Liver Transplantation: Updates

in Celebration of the 50th Year at Inonu University

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Editors

About the Journal

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Aim and Scope: The Journal of Inonu Liver Transplantation Institute is a peer-reviewed open-access e-only publication in the field of liver transplantation publishing research articles on clinical, experimental liver transplantation, combined liver and other organ transplantation, and liver diseases. The journal welcomes original research articles, reviews, meta-analyses, case reports, and letters.
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Aim and Scope

Aim

The Journal of Inonu Liver Transplantation Institute is a peer-reviewed open-access e-only publication in the field of liver transplantation publishing research articles on clinical, experimental liver transplantation, combined liver and other organ transplantation, and liver diseases. The journal welcomes original research articles, reviews, meta-analyses, case reports, and letters.

Overview

Journal of Inonu Liver Transplant Institute has been founded and established by Inonu Liver Transplant Institute in order to form a source of high-quality research in diseases and therapy of the liver and biliary tract. Both clinicians and basic science researchers are the target population of our journal.

Scope

Hepatobiliary disorders are a complex spectrum of diseases, usually requiring a multi-disciplinary approach that involves interventional radiologists, hepatologists, oncologists, hepatobiliary-transplant surgeons and translational researchers. The Journal of Inonu Liver Transplant Institute (JILTI) is internationally peer reviewed and provides a source for articles on prevention, diagnosis and cutting-edge therapy of hepatobiliary diseases and cancers which also includes liver transplantation, complex hepatobiliary surgical procedures, medical and immune therapies. In accordance with our aims, basic and translational research as applied to these diseases have utmost importance for our journal.

Keywords: Hepatobiliary diseases and cancers, liver surgery, liver transplantation, advanced therapy of hepatobiliary diseases, basic and translational research on hepatobiliary diseases.

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In accordance with the journal's policy, an approval of research protocols by an ethics committee in accordance with international agreements "WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (last updated: October 2013, Fortaleza, Brazil)" , "Guide for the care and use of laboratory animals (8th edition, 2011)" and/or "International Guiding Principles for Biomedical Research Involving Animals (2012)" is required for all research studies. If the submitted manuscript does not include ethics committee approval, it will be reviewed according to COPE's guideline (Guidance for Editors: Research, Audit and Service Evaluations). If the study should have ethical approval, authors will be asked to provide ethical approval in order to proceed the review process. If they cannot provide ethical approval, their manuscript will be rejected and also their institutions and when needed, the related bodies in their country will be informed that such studies must have ethics committee approval. If they provide approval, review of the manuscript will continue.
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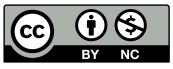

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Information for the Authors

THE JOURNAL

The Journal of Inonu Liver Transplantation Institute (The Journal) is an international, scientific, open access periodical published in accordance with independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Inonu Liver Transplantation Institute, and it is published in April, August and December, three times a year. The publication language of the journal is English.

The Journal aims to contribute to international literature by publishing high-quality manuscripts in the field of diseases and therapy of the liver and biliary tract. The journal's target audience includes academics and expert physicians working in transplantation surgery specialists.

REVIEW PROCESS

Manuscripts submitted to the Journal will undergo a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their field in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation process of manuscripts submitted by editors or by the editorial board members of the journal. The editor-in-chief is the final authority in the decision-making process for all submissions.

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Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ICMJE also notes that editors have the right to edit these letters for length, grammar, and style. However, all letters should contribute constructively to the academic discussion and critique, and those deemed irrelevant or unfounded may be rejected.

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Table 1. Limitations for each manuscript type.

Type of manuscript	Wordlimit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	4000-5000	350-400	40-50	6	6
Review Article	5000-6000	350-400	50-60	6	10
Meta analysis	5000	350	50	6	10
Case Report	1500	200	20	No tables	5
Letter to the Editor	1000	No abstract	10	No tables	1

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The full title of the manuscript as well as a short title (running head) of no more than 50 characters

Name, affiliation, ORCID ID number, and highest academic degree of the author(s)

Funding and other material support

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Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria

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Journal article: van Erk MD, Dam-Vervloet AJ, de Boer FA, Boomsma MF, van Straaten H, Bosschaart N. How skin anatomy influences transcutaneous bilirubin determinations: an in vitro evaluation. Pediatr Res 2019;86:471-7.
Epub ahead-of-print article: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead-of-print].
Manuscript published in electronic format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodIEID/cid.htm.
Book section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.
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Scientific or technical report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

REVISIONS

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Accepted manuscripts will be made available and citable online as rapidly as possible. The stages of publication are as follows;
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JOURNAL OF INONU LIVER
TRANSPLANTATION INSTITUTE

From the Editor

Forward to the Special Edition of the Journal of the Liver Transplant Institute (JILTI) to mark the 50th Anniversary of Inonu University.

Inonu University was established in 1975 in Malatya and was named after Ismet Inonu, the second president of the Republic of Turkiye, which in turn was founded in 1923 after the demise of the Ottoman Empire. The university includes the Turgut Ozal Medical Center, which contains the Inonu University Liver Transplant Institute, which is Europe's largest, a high volume transplant center that was in turn opened in 1996.

Key aspects of the Institute are the focus on living donor liver transplants with a resultant negligible transplant waiting list, and more recently, a paired liver exchange program. An increasingly important area of expertise in our Institution is hepato-biliary and other GI cancers and their multi-disciplinary management.

The 18 papers in this edition come from 13 institutions and cover various aspects of GI cancers, especially HCC. They reflect the excitement of recent progress in GI cancer understanding and their multiple modalities of management and also reflect the rapid changes in our understanding of cancer, including genetic and micro-environmental influences and the continued progress in liver transplantation.

