3]
Donald G. Mitchell[5]

OBJECTIVE. The objective of our study was to determine the optimal TE for superparamagnetic iron oxide (SPIO)-enhanced gradient-recalled echo (GRE) MRI for the detection of focal hepatic lesions.

MATERIALS AND METHODS. Ferucarbotran-enhanced GRE sequences, performed on a 1.5-T MR system, were used to evaluate 131 lesions (38 hepatocellular carcinomas, 37 metastases, 21 hemangiomas, 7 cholangiocarcinomas, 15 cysts, and 13 miscellaneous lesions) at four different TEs: 9, 13.5, 18, and 22.5 milliseconds. The lesion-to-liver signal difference-to-noise ratio (SDNR) was compared among the four GRE sequences by paired Student's *t* tests

Hyperintense Lesions on Gadoxetate Disodium–Enhanced Hepatobiliary Phase Imaging

Myeong-Jin Kim[1]
Hyung Jin Rhee[1,2]
Hyeon Tae Jeong[1]

OBJECTIVE. The purpose of this article is to illustrate various focal hepatic lesions that may show hyperintensity on hepatobiliary phase images on gadoxetate disodium–enhanced MRI.

CONCLUSION. Hyperintense lesions on gadoxetate disodium–enhanced MRI include focal nodular hyperplasia (FNH) or FNH-like nodules, hepatocellular adenoma, dysplastic nodules, and hepatocellular carcinoma. Understanding the contrast enhancement patterns on hepatobiliary phase images and other imaging findings is important to ensure correct diagnosis.

European Journal of Radiology 81 (2012) 2507–2512

Contents lists available at SciVerse ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Imaging features of small hepatocellular carcinomas with microvascular invasion on gadoxetic acid-enhanced MR imaging☆

Myeong-Jin Kim[a,*], Myungsu Lee[a], Jin-Young Choi[a], Young Nyun Park[b]

[a] Department of Radiology and Research Institute of Radiological Science, Yonsei University Severance Hospital, Seoul, South Korea
[b] Department of Pathology, Yonsei University Severance Hospital, Seoul, South Korea

Radiology

Single Hepatocellular Carcinoma: Preoperative MR Imaging to Predict Early Recurrence after Curative Resection[1]

Chansik An, MD
Dong Wook Kim, PhD
Young-Nyun Park, MD
Yong Eun Chung, MD
Hyungjin Rhee, MD
Myeong-Jin Kim, MD

Purpose: To identify magnetic resonance (MR) imaging features that enable prediction of early recurrence (<2 years) after curative resection of hepatocellular carcinoma (HCC) and to derive a preoperative prediction model.

Materials and Methods: This retrospective study was approved by the institutional review board. The requirement to obtain written

Abdominal Radiology

Abdom Radiol (2018)
https://doi.org/10.1007/s00261-018-1758-y

CrossMark

Imaging features related with prognosis of hepatocellular carcinoma

Chansik An [1] and Myeong-Jin Kim [1]

[1]Department of Radiology, Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, Seodaemun-Gu Yonsei-Ro 50-1, Seoul 03722, Republic of Korea

ORIGINAL RESEARCH • GASTROINTESTINAL IMAGING

Radiology

Hepatobiliary versus Extracellular MRI Contrast Agents in Hepatocellular Carcinoma Detection: Hepatobiliary Phase Features in Relation to Disease-free Survival

Dong Kyu Kim, MD • Chansik An, MD, PhD • Yong Eun Chung, MD, PhD • Jin-Young Choi, MD, PhD • Joon Seok Lim, MD, PhD • Mi-Suk Park, MD, PhD • Myeong-Jin Kim, MD, PhD

From the Department of Radiology, Severance Hospital, Research Institute of Radiological Science, Yonsei University College of Medicine, 50-1 Yonseiro, Seodaemun-gu, Seoul 03722, Korea. Received February 23, 2019; revision requested April 25; revision received August 12; accepted August 20. **Address correspondence to** M.J.K. (e-mail: *KIMNEX@yuhs.ac*).

Supported by a grant funded by the Research Supporting Program of The Korean Association for the Study of the Liver and The Korean Liver Foundation (grant KASLKLF2017-07).

Conflicts of interest are listed at the end of this article.

See also the editorial by Motosugi in this issue.

Radiology 2019; 293:594–604 • https://doi.org/10.1148/radiol.2019190414 • Content code: GI

Radiology

REVIEWS AND COMMENTARY • EDITORIAL

Improving Survival with Gadoxetic Acid–enhanced MRI for Hepatocellular Carcinoma

Myeong-Jin Kim, MD, PhD

Dr Myeong-Jin Kim is a professor of radiology at the Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. His research interests focus on optimizing hepatobiliary MRI and imaging of hepatocellular carcinoma and cholangiocarcinoma. Dr Kim is a member of the gastrointestinal subcommittee of RSNA, an associate editor of *Radiology*, and the vice president of the Asian Society of Abdominal Radiology.

respectively (6). Moreover, a survival benefit in the use of gadoxetic acid–enhanced MRI has been demonstrated in a single-center, retrospective study of 700 patients with a single nodular HCC lesion (7). The use of gadoxetic acid–enhanced MRI after CT enabled the detection of additional HCC nodules in 16% of patients (7). This resulted in lower recurrence rates and overall mortality compared with the use of CT alone. Kim et al (7) found that tumor stages determined with CT needed to be changed more frequently after gadoxetic acid–enhanced MRI (13%) compared with non–gadoxetic acid–enhanced MRI (6%).

Kim, M. J. (2020). Radiology 295(1): 125-126.

Radiology

ORIGINAL RESEARCH • GASTROINTESTINAL

Hepatocellular Carcinoma versus Other Hepatic Malignancy in Cirrhosis: Performance of LI-RADS Version 2018

Yeun-Yoon Kim, MD • Myeong-Jin Kim, MD, PhD • Eun Hwa Kim, MS • Yun Ho Roh, MS • Chansik An, MD, PhD

From the Department of Radiology (Y.Y.K., M.J.K., C.A.) and Biostatistics Collaboration Unit, Department of Biomedical Systems Informatics (E.H.K., Y.H.R.), Severance Hospital, Yonsei University College of Medicine, Seodaemun-gu Yonsei-ro 50-1, Seoul 03722, Republic of Korea. Received August 25, 2018; revision requested October 8; final revision received November 6; accepted December 6. **Address correspondence to** M.J.K. (e-mail: *kimnex@yuhs.ac*).

Conflicts of interest are listed at the end of this article.

See also the editorial by Furlan in this issue.

Radiology 2019; 00:1–10 • https://doi.org/10.1148/radiol.2019181995 • Content codes: GI OI

European Radiology (2019) 29:5101–5110
https://doi.org/10.1007/s00330-019-06030-0

GASTROINTESTINAL

Check for updates

Problematic lesions in cirrhotic liver mimicking hepatocellular carcinoma

Myeong-Jin Kim [1] · Sunyoung Lee [1] · Chansik An [1]

Received: 24 October 2018 / Revised: 21 December 2018 / Accepted: 22 January 2019 / Published online: 20 February 2019

RadioGraphics

EDUCATION EXHIBIT 683

Varying Appearances of Cholangiocarcinoma: Radiologic-Pathologic Correlation[1]

CME FEATURE
See accompanying test at http://www.rsna.org

Yong Eun Chung, MD • Myeong-Jin Kim, MD • Young Nyun Park, MD • Jin-Young Choi, MD • Ju Yeon Pyo, MD • Young Chul Kim, MD • Hyeon Je Cho, MD • Kyung Ah Kim, MD • Sun Young Choi, MD

Chung, Y. E., et al. (2009). Radiographics 29(3): 683-700.

European Journal of Radiology 113 (2019) 182–187

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Review

A dichotomous imaging classification for cholangiocarcinomas based on new histologic concepts

Myeong-Jin Kim[a,*], Hyungjin Rhee[a], Ha Young Woo[b]

[a] Department of Radiology, Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[b] Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

The 7th Yonsei Liver Summit
Honoring the Past, Empowering the Next

Session 3

Evolving Imaging and Interventions in Hepatocellular Carcinoma

좌장: 김기황 (서울의료원), 원종윤 (연세의대)

1. Prognostic Imaging Findings of HCC
   윤자경 (연세의대)
2. Recent Update of AI Application in Liver Imaging
   신재승 (성균관의대)
3. HCC Surveillance: The Cutting-Edge
   이형진 (연세의대)
4. Recent Update of Radioembolization
   현동호 (성균관의대)

주최 YONSEI UNIVERSITY HEALTH SYSTEM
세브란스병원 간센터 • 연세암병원 간암센터 • 연세간암연구회

Prognostic Imaging Findings of HCC

윤자경
(연세의대)

서론

간세포암(Hepatocellular carcinoma)은 생물학적으로 매우 이질적인(heterogeneous) 암종으로, 동일한 병기 내에서도 환자마다 각기 다른 예후를 보이기에 치료 전 예후 예측을 통한 최적의 치료 방법을 결정하는 것이 중요해졌다.[1-3] Barcelona Clinic Liver Cancer (BCLC) staging system을 포함한 많은 가이드라인에서는 주로 종양의 크기 및 개수에 중점을 두어 병기 설정 및 치료 방법을 제시하고 있다.[4,5] 하지만 이 외에도 조직학적 등급(grade)나 분화도, 미세혈관침습(microvascular invasion), 아형, 면역반응성 등의 조직병리학적 요인이나 유전적 및 분자적 특성이 조기 재발 및 생존율에 결정적인 영향을 미친다.[1,3] 조직검사는 침습적이라는 단점과 표본오차(sampling error)라는 한계가 있는 반면, MRI는 종양 전체의 생물학적 특성을 비침습적으로 평가할 수 있는 유용한 도구이다.[6] 따라서 이러한 조직병리학적 예후 인자를 비침습적으로 예측하여 최적의 치료 방법을 선택하고, 환자가 좋은 예후를 기대할 수 있도록 하는 영상의학적인 소견을 정립하는 것은 임상적으로 중요한 의미를 가진다.

간세포암의 예후와 관련된 주요 MRI 소견

간세포암의 불량한 예후를 예측하는 가장 중요한 지표인 미세혈관침습과 관련된 영상 소견으로는 매끄럽지 않은 종양 경계(non-smooth tumor margin), 테두리 동맥기 과조영증강(rim arterial phase hyperenhancement [APHE]), 주변부 동맥기 과조영증강(peritumoral APHE), 주변부 간담도기 저신호강도(peritumoral hepatobiliary phase [HBP] hypointensity), 간담도기 저신호강도(HBP hypointensity), 확산제한(diffusion restriction), 괴사(necrosis) 등이 보고된 바 있다.[7,8] 매끄럽지 않은 종양 경계는 공격적인 종양의 증식을 시사하며, 테두리 동맥기 과조영증강을 보이는 간세포암의 경우 종양 내부의 괴사 및 VETC(vessels encapsulating tumor clusters)와 밀접한 연관이 있다.[7,9,10] 주변부 동맥기 과조영증강 및 주변부 간담도기 저신호강도는 각각 간세포암의 주변 조직 침윤으로 인한 관류 변화 및 이로 인한 주변 간실질의 간세포 기능의 변화를 반영하며, 이는 고주파소작술(radiofrequency ablation, RFA)이나 수술 후 조기 재발을 예측하는 강력한 인자이다.[7,11-13] 간담도기 저신호강도는 나쁜 분화도(poor differentiation)을 시사하며, 미세혈관침습 및 치료 후 높은 재발률 등 불량한 예후와 밀접한 관련이 있다.[13-16] 또한, 확산강조영상(diffusion weighted image, DWI)에서의 확산제한은 높은 세포 충실도와 낮은 분화도를 의미하며, 종양 내 괴사와 마찬가지로 높은 혈관침범율 및 수술 후 조기 전이의 위험성을 시사한다.[11,17-20]