Kind regards,

Brian I. Carr MD,

FRCP, PhD. Inonu Liver Transplant Institute

JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

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Original Research

Effect of Ischemia Durations, Transport, Cryopreservation and Storage Conditions on Tissue Integrity, DNA, RNA, Protein Quality and Primary Cell Culture Initiation Capacity in Liver Tissues

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Abstract

Objectives: Standardization of pre-analytical factors is essential for ensuring the quality and reproducibility of tissue-based biomedical research. Factors such as ischemia time and freezing methods significantly impact sample integrity and the quality of downstream analyses. However, systematic evaluations of how ischemia time, transfer conditions, freezing methods, and storage parameters affect liver tissue quality remain limited. This study aimed to evaluate the effects of ischemia duration, freezing techniques, transfer conditions, and storage conditions and durations on liver tissue integrity, nucleic acid quality, protein yield, and primary cell culture initiation capacity.

Methods: Liver tissues from healthy male Wistar albino rats were subjected to varying cold ischemia durations (2h, 8h, 24h) and transfer conditions (+4°C, vacuum-sealed, culture medium) to assess tissue integrity, nucleic acid and protein quality, and cell culture initiation potential. Optimal conditions were selected for subsequent freezing techniques (controlled-rate, rapid freezing in liquid nitrogen, and freezing with isopentane) over different storage periods (3, 6, 9 months) at –80°C and –196°C. Histological assessment (HE and Masson trichrome staining) was performed to evaluate sample integrity. Nucleic acid, and protein yield and quality as well as primary cell culture initiation capacity, were tested.

Results: Tissue integrity remained stable for 0–2 hours under cold ischemia, with moderate degeneration observed after 24 hours. RNA and DNA yields were consistent across transfer conditions, with no significant differences detected. However, RNA integrity was more sensitive to ischemic conditions compared to total nucleic acid quantities. Freezing methods did not significantly differ in preserving tissue quality, and both –80 °C and –196 °C storage effectively maintained nucleic acid integrity up to 9 months. Primary cell cultures were successfully established from tissues subjected to a maximum of 8 hours of ischemia, but not from those exposed to 24 hours.

Conclusion: Optimized transfer conditions and appropriate freezing and storage methods are key to preserving liver tissue quality for biobanking and downstream analyses. This study provides valuable insights for developing standardized protocols for liver tissue biobanking, which could enhance reproducibility and reliability in translational research.

Keywords: Biobanking, Cold ischemia, cryopreservation, liver tissue, pre-analytical factors, translational research

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Proper preservation of tissue samples is vital for translational research and clinical studies. Since tissue samples, especially liver tissues, are sensitive to environmental changes, correct storage and handling are essential to maintain sample quality and usefulness for future genome, transcriptome, and proteome analysis. Improper storage or mishandling can cause degradation and contamination, which can be influenced by factors independent of the collection methodology, such as tissue type and the duration of ischemia during/after surgery. Especially, the cellular ischemia tolerance, sensitivity to freeze-thaw events, and cryopreservation conditions need to be tailored to specific tissue types.

Even short delays before freezing liver samples can induce biochemical and metabolic alterations greater than inter-individual differences.[1] Prolonged cold ischemia leads to autolysis, transcriptomic and proteomic changes, and histomorphological artifacts, with hepatocytes, endothelial cells, and bile duct epithelium especially susceptible to damage.[2–4] Such changes compromise RNA and protein integrity, immuno-histochemistry results, and ultimately the reliability of translational findings. Therefore, minimizing ischemia time, controlling freezing conditions, and applying tissue-specific protocols are crucial to preserving structural, metabolic, and molecular integrity.[5,6]

Biobanks are structured collections of biological samples and associated data, maintained for current or future scientific research, where each processing step critically impacts sample quality.[7] Standardization and optimisation are therefore essential to ensure high-quality samples, reproducibility of research, and inter-center comparability, ultimately transforming biobanks from mere storage facilities into reliable infrastructures for translational research.[8–10] Without such practices, samples risk becoming scientifically unusable, ethically questionable, or legally noncompliant.[11]

The liver is a particularly challenging tissue for biobanking due to its high enzymatic activity, metabolic turnover, and vulnerability to ischemia-induced degradation. RNA, proteins, and metabolites degrade rapidly in liver tissue, and standard cold ischemia thresholds established for other tissues may not be applicable.[12,13] While several studies have demonstrated ischemia-related alterations in gene expression, phosphorylation, and metabolic pathways,[14,15] systematic analyses comparing the effects of freezing techniques and storage conditions on multiple molecular classes in liver tissue remain limited. Furthermore, classic quality metrics, including RNA integrity number (RIN), do not fully capture ischemia-induced biological shifts, particularly in metabolomics and single-cell analyses.[16]

The lack of standardized recording of ischemia time, freezing methods, and storage duration in many biobank databases further reduces inter-center comparability and the translational value of research. Although optimal ischemia limits vary by tissue type, the specific impact of different freezing and storage methods on the molecular integrity of liver tissues has not yet been fully optimized. Controlled, tissue-specific studies are urgently needed to define analyte-specific thresholds and generate practical guidelines for hepatic biobanking.[12,17]

To address this, we evaluated the effects of transfer conditions, freezing methods, and storage durations on liver tissue morphology, DNA, RNA, and protein quality/quantity, as well as the success rate of establishing primary cell cultures. This study provides direct evidence on how liver tissues should be transferred, frozen, and stored by assessing multiple molecular parameters from the same samples under defined pre-analytical conditions. Our findings may contribute to the development of standardized operating procedures (SOPs) and SPREC-based guidelines specific to liver tissue biobanking, thereby enhancing the reliability, reproducibility, and clinical applicability of downstream genomics and proteomics research, as well as innovative ideas for improving preservation methods of liver allografts for transplantation studies.

Methods

Study Design

The study was designed to answer three questions: in the first step, the effect of ischemia time (2 hours, 8 hours and 24 hours) and transfer conditions (+4°C, vacuumed at +4°C and in culture medium at +4°C) on tissue integrity, nucleic acid quality (DNA and RNA), protein quality, primary cell culture initiation potential were analyzed; the second step were planned to examine the effects of freezing techniques (freezing in a controlled freezer at -1°C/min, rapid freezing with liquid nitrogen, and freezing in liquid nitrogen accompanied by isopentane) over storage durations of 3, 6, and 9 months. In the third step, storage conditions (–80°C freezer and –196°C liquid nitrogen tank) and storage times under these conditions were analyzed using the four parameters defined in previous steps. When analyzing tissue quality using HE staining, the A260/A230 and A260/A280 absorbance ratios were used to determine DNA quality, and the RIN (RNA Integrity Number) value was used to measure RNA quality. Protein quality was analyzed using the BCA (Bicinchoninic Acid) method. To determine cell culture initiation success, primary cell cultures were established and the viability and morphological status of the cells were examined using both trypan blue staining and microscopy (Fig. 1).

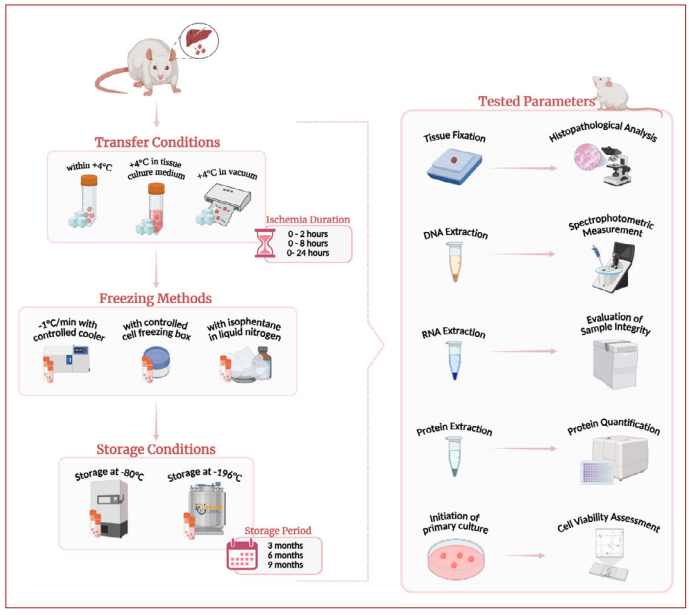

Figure 1. Schematic workflow of the experimental design. Liver tissues obtained from Wistar Albino rats were subjected to different transfer conditions, and the optimal protocol was selected based on histological analysis, DNA, RNA, protein, and cell viability. Using these same parameters, subsequent experiments investigated the effects of freezing methods, freezing conditions, and storage durations. The figure summarizes the workflow from tissue transfer to biomolecular and cellular analyses, where quality assessments served as a guiding criterion at each step.

Establishment of the Sample Collection

For this study, seven healthy male Wistar albino rats, aged 6–8 weeks and weighing 230–330 g, were obtained from the Vivarium unit of the Izmir Biomedicine and Genome Centre (IBG). Before the experiment, the animals were housed under standard laboratory conditions (12-hours light/dark cycle, 22±2°C temperature, 50–60% humidity) with free access to standard feed and water. Animal euthanasia was carried out by the institution's veterinary surgeon at the IBG-Vivarium unit in compliance with guidelines authorized by the IBG-Local Ethics Committee for Animal Experiments (IBG-HADYEK) (dated 29/11/2021, numbered 2021-022). Following euthanasia under deep anesthesia by cervical dislocation, macroscopic examination of the liver was performed. Subsequently, tissue samples were transferred to the IBG-Biobank under predefined conditions that reflect real clinical conditions. Ischemia times were planned according to scenarios routinely encountered in IBG-Biobank operations. Since the biobank is located within a health campus, some samples could be delivered within one hour, whereas in collaborations with distant centers, transfer could be delayed up to 24 hours. Accordingly, experimental conditions were established to evaluate how proximity of collection site, ischemia duration, and temperature influenced tissue integrity, nucleic acid quality/quantity and protein quantity, as well as cell viability. Samples were exposed to cold ischemia for 2 h, 8 h, and 24 h under three transfer conditions: (i) directly on ice at +4 °C in collection tubes, (ii) in tubes containing transfer medium/cell culture medium on ice at +4 °C, and (iii) in vacuum-sealed bags at +4 °C. Following ischemia, tissues were dissected into standardized pieces (5 mm^3/50 µg).

All procedures were documented using the BB_Vivarium_ Fresh Tissue Collection, Processing and Storage Tracking Form (Supplementary File 1). Sample information was registered in the biobank information management system (Openspecimen) and assigned a unique biobank code (PPID) (Table 1).

The entire sample collection, processing and storage processes were carried out in accordance with the SOP of the İBG-Biobank.