반대로 환자의 긍정적인 예후를 시사하는 영상 소견들도 존재한다. 문맥기나 지연기에서 종양을 매끄럽게 둘러싸는 저신호 띠 (hypointense halo)나 매끄러운 간담도기 저신호 띠 (smooth HBP hypointense rim)는 종양 피막(capsule)을 시사하는 소견이다.[21,22] 이는 종양의 침습적 성장을 억제하는 물리적 장벽으로 작용하여 낮은 미세혈관침습 발생률과 연관된다.[21,22] 또한 간담도기 고신호강도 (HBP hyperintensity)는 OATP1B3 수용체의 과발현을 시사하는데, 이는 대개 분화도가 좋은 초기 단계의 암이거나 특정 유전자 변이(CTNNB1)를 가진 비증식형(non-proliferative) 암종임을 예측할 수 있어 상대적으로 양호한 예후를 보인다.[23,24]

Table 1. Summary of Suggested Prognostic Imaging Features of Hepatocellular Carcinoma on Preoperative MRI

MRI Findings	Definition	Histopathologic Correlation	Pooled DOR* for MVI (39)	Prognosis
Non-smooth tumor margin	Irregular outer contour of margin, or has bulging, nodular projection, or infiltration (17)	Macrovascular invasion and MVI	3.2†	Poor
Rim APHE	APHE most pronounced in observation periphery (32)	MVI, VETCs, necrosis	4.2†	Poor
Peritumoral APHE	Non-mass-like area of APHE adjacent to the mass which fades in post-AP phases (17)	MVI	4.4†	Poor
Peritumoral HBP hypointensity	Non-mass-like hypointensity adjacent to the mass in HBP (17, 48)	MVI	8.2†	Poor
HBP hyperintensity	Tumor signal intensity higher than surrounding liver parenchyma on HBP (17)	Well- or moderate differentiation Overexpression of OATP1B3	N/A	Good
HBP hypointensity	Tumor signal intensity similar to or lower than that of vessels on HBP (17)	MVI Poor differentiation	2.1	Poor
Diffusion restriction	Hyperintensity compared to the liver on high b-value DWI (17)	Poor differentiation MVI	3.6	Poor
Necrosis	Non-enhancing area in a solid mass, not attributable to cystic portion, prior treatment or intratumoral hemorrhage (17)	Poor differentiation Vascular invasion	N/A	Poor
Intratumoral artery	Intratumoral vessel enhancing on arterial phase (83)	Moderate or poor differentiation MVI	N/A	Poor
Smooth HBP hypointense rim	Smooth rim on HBP with hypointensity compared to the tumor and liver parenchyma (79)	Fibrous capsule Less MVI	N/A	Good
Hypointense halo	A discrete rim of hypointensity circumscribing the tumor on both AP and PVP (20, 76, 83)	Fibrous capsule Less MVI	N/A	Good

*Pooled DOR of imaging findings for diagnosing MVI, as reported in reference (39).
†Imaging findings with statistically significant meta-analytic pooled DOR for MVI. Imaging findings without reported pooled DORs in the systematic review are marked as N/A.
AP = arterial phase, APHE = arterial phase hyperenhancement, DOR = diagnostic odds ratio, DWI = diffusion-weighted image, HBP = hepatobiliary phase, MVI = microvascular invasion, N/A = not available, OATP1B3 = organic anion transport polypeptide 1B3, PVP = portal venous phase, VETC = vessels encapsulating tumor clusters

영상의학적 생물표지자의 임상적 가치와 전망

결론적으로 MRI는 간세포암의 진단을 넘어 종양의 공격성과 환자의 생존 가능성을 예측하는 필수적인 도구로 자리 잡았다.[7] 예후 예측을 위한 다양한 영상 소견의 단독 사용은 물론, 이들의 조합 및 인공지능 기반의 기술을 활용한 접근이 환자 맞춤형 치료 전략 수립에 중요한 역할을 할 수 있을 것으로 기대된다.

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Recent Update of AI Application in Liver Imaging

신재승
(성균관의대)

MEMO

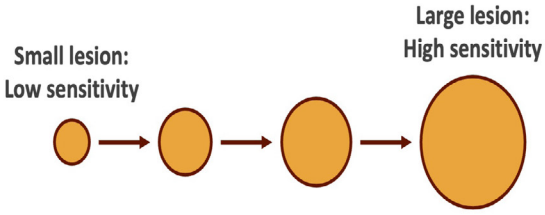
MEMO

HCC Surveillance: The Cutting-Edge

이 형 진
(연세의대)

Limitation of US based HCC surveillance

- **Limited sensitivity, especially for small lesions**
  - Generally, sensitivity of surveillance exams is highly dependent on tumor size
  - US shows particularly low sensitivity in small lesions (<2cm); approximately 20%



Reference standard: explant pathology

Table 2. Sensitivity of HCC Detection

Size	US	CT	MRI
Per-nodule	92/200 (46%)	126/194 (65%)	126/175 (72%)
<2 cm	20/96 (21%)	35/88 (40%)	33/70 (47%)
2–4 cm	44/71 (62%)	59/74 (80%)	66/77 (86%)
≥4 cm	28/33 (85%)	32/32 (100%)	27/28 (96%)
Per-patient	88/138 (64%)	113/149 (76%)	99/117 (85%)

Table 6. Specificity and Positive Predictive Value

	US	CT	MRI
Specificity[a]	281/292 (96%)	236/247 (96%)	86/99 (87%)
Positive predictive value[b]	92/104 (89%)	126/148 (85%)	126/145 (87%)
<2 cm	22/27 (82%)	42/57 (74%)	43/56 (77%)
≥2 cm	70/77 (91%)	84/91 (92%)	83/89 (93%)

[a]All patients.
[b]Lesion-based; excludes false-positive studies with nonmeasurable, indiscrete abnormalities.

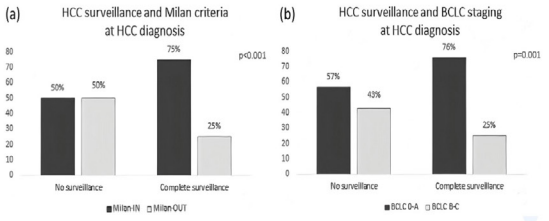
Clin Gastroenterol Hepatol. 2011;9(2):161-7

Limitation of US based HCC surveillance

- **Consequence of Limited Sensitivity: Surveillance failure**
  - Approximately 31.2% of HCCs were detected beyond the early stage in US based surveillance

Table 1 Results of the meta-analyses for the rate of surveillance failure and ORs of the risk factors for surveillance failure

Covariate	Subgroup (number of studies)	Pooled incidence of surveillance failure,* % (95% CI)	I^2 statistics (%)	Proportion of HCC detected beyond early stage (%)
Study design	Prospective (n=9)	2.2 (1.3 to 3.5)	95	24.6
	Retrospective (n=9)	3.1 (1.8 to 5.0)	88	31.8
Study population	Western (n=11)	3.1 (2.0 to 4.8)	90	36.0
	Eastern (n=7)	1.9 (1.1 to 3.3)	94	20.6
Proportion of cirrhosis patients	All cirrhosis (n=13)	3.6 (2.6 to 4.8)	89	32.7
	Others† (n=5)	1.1 (0.7 to 1.8)	74	21.5
Surveillance interval	6 months (n=10)	2.4 (1.5 to 3.7)	89	23.7
	6–12 months (n=4)	1.9 (1.0 to 3.8)	89	22.0
Study quality	High-quality study‡ (n=16)	2.5 (1.7 to 3.7)	91	26.2
	Low-quality study‡ (n=2)	2.7 (0.9 to 7.3)	99	37.4



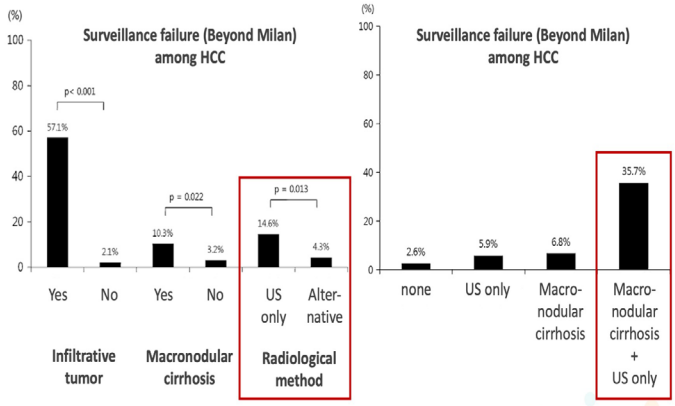
Surveillance failure rate:
US Surveillance: 25%, No Surveillance: 45-50%

Gut. 2022 Jan;71(1):212-213, Annals of Hepatology 25 (2021) 100344

Limitation of US based HCC surveillance

- **Factors related with surveillance failure**
  - Male, high BMI, high AFP
  - Macronodular cirrhosis, US only surveillance, infiltrative appearance
  - **→ Surveillance failure is frequent in patients with poor visualization**

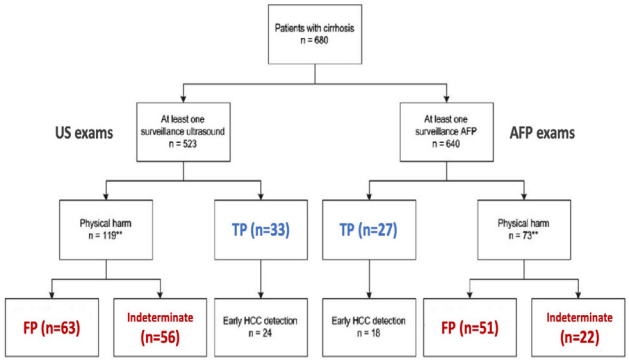
Risk factor	Pooled odds ratio (95% CI)	I^2 statistics	P value
Sex (male)	1.38 (1.02 to 1.86)	0	0.04
Age (≥65 years)	0.94 (0.01 to 79.98)	0	0.89
Diabetes mellitus	1.26 (0.01 to 137.81)	49	0.65
BMI (≥30 kg/m^2)	1.29 (1.27 to 1.30)	0	<0.01
Child-Turcotte-Pugh classification (B)§	1.36 (0.70 to 2.66)	32	0.19
Hepatitis B	1.42 (0.19 to 10.43)	0	0.27
Hepatitis C	0.29 (0.0 to 1.2×10^6)	75	0.49
Alpha-fetoprotein (≥100 ng/mL)¶	2.72 (1.15 to 6.43)	31	0.04
Inadequate echogenic window on US	1.51 (0.62 to 3.69)	0	0.19
Liver stiffness (>9.5 kPa)	1.73 (0.0 to 1.7×10^6)	64	0.70



Gut. 2022;71(1):212-213, Hepatol Int. 2013;7:1010–1018

Limitation of US based HCC surveillance

- **High false positive referral rate – related with potential harm of surveillance**
  - False positive in surveillance can cause
    - Physical harm – ex) complications with unnecessary biopsy
    - Financial harm – ex) cost of unnecessary dynamic CT/MRI
    - Psychological harm – ex) fear of HCC from false positive result
  - In US surveillance, false positive results are much more common than true positive results



n=60 : HCC (Early HCC: n=42)
n=192 : Overall FP+indeterminte

Gastroenterology 2019;157:54–64, Hepatology. 2017 Apr;65(4):1196-1205, Liver Transpl. 2019 Mar;25(3):369-37

Non-contrast abbreviated MRI: advantage

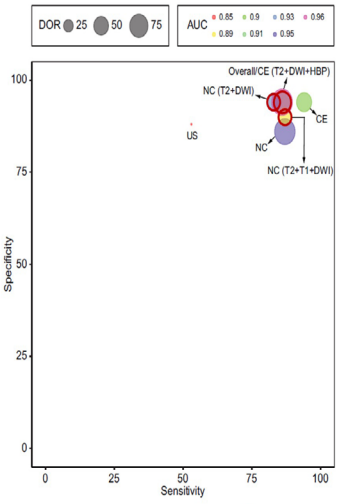
- **Advantage (1)** Comparable diagnostic performance with other AMRI protocols

Non-contrast protocol:
T2WI, DWI + (T1WI)

Diagnostic performance:
Non-contrast AMRI protocol
Sensitivity/specificity 86%/94%

HBP AMRI protocol
Sensitivity/specificity 87%/94%

1st Author	AMRI	Sequences used in AMRI
Kim YK	NC	T2W, T1W, DWI
Marks RM	CE	T2W, HBP T2W, HBP, DWI
Jalli R	NC	T2W, T1W DWI T2W, T1W, DWI
Sutherland T	NC	DWI
Besa C	CE	DWI T1W HBP T1W, DWI, CEMRI
Tillman BG	CE	T2W, HBP
Han S	NC	T2W, T1W, DWI
Khatri G	CE	Dynamic CEMRI
Kim JS	NC	T2W, DWI T2W, DWI, T1W
Chan MV	NC	T2W, T1W, DWI
Park HJ	NC	T2W, DWI
Brunsing RL	CE	T2W, DWI, HBP
Whang S	CE	T2W, T1W, DWI T2W, T1W, DWI, HBP
Vietti Violi N	CE	T2W, DWI T2W, DWI, HBP T2W, Dynamic CEMRI
Ahmed NNA	NC	T2W T2W, DWI

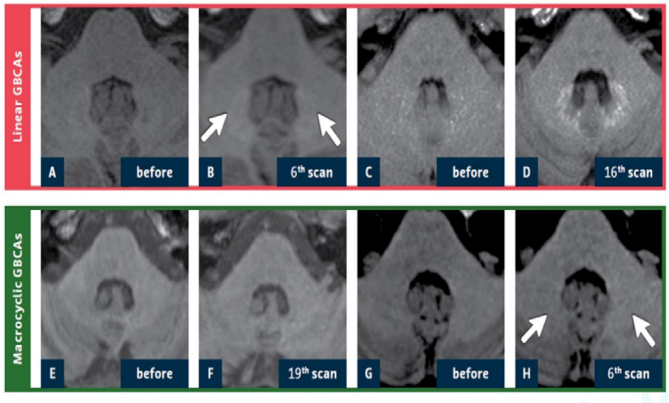


J Hepatol. 2021 Jul;75(1):108-119

THE 7TH YONSEI LIVER SUMMIT

Non-contrast abbreviated MRI: advantage

- **Advantage (2):** No contrast media injection
  - No cost for contrast media (approx. 20 USD for ECA agent, 100 USD for gadoxetic acid)
  - No risk of contrast media-related complication (e.g., NSF, gadolinium deposition)
  - No intravenous setup required
  - No waiting time for HBP



JPERM 2019;11:72-83

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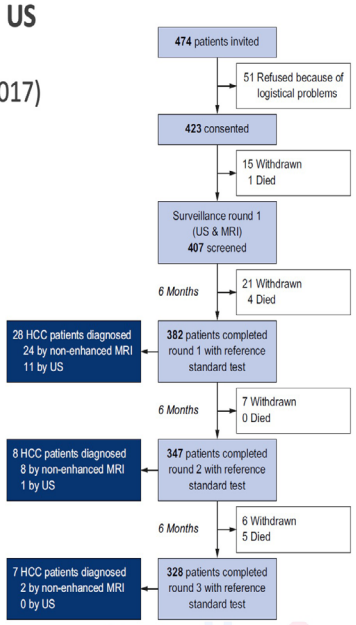
Non-contrast abbreviated MRI: Diagnostic performance

- **Non-contrast AMRI shows better sensitivity when compared with US**
  - Secondary analysis of prospective study
    (PRIUS, Full gadoxetic acid-enhanced MRI surveillance, Jama oncol. 2017)
  - Cirrhotic patients (annual risk >5%)
  - Intra-individual design: 3 cycles of simulated AMRI (T2, DWI) and US

	Non-enhanced MRI	Ultrasound	*p* value
Per-lesion			
Sensitivity	77.1 (37/48, 63.2–86.8)	25.0 (12/48, 14.8–39.1)	<0.001
Per-exam			
Sensitivity	79.1 (34/43, 64.4–88.7)	27.9 (12/43, 16.6–43.0)	<0.001
Specificity	97.9 (993/1,014, 96.8–98.7)	94.5 (958/1,014, 92.9–95.7)	<0.001

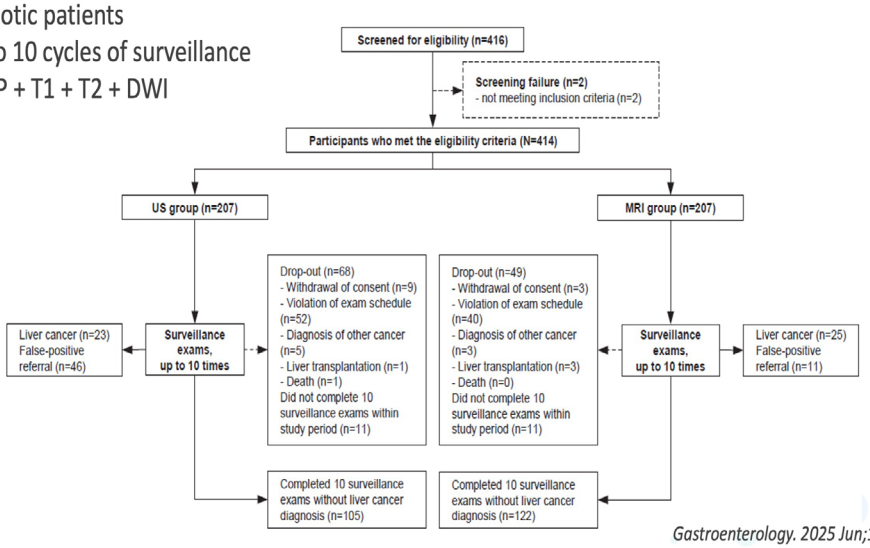
Full gadoxetic acid-enhanced MRI (Category 4,5):
Sensitivity 86%
Specificity 97%



J Hepatol. 2020 Apr;72(4):718-724, JAMA Oncol. 2017;3(4):456-463

Non-contrast abbreviated MRI: Stage and false-positive referral

- **Earlier stage at diagnosis and low false positive referral than US**
  - Randomized, single center trial
    : biannual ncMRI + AFP vs. US + AFP
  - Cirrhotic patients
  - Up to 10 cycles of surveillance
    IP/OP + T1 + T2 + DWI

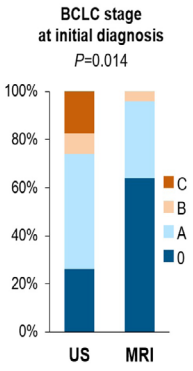


Gastroenterology. 2025 Jun;168(6):1170-1177

Non-contrast abbreviated MRI: Stage

- **Non-contrast MRI: Earlier stage at diagnosis than US**

	Liver cancers in US group (n=23)	Liver cancers in MRI group (n=25)	P value
BCLC stage, No. (%)			0.014
0	6 (26%) [10 – 48%]	16 (64%) [43 – 82%]	
A	11 (48%) [27 – 69%]	8 (32%) [15 – 54%]	
B	2 (9%) [1 – 28%]	1 (4%) [0.1 – 20%]	
C	4 (17%) [5 - 39%]	0 (0%)	
Surveillance failure, No. (%)	6 (26%)	1 (4%)	
Number of liver cancer lesions on dynamic imaging, No. (%)			
1	17 (74%)	21 (84%)	
2	5 (22%)	2 (8%)	
3	1 (4%)	1 (4%)	
>4	0 (0%)	1 (4%)	
Size of the liver cancer, median (IQR), mm	25 (20-33)	17 (13-20)	
Macrovascular invasion, No. (%)	3 (13%)	0 (0%)	
Extrahepatic metastasis, No. (%)	1 (4%)	0 (0%)	
Result of last surveillance exam, No. (%)			
Positive in both image and AFP	5 (22%)	7 (28%)	
Positive only in image	5 (22%)	16 (64%)	
Positive only in AFP	7 (30%)	2 (8%)	
False-negative	6 (26%)	0 (0%)	



Gastroenterology. 2025 Jun;168(6):1170-1177

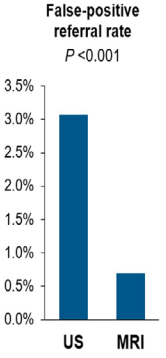
THE 7TH YONSEI LIVER SUMMIT

Non-contrast abbreviated MRI: False-positive referral

- **Non-contrast MRI: Low false positive referral than US**

	US group (n=207)	MRI group (n=207)	P value
Rate of false-positive referral, % (No./total No.)	3.1% [2.3 – 4.1%] (46/1496)	0.7% [0.4 – 1.2%] (11/1575)	<0.001

	US group	MRI group
Rate of unscheduled dynamic exams, % (No./total No.)	23/1496 (1.5%)	7/1575 (0.4%)
Reason for unscheduled dynamic exams, No. (%)		
Unspecified	6 (26%)	2 (29%)
Gastrointestinal tract bleeding	5 (22%)	1 (14%)
Poor echo window	3 (13%)	0 (0%)
Elevated PIVKA-II	2 (9%)	0 (0%)
Liver failure	1 (4%)	0 (0%)
Suspected liver lesion in images taken at outside hospital	1 (4%)	1 (14%)
Suspected liver lesion in images taken at emergency room	1 (4%)	1 (14%)
Subcentimeter hepatic nodule evaluation	1 (4%)	1 (14%)
Evaluation for liver transplantation	1 (4%)	0 (0%)
Evaluation for BRTO	1 (4%)	0 (0%)
Hemangioma follow-up	1 (4%)	0 (0%)
Elevated AFP at outside hospital	0 (0%)	1 (14%)



Gastroenterology. 2025 Jun;168(6):1170-1177

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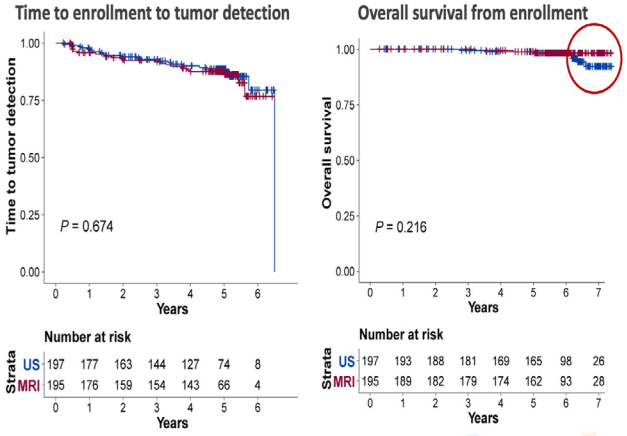
Non-contrast abbreviated MRI: Outcome

- **Non-contrast MRI: Higher curative treatment rate than US, but outcome?**
  - To delineate the survival benefit,
    large scale multicenter trial (>1000 subjects) with long term follow-up (>10 years) might be needed

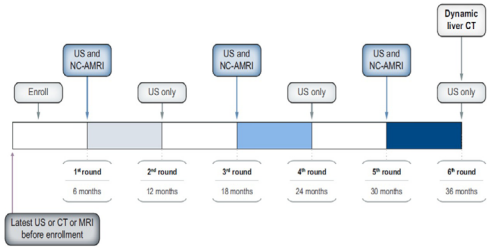
	Liver cancers in US group (n=21)	Liver cancers in MRI group (n=23)
Initial treatment		
Resection	6 (29%)	13 (57%)
Ablation	1 (5%)	5 (22%)
Ablation + TACE	1 (5%)	0 (0%)
Transplantation	0 (0%)	1 (4%)
External beam RTx	2 (10%)	1 (4%)
TACE	11 (52%)	3 (13%)
Curative initial treatment	38% (8/21)	83% (19/23)

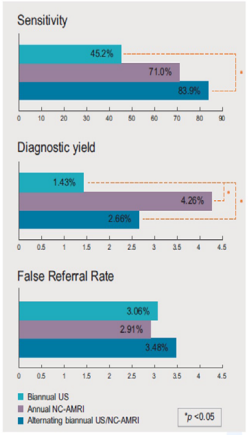


Gastroenterology. 2025 Jun;168(6):1170-1177

Annual ncMRI or alternating ncMRI-US strategy

- **Annual ncMRI shows marginally better sensitivity than biannual US**
  - Prospective, multicenter study
  - Cirrhotic patients (annual risk >5%)
  - Intra-individual design: biannual US + annual ncMRI (IP/OP, T1, T2, DWI)