Evaluation of Freezing Methods and Storage Conditions on Liver Tissue Quality

Three freezing methods and two freezing conditions were compared. Each tissue sample was subjected (i) controlled freezer (PLANER; #Kryo560-16) (-1°C/min), (ii) rapid freezing in liquid nitrogen (LN2), and (iii) freezing in LN2 accompanied by isopentane, as well as all samples were treated with two different freezing conditions:(i) a freezing medium (70% complete RPMI1640, 20% FBS, and 10% DMSO) and (ii) fresh frozen tissue samples

Table 1. Sample record registered in Openspecimen with the project code

PPID	Registration Date	Gender	Animal Info ID	Genus	Weight (g)
V150	23-03-2023	Male	40082	Wister Albino	327.12
V151	12-06-2023	Male	40450	Wistar Albino	315
V152	11-07-2023	Male	40583	Wistar Albino	231.43
V184	05-10-2023	Male	41982	Wistar Albino	263.25
V183	05-10-2023	Male	41983	Wistar Albino	261.03
V185	12-10-2023	Male	42147	Wistar Albino	262.33
V291	06-02-2024	Male	47107	Wistar Albino	327.8

without medium. Then all samples with different freezing conditions were preserved under two different storage conditions: a -80°C deep freezer and a -196°C LN2 tank. Storage periods were set at times for 0, 3, 6, and 9 months. Thus, the effects of different freezing methods on each combination of storage temperature and storage duration were analysed (Fig. 1).

a. Histopathological Analyses

Tissue samples processed according to different ischemia periods and transfer and storage conditions were fixed in 10% buffered formalin solution for 48-72 hours for routine histopathological examinations. During the tissue processing procedure, samples were subjected to a stepwise alcohol series (70°, 80°, 90°, 96°, and 100°), xylene, and paraffin series in a tissue processor (Sakura Tissue-Tek Vip6-E2) before being embedded in paraffin blocks. Sections 4-6 µm thick were cut from these blocks using a microtome (Leica/Rm2245) and placed on slides. The sections were stained with Hematoxylin and Eosin (HE) in an automatic staining device (Leica/Stainer XI) and made ready for examination. Masson's Trichrome staining was used to analyze the integrity of the ECM[18] by using a commercial kit (BIO-OPTICA BO 04-010802). Sections of tissue samples obtained from each test condition were compared with sections prepared from fresh samples collected during necropsy. These analyses were performed under a light microscope (Olympus; BX53F), and microphotographic images were recorded using a camera (Olympus; DP27). Tissue integrity was evaluated by two veterinary pathologists using a scoring system: no damage = 0, minimal damage. = 1, moderate damage = 2, and severe damage = 3 according to preservation of cellular and ECM structural integrity, tissue architecture, and levels of autolysis.

b. DNA isolation and Quality Controls

Genomic DNA isolation was performed using the DNeasy Blood and Tissue Kit (QIAgen; #69504). The quantity and purity of the genomic DNA were determined using a NanoDrop (Thermo Scientific; ND-2000). DNA concentration was measured in ng/µL, and purity values were determined using the A260/A230 and A260/A280 absorbance ratios.

c. RNA isolation and Quality Control

Total RNA isolation was carried out using NucleoZOL (Macherey-Nagel; #69504). The homogenisation step was performed by a TissueLyser LT (Qiagen; #85600) device with 5 mm stainless steel beads (Qiagen; #69989) at a frequency of 50 Hz for 3 minutes, followed by the isolation process. RNA concentration was measured in ng/µL, and purity values were determined using the A260/A230 and A260/A280 absorbance ratios. RNA integrity and quality were analysed using the Agilent RNA 6000 Nano Kit (Agilent Technologies; #5067-1511) with the 2100 Bioanalyzer device (Agilent Technologies; #G2939BA). In this analysis, RIN (RNA Integrity Number) values were determined.

d. Protein Isolation and Quantitation

The isolation process was carried out using RIPA buffer (Radioimmunoprecipitation Buffer). The homogenization step was performed as described in RNA isolation section using a Tissue Lyser LT (Qiagen; #85600) device The protein concentration was determined using the BCA (Bicinchoninic Acid) method.[19] For this, a standard curve was created using bovine serum albumin (BSA) at known concentrations. The absorbance values of the samples were measured at 562 nm using a Varioskan Flash (Thermo Scientific; #5250030), and the protein quantities were calculated using the BSA standard curve with Microsoft Excel.

e. Assessment of Primary Cell Culture Initiation Capacity

A portion of the multiple samples were divided into five pieces of approximately 0.5 mm^3 each using a sterile scalpel in a cell culture dish.[20] The first tissue sample was directly cultured to analyze its potential for starting a cell culture. Four of these pieces were placed in cryotubes containing 1.5 mL of freezing medium and frozen using two different methods for further testing their primary cell culture initiation capacity: (i) two tissue pieces were placed in a CRF), (ii) two tissue pieces were placed in a CFE. These tissue samples were cut into as small pieces as possible using a sterile scalpel and washed with PBS after passing through a 100 µm filter. The tissue pieces remaining on the filter were washed repeatedly with PBS using a pipette until they were completely filtered out, resulting in a cell suspension.[20,21] The cells were seeded into 10 cm cell culture plates and incubated at 5% CO_2 and 37°C. The viability and morphological status of the cultured cells were analyzed both by trypan blue staining and under a microscope.

Statistical Analysis

For each condition, at least three biological replicates were generated, and when necessary, three technical replicates were included to ensure statistical robustness. Statistical analyses were performed using GraphPad Prism9. Comparisons across multiple groups were conducted with two-way ANOVA and mixed-effects models. Data are presented as mean and error (SEM), and p-values < 0.05 were considered statistically significant.

Results

To systematically evaluate the impact of different preanalytical variables on liver tissue quality, we first examined the influence of ischemia duration and transfer conditions on nucleic acid and protein quality, and the initiation capacity of primary cell culture.

1- The influence of transfer conditions and ischemia duration on tissue integrity, nucleic acid and protein quality:

No morphological changes were observed within 0–2 hours under cold ischemia (score:1±1). Under vacuum transfer conditions, signs of degeneration became evident at 8 hours score:2±1). After 24 hours of ischemia, moderate degeneration (score:3±1), was observed in the liver across all transfer conditions.