	Biannual US	Annual NC-AMRI	Alternating biannual US/NC-AMRI*	p value†	p value‡
All HCCs (n = 31)					
Sensitivity	45.2 (14/31, 27.8–63.7)	71.0 (22/31, 51.8–85.1)	83.9 (26/31, 65.5–93.9)	0.077	0.006
Specificity	88.7 (157/177, 82.9–92.8)	92.7 (164/177, 87.5–95.9)	84.7 (150/177, 78.4–89.5)	0.281	0.146
Positive predictive value	31.8 (14/44, 19.0–48.2)	59.5 (22/37, 42.0–74.8)	43.3 (26/60, 30.5–57.1)	0.006	0.043
Negative predictive value	98.6 (923/936, 97.6–99.2)	100 (479/479)	99.8 (916/918, 99.1–100)	n.a.	0.004
Diagnostic yield	1.43 (14/980, 0.84–2.41)	4.26 (22/516, 2.82–6.41)	2.66 (26/978, 1.80–3.90)	<0.001	<0.001
False referral rate	3.06 (30/980, 1.96–4.76)	2.91 (15/516, 1.66–5.04)	3.48 (34/978, 2.38–5.05)	0.885	0.453
Very early-stage HCC (n = 20)					
Sensitivity	40.0 (8/20, 20.0–63.6)	75.0 (15/20, 50.6–90.4)	85.0 (17/20, 61.1–96.0)	0.070	0.008

J Hepatol. 2024 Sep;81(3):461-470

Non-contrast abbreviated MRI: Real-world experience

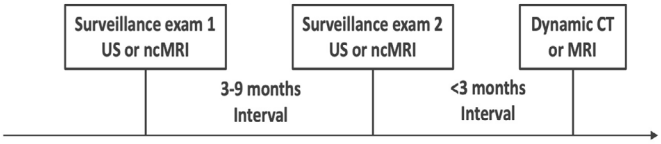
- **In our institution, ncMRI is utilized as surveillance test in clinical practice**
  - Comparison of US and ncMRI in a real-world setting
  - ncMRI shows higher diagnostic performance and lower surveillance failure rates

HCC-high risk patients underwent one or more "Diagnostic round" (n = 421)

Diagnostic round: "1st surveillance exam – 2nd surveillance exam - diagnostic exam" in sequence
- Interval between 1st and 2nd surveillance exams: 3-9 months
- Interval between 2nd surveillance exam and diagnostic exam: less than 3 months
- 2nd surveillance exam: Jan 2018 – Dec 2023

Excluded (n =83)
- Prior history of HCC at 2nd surveillance (n = 83)

338 patients with 345 diagnostic rounds
- 164 focal hepatic lesions were detected on 2nd surveillance exam



Four groups according to the surveillance exam 1 and 2
- US-US group
- ncMRI-US group
  } US group
- US-ncMRI group
- ncMRI-ncMRI group
  } ncMRI group

Kim et al, manuscript in prepration

Non-contrast abbreviated MRI: Real-world experience

- **In our institution, ncMRI is utilized as surveillance test in clinical practice**
  - Comparison of US and ncMRI in a real-world setting
  - ncMRI shows higher diagnostic performance and lower surveillance failure rates

	US group (n = 242)	ncMRI group (n = 103)	P value
Per-lesion, % (95% CI)			
Sensitivity	46.2 (36.1 – 56.5)	97.9 (86.8 – 99.7)	< 0.001
PPV	40.0 (30.3 – 50.6)	62.2 (50.2 – 72.8)	0.006
Per-patient, % (95% CI)			
Sensitivity	58.1 (49.5 – 66.2)	100 (100 – 100)	< 0.001
Specificity	72.6 (65.6 – 78.6)	60.0 (47.1 – 71.7)	0.069
PPV	42.4 (32.3 – 53.0)	64.2 (52.1 – 74.7)	0.008
NPV	83.3 (78.0 – 87.6)	100 (100 – 100)	< 0.001

	US group (n = 62)	ncMRI group (n = 43)	P value
Diameter of largest tumor (cm)	2.8 (1.9 – 3.7)	1.8 (1.4 – 2.5)	< 0.001
Number of tumors			0.204
1	50 (80.6)	40 (93.0)	
2	8 (12.9)	2 (4.7)	
≥ 3	4 (6.5)	1 (2.3)	
BCLC stage			0.002
0	14 (22.6)	25 (58.1)	
A	32 (51.6)	14 (32.6)	
B	8 (12.9)	3 (7.0)	
C	8 (12.9)	1 (2.3)	
Surveillance failure rate, %	25.8	9.3	0.034
Initial treatment, n (%)			0.301
Hepatic resection	18 (29.0)	17 (39.6)	
Liver transplantation	0 (0.0)	2 (4.7)	
Ablation	7 (11.3)	5 (11.6)	
TACE	25 (40.3)	12 (27.9)	
TARE	2 (3.2)	1 (2.3)	
EBRT	4 (6.5)	1 (2.3)	
Systecmic treatment	2 (3.2)	4 (9.3)	
Follow up loss or no treatment	2 (3.2)	4 (9.3)	
Curative treatment rate, %	40.3	55.8	0.118

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Non-contrast abbreviated MRI: Real-world experience

- **In our institution, ncMRI is utilized as surveillance test in clinical practice**
  - Comparison of US and ncMRI in a real-world setting
  - ncMRI shows higher diagnostic performance and lower surveillance failure rates
  - Not only the surveillance exam immediately prior to HCC diagnosis, but the preceding exams are also important for early HCC detection.

	US-US group (n = 59)	ncMRI-US group (n = 3)	US-ncMRI group (n = 20)	ncMRI-ncMRI group (n = 23)	P value
Diameter of largest tumor (cm)*	2.8 (2.0 – 3.9)	1.3 (1.1 – 1.5)	1.8 (1.4 – 3.1)	1.8 (1.3 – 2.2)	< 0.001
Number of tumors					0.577
1	47 (79.6)	3 (100.0)	18 (90.0)	22 (95.7)	
2	8 (13.6)	0 (0.0)	1 (5.0)	1 (4.3)	
More than 3	4 (6.8)	0 (0.0)	1 (5.0)	0 (0.0)	
BCLC stage					0.015
0	12 (20.3)	2 (66.7)	11 (55.0)	14 (60.9)	
A	31 (52.5)	1 (33.3)	6 (30.0)	8 (34.8)	
B	8 (13.6)	0 (0.0)	3 (15.0)	0 (0.0)	
C	8 (13.6)	0 (0.0)	0 (0.0)	1 (4.3)	
Surveillance failure rate, %	27.1	0.0	15.0	4.3	0.085

Kim et al, manuscript in prepration

ncMRI for post-treatment surveillance

- **ncMRI also shows good diagnostic performance in post-treatment setting**
  - s/p Resection or ablation
  - Comparison of ncMRI vs. full gadoxetic acid enhanced MRI
    - No significant difference in diagnostic performance when >1-2 years have passed since treatment
    - Aggressive recurrence immediately after treatment (e.g., tiny intrahepatic metastasis, portal vein tumor thrombosis, extrahepatic metastasis) could be a cause of lower performance of ncMRI.

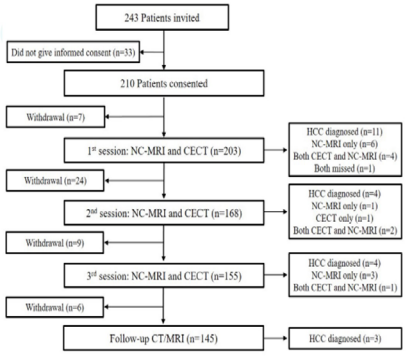
	Modality	TP	TN	FP	FN	Az value (95% CI)	Sensitivity	Specificity	Accuracy	PPV	NPV
Consensus	Non-contrast MRI	107	364	6	6	0.972 (0.951,0.993)	94.7	98.4	97.5	94.7	98.4
	Whole MRI	112	367	3	1	0.994 (0.985,1)	99.1	99.2	99.2	97.4	99.7
	p-value[a]					0.027	0.025	0.257	0.021	0.234	0.026

	Modality	TP	TN	FP	FN	Az value (95% CI)	Sensitivity	Specificity	Accuracy	PPV	NPV
<1 year (*n* = 360)	Non-contrast MRI	84	267	5	4	0.975 (0.953,0.998)	95.5	98.2	97.5	94.4	98.5
	Whole MRI	87	269	3	1	0.992 (0.98,1)	98.9	98.9	98.9	96.7	99.6
	p-value[a]					0.098	0.083	0.414	0.096	0.387	0.084
1–2 years (*n* = 94)	Non-contrast MRI	16	76	0	2	0.943 (0.865,1)	88.9	98.7	96.8	94.1	97.4
	Whole MRI	18	76	0	1	1 (1,1)	100.0	100.0	100.0	100.0	100.0
	p-value[a]					0.155	0.500	1.000[a]	0.250	0.330	0.163
≥2 years (*n* = 29)	Non-contrast MRI	7	22	0	0		100.0	100.0	100.0	100.0	100.0
	Whole MRI	7	22	0	0		100.0	100.0	100.0	100.0	100.0
	p-value[a]					N.A	N.A	N.A	N.A	N.A	N.A

Br J Radiol. 2018 Oct;91(1090):2018017, J Magn Reson Imaging. 2023 Nov;58(5):1375-1383

ncMRI for post-treatment surveillance

- **ncMRI also shows good diagnostic performance in post-treatment setting**
  - Prospective, multicenter study, 3 cycles of post-treatment surveillance
  - Patients underwent resection or ablation, and >2 years passed
  - Intra-individual comparison of ncMRI vs. dynamic CT



	Contrast enhanced CT		Non-contrast MRI		P-value
	Estimates, % (n/N)	95% CI, %	Estimates, % (n/N)	95% CI, %	
Accuracy	91.6% (186/203)	87.8-95.5	96.6% (196/203)	94.0-99.1	0.006
Sensitivity	36.4% (8/22)	14.5-58.2	77.3% (17/22)	58.3-96.3	0.012
Specificity	98.3% (178/181)	96.5-100	98.9% (179/181)	97.4-100	0.999
Positive predictive value	72.7% (8/11)	41.4-100	89.5% (17/19)	74.3-100	0.236
Negative predictive value	92.7% (178/192)	89.0-96.4	97.3% (179/184)	94.9-99.7	0.043
Diagnostic yield	1.5% (8/528)	0.5-2.6	3.2% (17/528)	1.7-4.7	0.004
False referral rate	0.9% (5/528)	0.1-1.8	0.8% (4/528)	0.1-1.5	0.999

Clin Mol Hepatol. 2025 Jun 13. doi: 10.3350/cmh.2025.0258

Current status and future perspectives

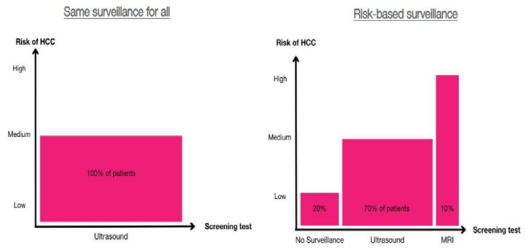
- **ncMRI shows superior diagnostic performance for HCC surveillance compared to US**

	US (biannual)	ncMRI (biannual)
Sensitivity (per patient)	20-50%	80-100%
False positive referral rate	3%	<1%
Surveillance failure rate	25-30%	5%
Survival benefit		?

  - However, all prospective studies to date have been conducted exclusively in South Korea
  - Further high-level evidence is required from diverse populations, across various underlying liver diseases, and must demonstrate a survival benefit

Current status and future perspectives

- **ncMRI cannot universally replace US for HCC surveillance due to costs and resource limitations**
  - Proposed candidates for ncMRI-based surveillance include:
    - Patients with poor US visualization (LI-RADS visualization score C)
    - Patients at very high risk of HCC (annual HCC risk >3-5%)



EASL Policy Statement (2023)
"Risk-based surveillance for HCC"

  - More studies are needed to make ncMRI more cost-effective
    - Reduce scan time – ex) breath-hold DWI
    - Increase interval – ex) alternating biannual US and ncMRI, or annual ncMRI

Current status and future perspectives

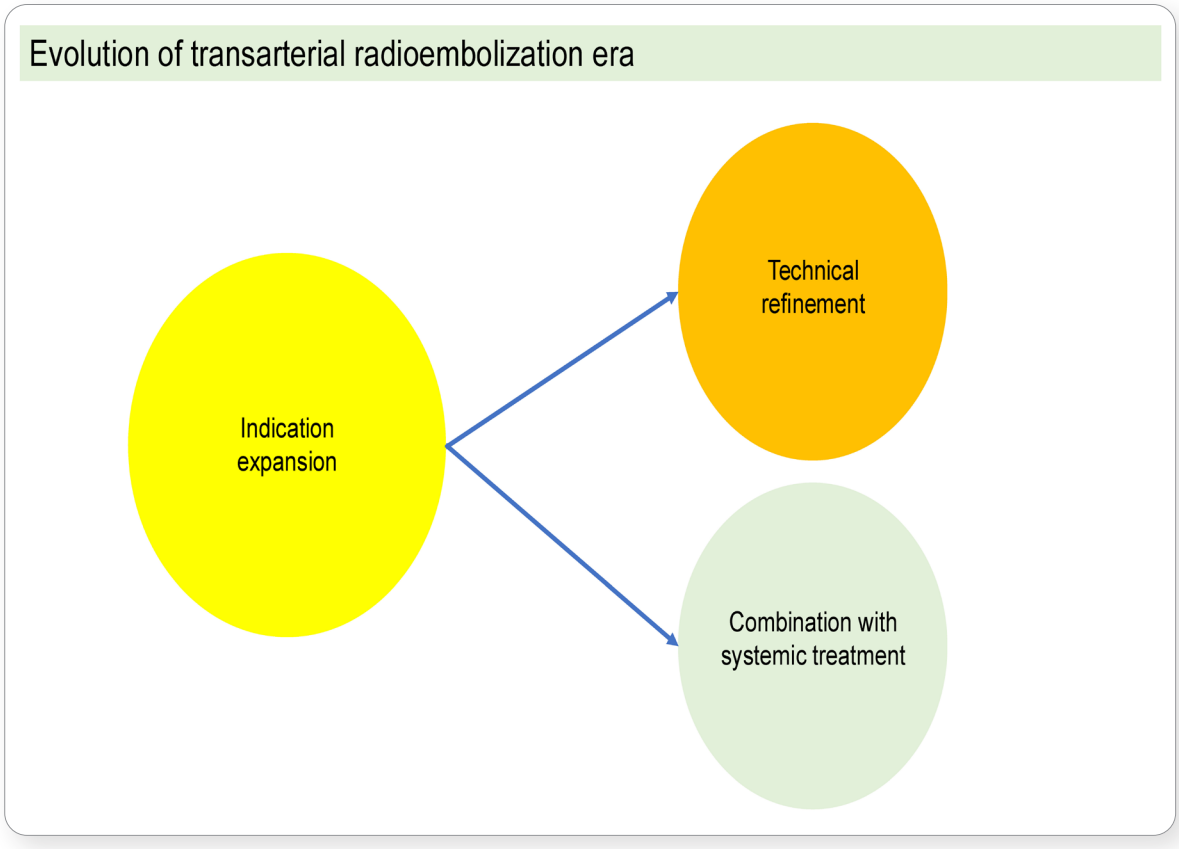
- **New frontier of ncMRI: post-treatment surveillance**
  - In patients who had undergone curative treatment at least two years earlier,
    - ncMRI shows similar detection performance to gadoxetic acid-enhanced MRI
    - ncMRI shows better performance than dynamic CT
  - ncMRI could be an attractive option in patients with chronic renal disease, and in young patients who have concerns about repeated radiation exposure

	Post-treatment		
	<1yr	**1-2yr**	**>2yr**
ncMRI vs. EOB-MRI	ncMRI < EOB-MRI	ncMRI < EOB-MRI (but not significant)	ncMRI ≒ EOB-MRI
ncMRI vs. dynamic CT	?	?	ncMRI > dyn-CT

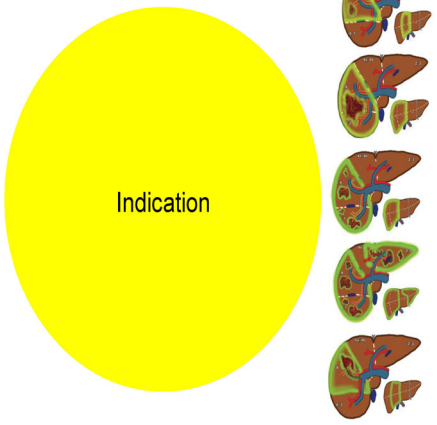
  - However, ncMRI has limited performance in cases with aggressive recurrence patterns
  - Further study is needed to optimize the ideal candidates for post-treatment ncMRI surveillance

Recent Update of Radioembolization

현동호
(성균관의대)



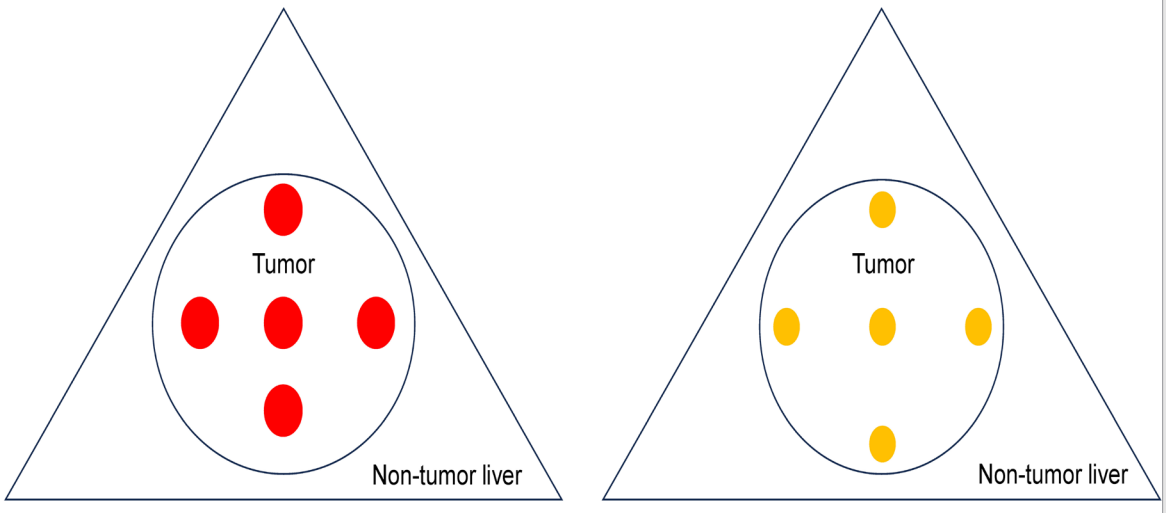
Target



Clinical scenario	Treatment intent	Ideal liver function (Child-Pugh)	Primary recommended dosimetry model	Dose goal[a]	
				Glass	Resin
Radiation segmentectomy (Y90-RS)	Curative	A–B7 >B7[b]	Single compartment (MIRD model)	>400 Gy to angiosome	>250 Gy[c] to angiosome
Radiation lobectomy (Y90-RL)	Potentially curative; contralateral hypertrophy; "test of time"	A	Multicompartment (partition model)	Non-tumor: >88 Gy Tumor: >205 Gy	Non-tumor dose: >70 Gy Tumor: >250 Gy[c] ideally
Multifocal unilobar	Palliative	A–B7	Multicompartment (partition model)	Non-tumor w/ CP A: 100–120 Gy[c] Non-tumor w/ CP B: <70 Gy[c] Tumor: >205 Gy (ideally >250 Gy)	Non-tumor: 40–70 Gy[c] Tumor: >250 Gy ideally
Multifocal bilobar	Palliative	A	Multicompartment (partition model)	Non-Tumor: 40-70 Gy Tumor: >205 Gy (Ideally >250 Gy)	Non-tumor: 30–40 Gy Tumor: >100 Gy[c]
HCC with microvascular invasion and/or portal vein thrombus	Palliative	A[b] Ideally, must have good Tc-99m MAA uptake in MVI[c]	Multicompartment (partition model)	If unilobar MVI/PVT: R90-RL vs. Y90-unilobar approach[c] If bilobar MVI/PVT: Y90-bilobar approach[c]	If unilobar MVI/PVT: R90-RL vs. Y90-unilobar approach[c] If bilobar MVI/PVT: Y90-bilobar approach[c]

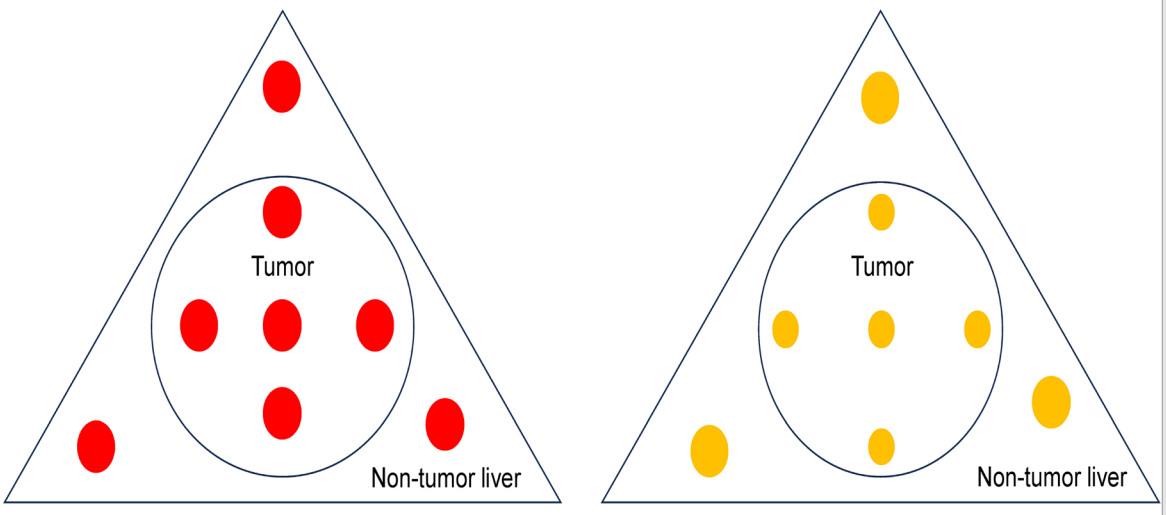
Semin Intervent Radiol 2024;41:63

Spheres : particle loading



Ideal delivery

Spheres : particle loading

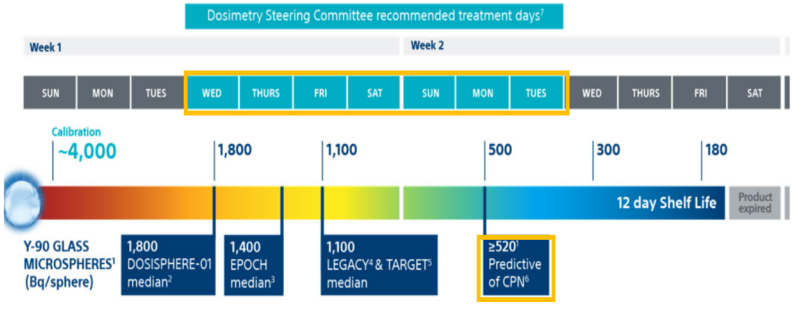


Real delivery

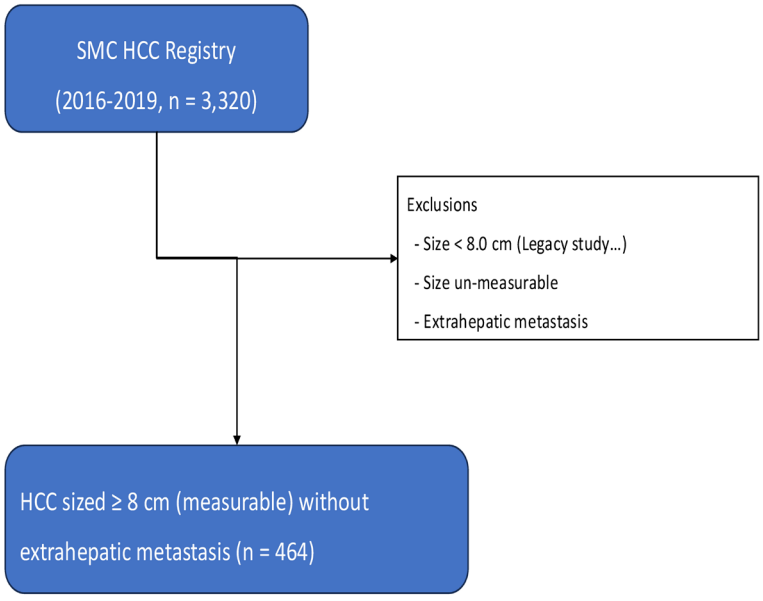
Spheres : sphere activity

Radiation per microsphere (RPM)