When we evaluated the effects of transfer duration for samples transferred on ice at +4 °C, independent of transfer condition, RNA, DNA and protein yields were between 100-300 ng/µl, 50-100 ng/µl, 20-35ug/µl, respectively (Fig. 2A, 2B, 2C). Although RNA yield was 2-3 times higher in samples transferred in tissue culture medium and in vacuum bags than in those directly transferred at +40C for 0-2 hours ischemia duration, no statistically significant differences were detected in any freezing and transfer conditions tested ($p<0.05$).

Despite this quantitative stability, RNA integrity showed

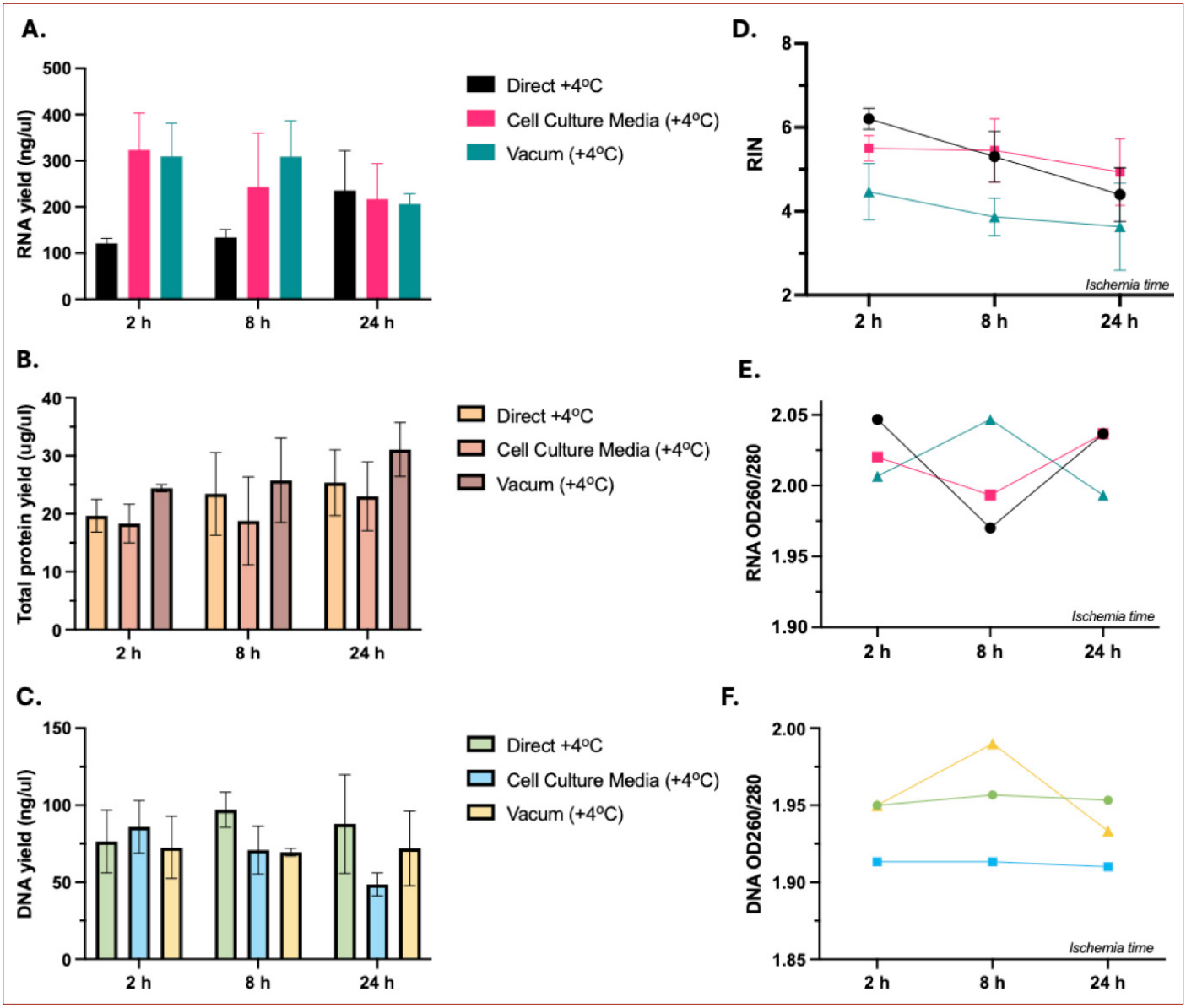

Figure 2. Effect of cold ischemia duration and transfer conditions on the quality and quantity of DNA, RNA, and proteins extracted from liver tissue samples.

condition-dependent variation. Samples transferred directly on ice consistently displayed preserved integrity, with RNA Integrity Numbers (RIN) ≥6 (Fig. 2D). RIN values remained around 6 when tissues were transferred in culture medium at +4 °C, but were substantially lower under vacuum transfer conditions (Fig. 2D) . However, there were no statistically significant differences ($p< 0.05$) in any freezing and transfer conditions compared to controls.

Furthermore, purity assessments confirmed optimal quality across all groups, with OD260/280 ratios of 1.8–2.1 for RNA and 1.7–2.0 for DNA. Taken together, these results demonstrate that nucleic acid amount and quality for all transfer conditions are suitable for downstream applications (Fig. 2D–F).

Across all ischemia durations tested (2, 8 and 24 h, +4 °C), the total yields of RNA, DNA, and proteins remained largely unchanged in liver tissues, with no statistically significant differences between transfer conditions.