Activity (± 10% GBq)	Prior Spheres / Vial (millions)	Refined Spheres / Vial (millions)
3	1.2	0.75
5	2	1.25
7	2.8	1.75
10	4	2.50
15	6	3.75
20	8	5.00

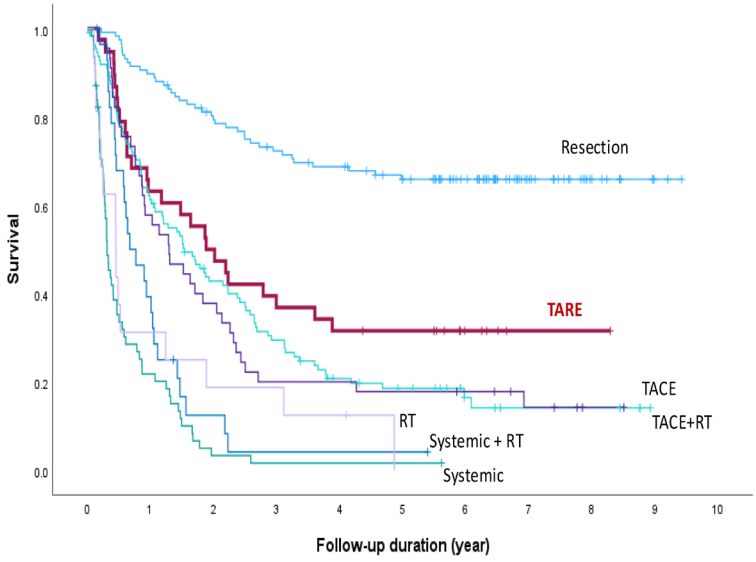


SMC experience



SMC experience

OS according to initial modalities



Initial treatment modality	N (%)
Resection	117 (25.2)
TACE	112 (24.1)
Systemic (TKI, ICI)	62 (13.4)
TACE+RT	45 (9.7)
TARE	**38 (8.2)**
Systemic + RT	29 (6.3)
EBRT	16 (3.4)

SMC experience

TARE for large (>= 8cm) HCC (n=38)

- 5-years survival rate: 32%
- 5-years cancer survivor: 11/38 (29%)
- **NED after single TARE treatment : none (0%)**
- NED after TARE based treatment: 3/38 (8%)
  - Single large tumor without vascular invasion
    - TACE + resection: 1 patients
    - TACE + PBT: 2 patients

KURE-YTT-HCC study

A Korean multicenter prospective observational study

On efficacy of ^{90}Y for hepatocellular carcinoma

Prospective observational, single-arm, multicenter study in five Korean sites **(n=200)**

October 2024

Enroll period: April 1, 2022 ~ March 31, 2024 (2 yrs)
Follow-up until December 31, 2025 **(22 ~ 45 months)**

Inclusion criteria

A. Patients receiving TARE using TheraSphere®
B. Treatment naïve BCLC 0 or A single HCC up to 8 cm (diagnosed according to diagnostic criteria of KLCA-NCC)
C. Tumor involvement < 50% of total liver volume based on dynamic CT or MRI
D. Age > or = 18
E. ECOG performance status 0
F. AST/ALT < or = 5 times the upper limits of normal
G. A life expectancy > 3 months
H. Non-pregnant with an acceptable contraception in premenopausal women
I. Ability to provide written informed consent and to comply with all study conditions

대한방사선색전술연구회 THE KOREAN RADIOEMBOLIZATION ASSOCIATION
SNUH 서울대학교병원
SAMSUNG 삼성서울병원
국립암센터 NATIONAL CANCER CENTER
세브란스 SEVERANCE

Primary endpoint : overall survival, best target lesion response
Secondary endopoint: Time to target lesion progression, time to overall progression, treatment-related adverse events rate

KURE-YTT-HCC, interim analysis

Baseline characteristics

			n=154
Age (year)	68.9 (40~88)		
Gender			
	men	108	70.1%
	women	46	29.9%
HCC etiology			
	HBV	91	59.1%
	HCV	15	9.7%
	Alcohol	13	8.4%
	NAFLD	12	7.8%
	Others	23	14.9%
Tumor size (cm)	3.95cm (median)	(1.2 ~ 8.0 cm)	3.98cm (mean)
	<3	48	31.1%
	3 ~ 5	66	42.8%
	5 ~ 8	40	25.9%
CP score			
	5	132	85.7%
	6	20	12.9%
	7	2	1.2%

Etiology representing domestic causes

Well balanced tumor size distribution

Tumor markers		
AFP	614.2	(1.1~ 25562)
PIVKA-II	1402.6	(1.4 ~ 29521)

LEGACY study		Treated Population (n = 162), n (%)
Age	18-64	69 (42.6%)
	65-74	64 (39.5%)
	≥75	29 (17.9%)
Gender	Male	123 (75.9%)
	Female	39 (24.1%)
Race	White	80 (49.4%)
	Black or African-American	16 (9.9%)
	Asian	13 (8.0%)
	Native American, Alaska Native	2 (1.2%)
	Native Hawaiian, Pacific Islander	2 (1.2%)
	Not reported	49 (30.2%)
HCC etiology	HBV	15 (9.3)
	HCV	112 (69.1%)
	NASH	23 (14.2%)
	Autoimmune disease	3 (1.9%)
	Alcohol	48 (29.6%)
	Unknown	4 (2.5%)
	Other	1 (0.6%)
Tumor size	<3 cm	100 (61.7%)
	3-5 cm	50 (30.9%)
	>5-8 cm	9 (5.6%)
	Missing	3 (1.9%)
BCLC/ECOG score	BCLC A (ECOG 0)	98 (60.5%)
	BCLC C (ECOG 1)	64 (39.5%)
Child-Pugh score	A5	108 (66.7%)
	A6	54 (33.3%)

Median 2.7cm (1.0 ~ 8.1cm)

KURE-YTT-HCC, interim analysis

Radioembolization specification

Lung shunt fraction (%, n=90)	2.88% (0.76~7.92)
Lung dose (Gy, n=90)	5.71 (0.56~14.75)
Mean absorbed dose (Gy, n=154)	481.2 (54~1958)

Treatment level		
Lobar	11	7.1%
Radiation segmentectomy	141	91.5%
Multisegmental (feeders>3)	2	1.2%

LEGACY study		Treated Population (n = 162), n (%)
Treatment approach and goal	Radiation segmentectomy	95 (58.6%)
	Radiation lobectomy	4 (2.5%)
	Downsizing to surgery	4 (2.5%)
	Bridge to LT	36 (22.2%)
	Treat to local tumor control	9 (5.6%)
	Other	1 (0.6%)
	Unknown	13 (8.0%)
Lung shunt fraction mean (SD), median [IQR]		4.5, (3.4), 4.0 [2.3, 5.]
Total number of vials administered (first treatment)	1	118 (72.8%)
	2	38 (23.5%)
	3	6 (3.7%)
Type of infusion	Selective	155 (95.7%)
	Lobar	3 (1.9%)
	Mixed	4 (2.5%)
Absorbed dose to treated liver volume (Gy), mean (SD), median [IQR] (n = 155)		578.6 (540.1), 410 [199.7, 797.7]
Number of ^{90}Y treatments	1	130 (80.2%)
	≥ 2	32 (19.8%)

KURE-YTT-HCC, interim analysis

Results

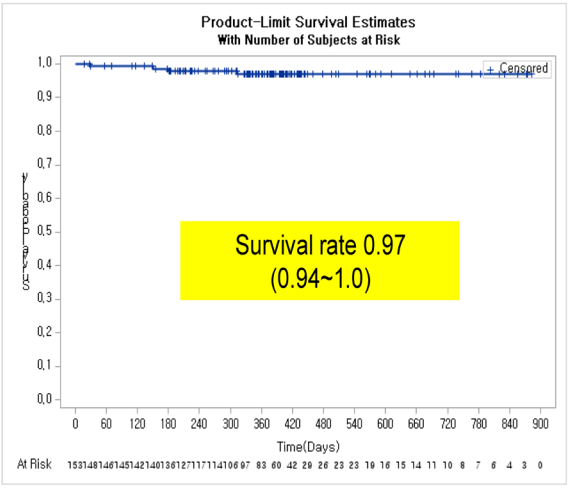
Follow-up period	311 days (28 ~ 883) median	
Follow-up status		
Active (alive)	135	87.6%
Lost-to-follow-up	15	9.7%
Died	4	2.6%

* Unknown (2), varix bleeding (1), dz progression (2)

All adverse events		
None	138	89.6%
Ascites without jaundice	1	0.6%
REILD	1	0.6%
Bile duct dilatation	4	2.5%
Radiation pneumonitis	0	0%
Others	**10	6.4%

** asymptomatic PV thrombosis (n=2), flank pain (n=1), pneumonia (n=1), focal hepatic necrosis (n=2), pleural effusion (n=4)

Treatment related adverse event (CTCAE)
High grade (n=1)



Overall survival
Median OS not reached

KURE-YTT-HCC, interim analysis

Results

Follow-up period	9 months	(1~19)
Follow-up status		
Acitve	88	90.70%
Lost-to-follow-up	8	8.20%
Died	*1	1%

* Disease progression

All adverse events		
None	89	91.80%
Ascites without jaundice	1	1%
Bile duct dilatation	1	1%
Radiation pneumonitis	0	0%
Others	**5	5.20%

** asymptomatic PV thrombosis (n=2), flank pain (n=1), pneumonia (n=1),
Acute gastric mucosal lesion (n=1)

Treatment related adverse event (CTCAE)
High grade (n=0)

Results

Follow-up period	10.3 months median	(1 ~ 29)
Follow-up status		
Active (alive)	135	87.6%
Lost-to-follow-up	15	9.7%
Died	4	2.6%

* Unknown (2), varix bleeding (1), dz progression (2)

All adverse events		
None	138	89.6%
Ascites without jaundice	1	0.6%
REILD	1	0.6%
Bile duct dilatation	4	2.5%
Radiation pneumonitis	0	0%
Others	**10	6.4%

mbosis (n=2), flank pain (n=1), pneumonia (n=1),
=2), pleural effusion (n=4)

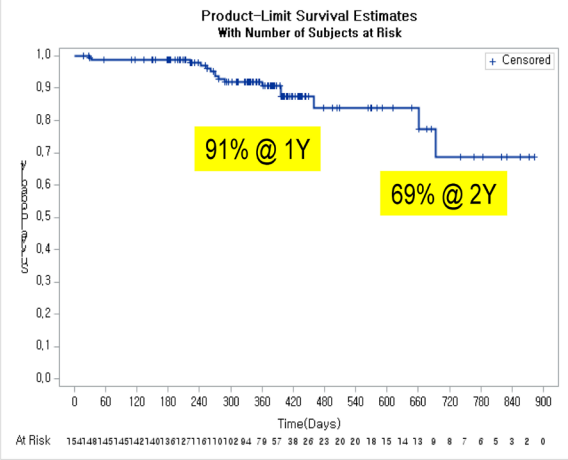
No radiation pneumonitis
In patients without Tc-99m scan

Treatment related adverse event (CTCAE)
High grade (n=1)