The effects of transfer conditions and ischemia duration on primary cell culture initiation capacity

Primary cultures were successfully established from tissues transferred directly at +4°C or in culture medium/vacuum sealed conditions, and from tissues subjected to both 2 and 8 h ischemia, and they showed characteristic morphological features, whereas primary cultures could not be established from tissues subjected to 24 h ischemia (Fig. 3A and 3B).

These results demonstrated that only tissues transferred under 2 h ischemia, either in culture medium or vacuum-sealed at +4 °C, supported the successful establishment and maintenance of primary cell cultures. Under these conditions, cultures retained characteristic morphology, survived passaging, and enabled cryopreservation. Based on these optimized transfer conditions, subsequent analyses focused on evaluating the effects of different freezing techniques and storage conditions on tissue integrity and molecular quality.

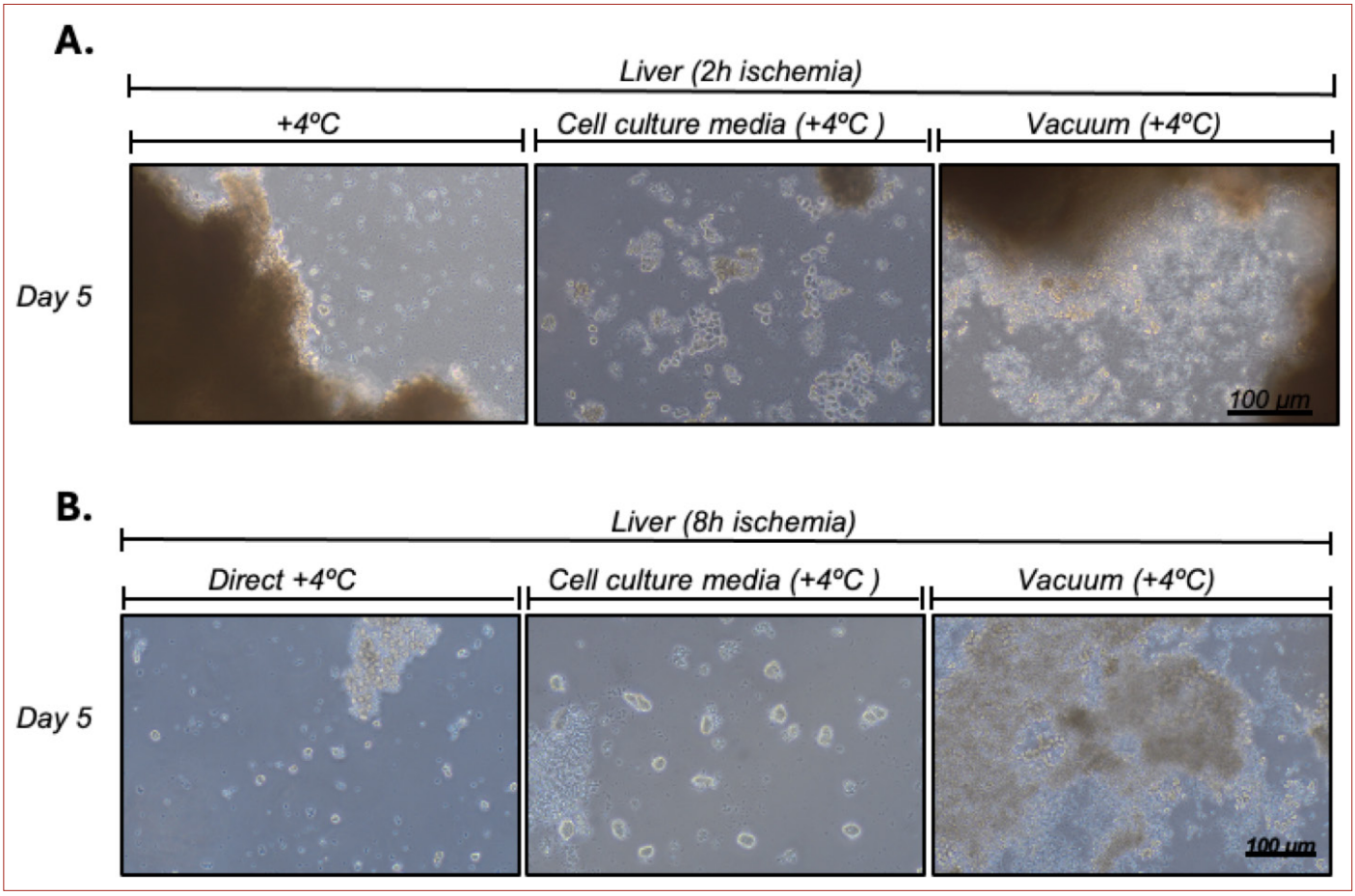

Figure 3. Primary liver cell culture outcomes following different cold ischemia durations and transfer conditions: Explants were prepared from transferred liver tissues and cultured under sterile conditions; cultures were monitored daily by light microscopy. **(A)** Representative phase-contrast image of a culture derived from tissue transferred in culture medium at 0–2 h cold ischemia, showing typical hepatocyte-like morphology, successful survival after passaging and attainment of confluence. **(B)** Representative image of a culture from the 2–8 h group showing initial attachment and morphological features, but failure to survive after passaging.

2- The influence of storage conditions on sample quality for samples frozen by different methods

To assess the impact of different freezing methods , liver tissue samples transferred under the previously identified optimal condition (direct transfer on ice at +4 °C) were frozen using three approaches as shown in Figure 1.

a. Effects on tissue integrity

No morphological changes or tissue damage were observed within 2 hours of cold ischemia compared to control conditions in FrFz and CFC and tissues (score:1±1), whereas low or moderate damage was observed for the IPA condition (score:2±1). In contrast, the damage score was determined as 2±1 for all storage conditions tested (3,6, and 9 months), supporting that FrFz of liver tissues transported at +40C is the best condition to prevent tissue integrity. Damage score for storing all frozen liver tissues at either -80 °C freezers or LN2 decreases tissue integrity slightly. No remarkable decrease was observed between storage at -80 °C freezers or LN2 up to 9 months.

b. Nucleic acid quality

Genomic DNA and RNA concentrations, RIN and A260/280 values from liver samples were measured as described in the Materials and Methods. The RIN value was determined as 6 at T0, and no differences were observed between

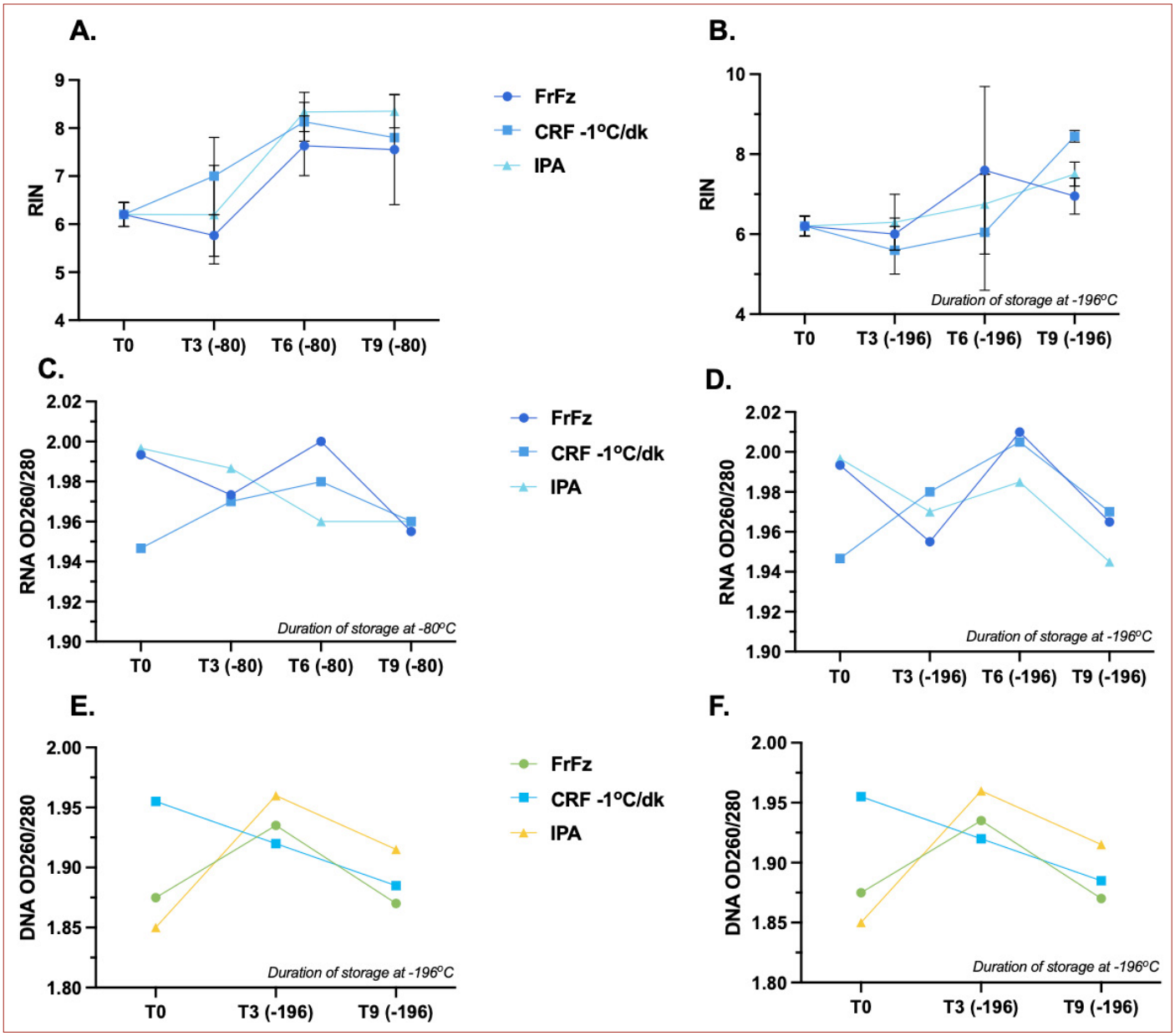

Figure 4. Evaluation of the impact of storage conditions (–80 °C and –196 °C) and storage durations (3, 6, and 9 months) on quality parameters for liver tissues.