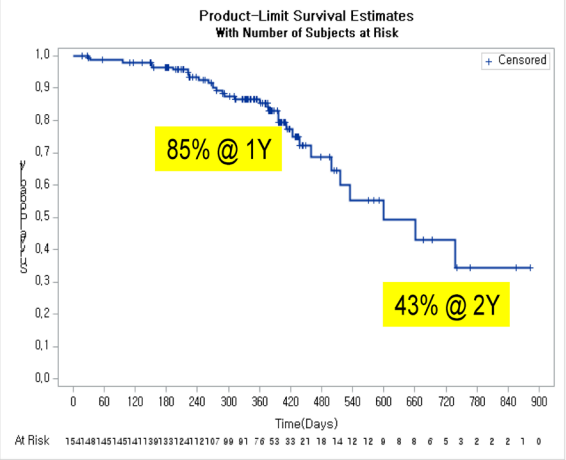
KURE-YTT-HCC, interim analysis

Results

Target lesion progression free survival



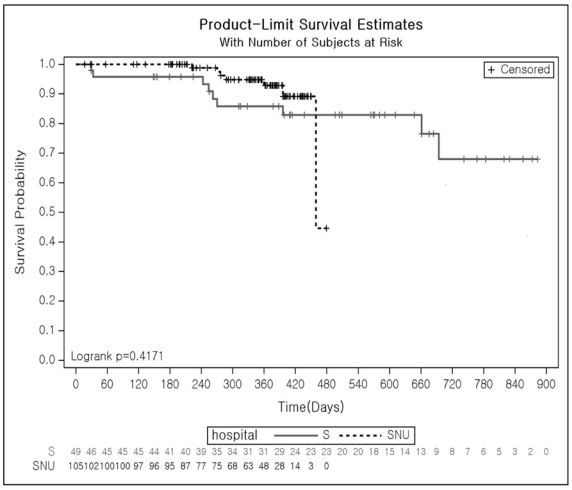
Overall progression free survival



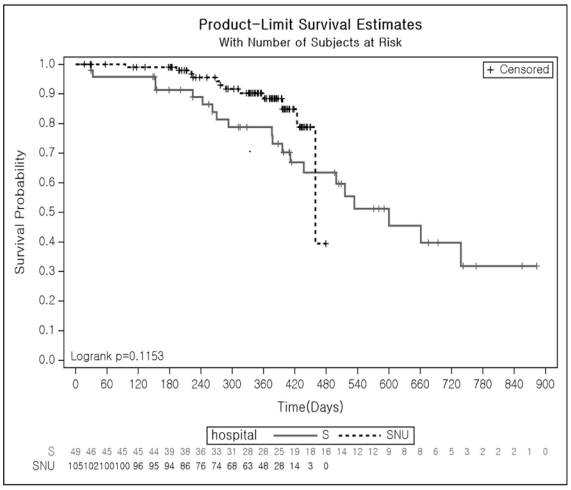
KURE-YTT-HCC, interim analysis

Results per institution

Target lesion progression free survival



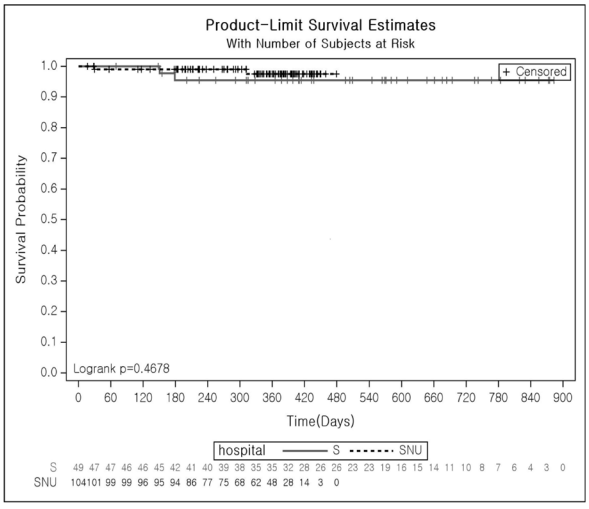
Liver progression free survival



KURE-YTT-HCC, interim analysis

Results per institution

Overall survival



Target lesion progression
Liver progression
Overall survival

No difference between the institutions

KURE-YTT-HCC, interim analysis

Best target lesion response (up to 19m f/u)

ORR 100%

CR	74	76.30%
PR	23	23.70%
SD	0	0%
PD	0	0%

Best target lesion response (up to 29m f/u)

ORR 97.9%

CR	135	87.6%
PR	16	10.3%
SD	2	1.2%
PD	1	0.6%

LEGACY study

	Localized mRECIST, n (%)	mRECIST, n (%)
ORR, confirmed response, n (%) [95% CI]	117 (72.2%) [64.9%, 78.5%]	111 (68.5%) [61.0%, 75.2%]
ORR, best response, n (%) [95% CI]	143 (88.3%) [82.4%, 92.4%]	140 (86.4%) [80.3%, 90.9%]
Best overall response		
CR	136 (84%)	133 (82.1%)
PR	7 (4.3%)	7 (4.3%)
Stable disease	0	0
PD	0	3 (1.9%)

Summary (I)

1. KURE-YTT-HCC study (Korean Legacy study) reflects etiology representing domestic causes of liver cirrhosis.

2. KURE-YTT-HCC study has well-balanced distribution of tumor size
   (<3cm [31%] and 3~5 cm [43%] and 5~8cm [26%]).
   - Median tumor size 3.9 cm which is larger than 2.7 cm in Legacy study.

3. Simulation test was skipped in 58.4% of enrolled patients. However, radiation pneumonitis did not occur.

4. During the follow-up period of 311 days (median),
   - Best ORR was 97.9% (CR 87.6%, PR 10.3%) for target lesion
   - Target lesion progression free survival was 91% at 1Y and 69% at 2Y.
   - Overall progression free survival was 85% at 1Y and 43% at 2Y.
   - Median overall survival has not reached; 97% at 2Y.

5. Radiation pneumonitis has not occurred.
   REILD occurred in one patient (0.6%).

6. Outcomes were not significantly different between the participating institutions; Good reproducibility.

Summary (II)

1. ^{90}Y radioembolization is evolving in terms of indication, techniques, and the role in the management of HCC.

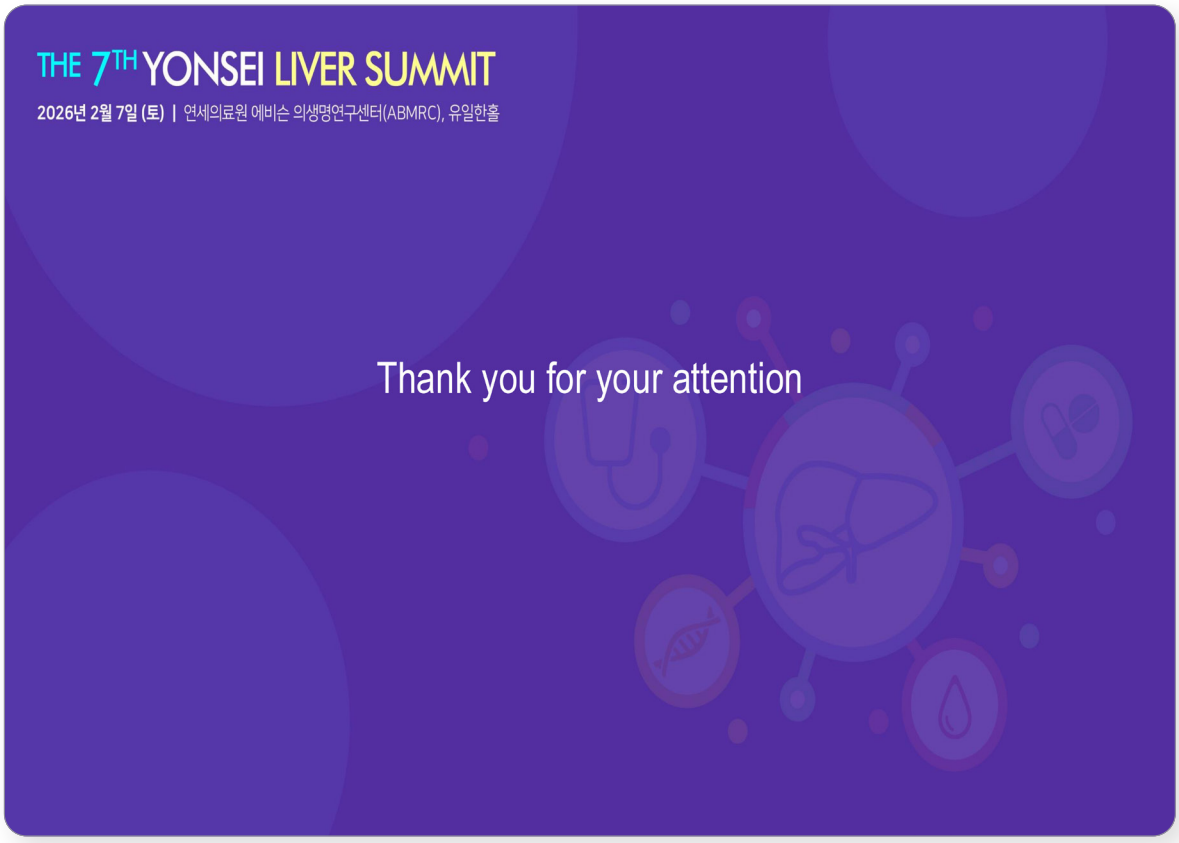
2. Regarding techniques, personalized dosimetry has become a standard of care.

3. Instead of personal experience, standardized method for dosimetry is available with a dedicated software.

4. Particle loading and radiation per microsphere (RPM) need to be considered during dosimtery although evidence has to be bulit up.

5. Radiation dose – tumor biology (histopathologic features…) relationship need to be further studied.

6. Multicenter domestic studies are valuable for validation of the international HCC guidelines and revision of Korean HCC guidelines.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2026년 2월 7일 (토) | 연세의료원 에비슨 의생명연구센터(ABMRC), 유일한홀
Thank you for your attention

The 7th Yonsei Liver Summit
Honoring the Past, Empowering the Next

Session 4

Updated Multidisciplinary Approach for Hepatocellular Carcinoma

좌장: 성진실 (연세의대), 김경식 (연세의대)

1. Tailored Curative Treatments for Early HCC Based on the Preoperative Tumor Characteristics
   김나름 (연세의대)
2. Regional and Systemic Treatments Focusing on Conversion Surgery in Patients with Locally Advanced HCC
   이혜원 (연세의대)
3. Downstaging with Immune Checkpoint Inhibitors or TARE in Advanced HCC: Post-Liver Transplantation Outcomes at Severance
   김덕기 (연세의대)
4. Carbon-Ion Radiation Therapy: Curative and Combined Approaches for HCC
   이익재 (연세의대)

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Tailored Curative Treatments for Early HCC Based on the Preoperative Tumor Characteristics

김나름
(연세의대)

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Early-stage hepatocellular carcinoma (HCC) represents the most meaningful "curative window," in which long-term survival can be achieved through surgical resection, local ablation (radiofrequency ablation, RFA), or liver transplantation. Several guidelines such as BCLC and KLCA-NCC guideline, define early-stage disease largely by tumor burden (size and number), preserved performance status, and absence of extrahepatic spread or macroscopic vascular invasion, and recommend resection and ablation as core curative-intent options in appropriately selected

patients.

Despite these structured recommendations, recurrence risk among patients labeled "early HCC" remains highly variable, suggesting that a purely stage-based approach does not adequately capture tumor biology. This gap provides a strong rationale for a tailored curative strategy that incorporates preoperative tumor characteristics, especially the likelihood of microvascular invasion (MVI), to optimize both the choice of curative modality and, when surgery is selected, the surgical plan.

MVI is a pathologic surrogate of aggressive tumor biology and a major driver of early recurrence and intrahepatic metastasis. Although MVI is confirmed histologically, modern preoperative assessment can estimate MVI risk using a combination of tumor markers and MRI-based peritumoral findings. The value of this approach is not to "diagnose" MVI with certainty, but to **identify a clinically meaningful high-risk subgroup** in which the expected pattern of microscopic spread is more likely and the margin-for-error of local therapy becomes smaller. In this context, the key clinical implication is straightforward: **when preoperative features suggest high MVI risk, surgical resection tends to provide more reliable early recurrence control than RFA**, whereas for biologically favorable tumors with low predicted MVI risk, **RFA may remain an appropriate curative option** when technical conditions are favorable. Therefore, rather than applying one uniform curative modality to all early-stage patients, a practical strategy is to use preoperative risk estimation to align treatment intensity with individualized recurrence risk.

From a "tailored curative planning" standpoint, the goal is to translate preoperative tumor characteristics into a simple, actionable treatment plan that can be explained

to patients and implemented consistently. A pragmatic way to apply this concept is as follows:

Step 1 — Confirm curative eligibility (foundation)

- Preserved liver function and adequate future liver remnant
- No extrahepatic spread and no macroscopic vascular invasion
- Performance status allowing curative treatment

Step 2 — Estimate biological risk (focus on MVI likelihood)

- Use preoperative information (tumor markers + MRI impression) to classify patients into: Low predicted MVI risk/ High predicted MVI risk
- The exact imaging "marker list" is less important than consistent risk stratification into low vs high.

Step 3 — Choose the curative modality (RFA vs resection)

- **Low predicted MVI risk + technically favorable tumor location**

➡ RFA is reasonable as a curative option (minimally invasive, organ-sparing)

- **High predicted MVI risk and/or technically unfavorable location for ablation (e.g., perivascular/periportal)**

➡ Favor **surgical resection** to improve oncologic reliability and reduce early recurrence risk

- In borderline cases, discuss both options explicitly with the patient using the same "risk-based" language: "We can do ablation, but based on preoperative risk, surgery offers a more secure oncologic margin."

Step 4 — Tailor the surgical strategy (when resection is selected)

- In high predicted MVI risk, consider a territory-based/anatomic resection concept when feasible, because the concern is not only the index lesion but also microscopic spread along portal territory.
- "Major hepatectomy" should be framed as **selective**—considered only when it meaningfully improves oncologic coverage and liver reserve allows—rather than a routine escalation.

In summary, early-stage HCC should be approached as a stage where multiple curative options exist, but outcomes are driven by more than tumor size and number. A concise and clinically useful principle is to integrate preoperative tumor characteristics—particularly the likelihood of MVI—into a risk-based plan: **low-risk tumors can be treated with minimally invasive curative approaches such as RFA when technically appropriate, while high-risk tumors should be steered toward surgical resection and, when indicated, territory-based surgical strategies to reduce early recurrence**. This framework preserves guideline-based eligibility while enabling patient-specific curative planning that better reflects biological heterogeneity within "early" disease.

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Regional and Systemic Treatments Focusing on Conversion Surgery in Patients with Locally Advanced HCC

이혜원
(연세의대)

Hye Won Lee

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Patients with locally advanced hepatocellular carcinoma (HCC) are frequently deemed unsuitable for surgical resection at initial diagnosis due to large or multifocal tumors, vascular invasion, or limited hepatic reserve, and have therefore traditionally been managed with palliative intent. However, recent advances in systemic therapies, particularly immune checkpoint inhibitor–based regimens, along with refinements in regional treatment modalities, have led to a paradigm shift in the management of this disease. In a subset of patients, meaningful tumor regression and durable disease control can now be achieved with non-surgical therapies, thereby enabling curative-

intent resection, a strategy referred to as conversion surgery.

In locally advanced HCC, conversion surgery describes a treatment pathway in which patients initially considered unresectable become eligible for surgical resection following systemic therapy, regional therapy, or their combination, while preserving adequate liver function. This approach extends beyond simple tumor downsizing and can be viewed as a process of biological selection, identifying patients with favorable tumor behavior who may derive long-term benefit from curative surgery.

Regional treatment modalities, including transarterial chemoembolization, hepatic arterial infusion chemotherapy, radioembolization, and radiotherapy, contribute to local tumor control and cytoreduction. When combined with modern systemic therapies, these approaches may enhance the depth and durability of treatment response. Advances in systemic therapy have also improved objective response rates and intratumoral necrosis, thereby expanding the population potentially eligible for conversion surgery. Careful assessment of treatment response, incorporating imaging-based criteria alongside dynamic evaluation of liver function and patient performance status, is essential.

Consideration of conversion surgery requires a comprehensive evaluation of multiple factors, including the magnitude and sustainability of tumor response, changes in vascular invasion, future liver remnant and hepatic functional reserve, and overall surgical risk. Given the persistent risk of recurrence even after successful resection, appropriate timing of surgery and postoperative management remain critical. Ultimately, conversion surgery represents an emerging therapeutic strategy that, through close multidisciplinary collaboration, may offer selected patients with

locally advanced HCC an opportunity for long-term survival beyond conventional palliative treatment.

Downstaging with Immune Checkpoint Inhibitors or TARE in Advanced HCC: Post-Liver Transplantation Outcomes at Severance

김덕기
(연세의대)

Recent advances in immunotherapy have dramatically altered the treatment landscape for advanced hepatocellular carcinoma (HCC). The combination of atezolizumab and bevacizumab (Atezo-Beva) has emerged as a pivotal regimen, not only improving survival in unresectable cases but also offering new possibilities for curative surgery. Historically, patients with macrovascular invasion, extrahepatic metastasis, or extensive tumor burden were excluded from potentially curative approaches such as liver transplantation (LT) or hepatectomy. However, the remarkable responses seen with immune checkpoint inhibitors (ICIs) have introduced the concept of immunotherapy-induced down-staging, allowing certain patients initially deemed inoperable to become candidates for curative interventions. The ultimate goal of this strategy is to expand surgical opportunities, reduce LT waitlist dropout, and potentially eradicate micrometastatic disease.

In the pre-ICI era, the mainstay of down-staging relied on locoregional therapy (LRT), such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA), or selective internal radiation therapy (TARE). Patients successfully down-staged to within Milan or UCSF criteria could be listed for LT, and their post-transplant survival was predicted using models such as Metroticket 2.0. These protocols defined acceptable outcomes as 5-year HCC-specific survival exceeding 70% and overall survival beyond 50%. In the ICI era, however, the landscape is evolving toward broader inclusion criteria. Trials such as ImmunoXXL (J Hepatol 2024) are testing Atezo-Beva as a universal down-staging therapy, regardless of prior LRT or initial tumor stage, excluding only diffuse or extensive extrahepatic metastasis. In contrast, in Korea, strict insurance regulations limit the indication for Atezo-Beva to cases defined as “unresectable” or “LRT-unfit,” making intentional down-staging strategies difficult to implement within the current reimbursement framework.

A major therapeutic concept gaining attention is the combination of LRT with Atezo-Beva. Locoregional therapies can induce tumor necrosis and enhance antigen exposure, while bevacizumab-mediated VEGF inhibition may counteract the immunosuppressive tumor microenvironment. This synergy potentially enhances the antitumor efficacy of atezolizumab and improves the chance of successful down-staging. Combining TACE, RFA, TARE, or EBRT with Atezo-Beva may therefore serve as a bridge to LT, particularly for patients with locally advanced but liver-confined disease. Clinical implementation must still consider bleeding risks due to bevacizumab, hepatic decompensation potential, and each patient’s hepatic functional reserve.

A key challenge in the era of immunotherapy is managing the timing of LT after ICI exposure. Although ICIs offer tumor control, they also carry a risk of precipitating severe allograft rejection if transplantation occurs too soon after the last dose. Multicenter studies (J Hepatol 2025) report a 20% overall rejection rate among LT recipients previously treated with ICIs. The likelihood of rejection exceeds 30% when the washout period is shorter than 50 days. Statistical modeling suggests that a washout duration of approximately three months (about 90 days) minimizes the rejection risk below 20%. However, prolonged washout increases the danger of tumor progression, highlighting the delicate balance between maintaining oncologic control and ensuring graft safety. The optimal timing likely depends on tumor kinetics, immune activity, and the urgency of transplantation.

In LDLT-dominant regions, such as Korea, the situation offers unique advantages and challenges. Because LDLT allows flexible scheduling, “fast-track” transplantation following successful Atezo-Beva down-staging can minimize the risk of tumor progression during the washout period. Nevertheless, LDLT introduces the so-called “triple equipoise,” where donor safety, recipient oncologic benefit, and graft quality must all be weighed simultaneously. Small-for-size grafts, ABO-incompatible transplantation, or the need for multiple plasma exchanges can further amplify immunologic and oncologic risks in this high-stakes population.

At Severance Hospital, the initial institutional experience reflects both promise and caution. Among 18 patients who received Atezo-Beva prior to LT, acute rejection occurred in 39%, and 22% developed steroid-refractory rejection. Most cases of acute rejection were associated with a washout interval shorter than 90 days.

However, even patients with a longer washout were not entirely free from rejection, suggesting that immune reactivity can persist well beyond drug clearance. In this context, dynamic monitoring of tumor marker trajectories (AFP and PIVKA-II) provides valuable information not only for oncologic assessment but also for determining the appropriate timing for transplantation.

Collectively, these data emphasize several key take-home messages. First, combining Atezo-Beva with locoregional therapy can broaden the indications for curative surgery, potentially extending LT eligibility to patients with portal vein tumor thrombosis (PVTT), lymph node metastasis, or limited lung lesions. Second, a 5-year overall survival target of at least 60% should serve as the clinical benchmark for determining acceptable transplant outcomes after down-staging. Third, achieving the proper balance between tumor control and rejection risk requires an individualized washout strategy of approximately 50 to 90 days, with closer coordination between oncologists and transplant teams. Fourth, Korea needs a tailored protocol that reflects the predominance of LDLT, local insurance restrictions, and patient characteristics typical of advanced-stage HCC. Finally, for patients in whom LT is not feasible due to donor limitations or insurance constraints, conversion hepatectomy after immunotherapy may represent a viable alternative, though further evidence from prospective studies is required to establish its oncologic validity.

In conclusion, the Atezo-Beva era has opened a new frontier in surgical oncology for advanced HCC. Immunotherapy-based down-staging strategies hold the potential to convert unresectable disease into curable conditions, redefining the boundaries between systemic and surgical treatment. The challenge moving forward lies in

integrating these strategies safely into transplant and surgical protocols, guided by sound oncologic judgment, immunologic understanding, and ethical consideration of donor safety. Ongoing multicenter collaborations and tailored national guidelines will be essential to fully realize the curative potential of immunotherapy in advanced HCC.

Carbon-Ion Radiation Therapy: Curative and Combined Approaches for HCC

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Abstract

Carbon ion radiotherapy (CIRT) leverages the Bragg peak phenomenon and high relative biological effectiveness (RBE, 2-3 times higher than X-rays) to deliver precise, tumoricidal doses while substantially sparing normal liver parenchyma. This physical and biological profile is particularly advantageous for hepatocellular carcinoma (HCC), which often exhibits radioresistance due to intratumoral hypoxia—a common sequela of hepatic cirrhosis and prior transarterial chemoembolization (TACE). Japanese

studies from the National Institute of Radiological Sciences (NIRS) report 3-year local control rates of 81-96% and overall survival of 50-88% for HCC treated with CIRT doses of 52.8-79.5 Gy(RBE) in 4-15 fractions. Building upon this evidence, Yonsei Cancer Center Heavy Ion Therapy Center initiated CIRT for moving organs including liver cancer following fixed-beam room activation in April 2024.

Dosimetric superiority versus photon SBRT was confirmed: mean liver dose 8.1±1.4 Gy(RBE) versus 16.1±2.5 Gy ($p<0.05$), liver V5 20.2±3.2% versus 53.8±7.2% ($p<0.05$), and V20 14.2±2.5% versus 31.5±6.2% ($p<0.05$). These findings align with multicenter Japanese data and our institutional proton therapy experience, validating CIRT's normal liver sparing capacity. Compared to photon radiotherapy systematic reviews, CIRT demonstrates equivalent survival for small HCC (≤3 cm) but superior 2-year overall survival (67% vs 42%) for large tumors (mean 7.2 cm).

Technical implementation required meticulous attention to fiducial placement avoiding beam paths, respiratory motion management via 4D imaging, and superconducting gantry optimization. Our infrastructure supports ongoing investigations including CIRT following TARE for residual/recurrent lesions (primary endpoint: objective response rate) and atezolizumab/bevacizumab combination for portal vein-invading HCC (primary endpoint: progression-free survival). KFDA post-marketing surveillance (700 cases planned through 2027) and Korean Radiation Oncology Group cohorts will generate long-term Korean data.

In conclusion, our initial experience confirms CIRT's feasibility, promising early efficacy, and excellent tolerability for primary liver cancer including high-risk features (large size, hilar proximity, impaired liver function, prior therapy). CIRT addresses

key unmet needs in HCC management—hypoxia overcoming, reirradiation feasibility, and superior dosimetry for compromised livers—positioning it as a valuable addition to the Korean multidisciplinary therapeutic arsenal. Prospective trials and registry studies remain essential to optimize integration with systemic therapies and establish durable survival benefits.

Keywords: Carbon Ion Radiotherapy, Hepatocellular Carcinoma, Particle Therapy, Respiratory Gating, Liver Cancer

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