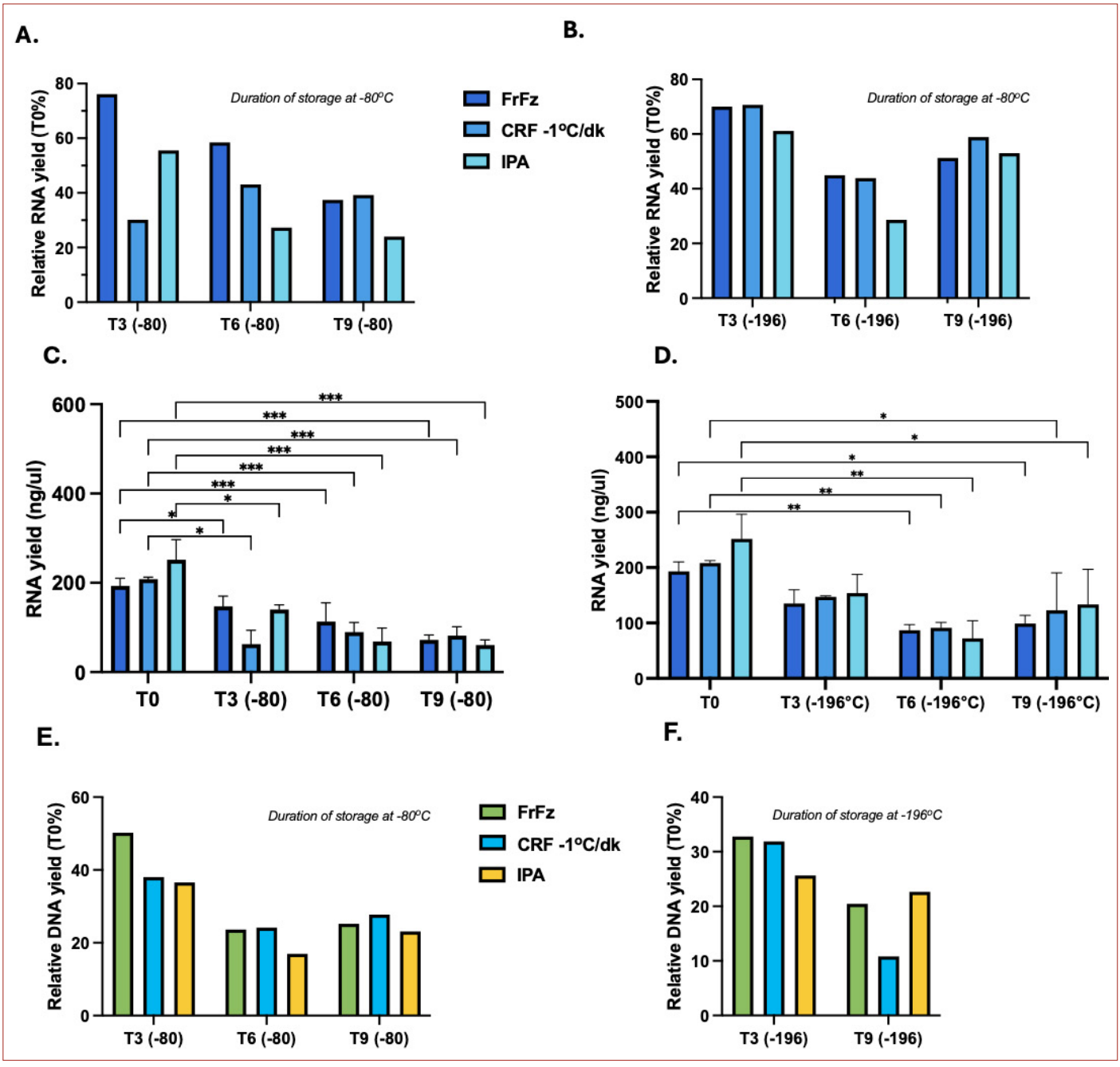

Figure 5. Evaluation of the impact of storage conditions (−80 °C and −196 °C) and durations (3, 6, and 9 months) on RNA and DNA quantity during the preanalytical phase. Comparisons across multiple groups were conducted with two-way ANOVA and mixed-effects models. Data are presented as mean and error (SEM), and p-values < 0.05 were considered statistically significant. Values presented as mean extraction yields from three biological replicates.

the freezing methods (Fig. 4 A-B). Similarly, no significant changes were detected across storage durations of 3, 6, and 9 months, representing short- to medium-term storage. RNA exhibited OD260/280 ratios of 1.89–2.11 (Fig. 4 C-D) while, DNA showed OD260/280 ratios ranging from 1.77 to 2.04 (Fig. 4 E-F). Overall, no statistically significant differences in nucleic acid quality were observed among the three freezing methods, storage durations, or temperatures (Fig. 4).

Extraction yields, expressed as micrograms of DNA or RNA per milliliter, were calculated for all samples. For each subject, a baseline yield (T0) was defined as the mean extraction yield obtained from three biological replicates processed immediately after collection. Comparisons across multiple groups were conducted with two-way ANOVA and mixed-effects models. Data are presented as mean and error (SEM), and p-values <0.05 were considered statistically significant.

The T0 value was used as a reference to calculate relative DNA or RNA yields (% of T0) for samples stored under different conditions. Relative RNA extraction yields under the different storage conditions relative to T0 are summarized in Figure 5A and 5B. The mean coefficient of variation (CV) at T0 RNA was 15%. Compared with T0, significant differences in nucleic acid yields were detected under −80 °C storage conditions at all durations, whereas samples stored at −196 °C showed changes in DNA and RNA amounts at T6 and T9. Similar analyses were performed for DNA; relative DNA extraction yields under the different storage conditions relative to T0 are summarized in Fig. 5E and 5F. The mean coefficient of variation (CV) at T0 DNA was 14%. Because no statistically significant differences were observed among the baseline samples yield, raw data were re-analyzed to compare relative changes over time and no significant differences were observed in either analysis (no data shown). Comparisons across multiple groups were conducted with two-way ANOVA and mixed-effects models. Data are presented as mean and error (SEM), and p-values < 0.05 were considered statistically significant.

c. Primary cell culture initiation capacity

The primary cell culture initiation, primary cell cultures were successfully established from liver tissues stored for 3 and 6 months under both freezing methods and storage temperatures (Fig. 6); however, the cells did not survive after passaging.

Discussion

In translational research, collaborative approaches combined with high-quality clinical data are essential to collect sufficient samples, while maintaining sample quality and homogeneity is crucial.[22] Low reproducibility remains a significant challenge for the development of clinical biomarkers for diagnosis, treatment, and monitoring.[23] Therefore, analyses and records used to assess tissue quality are critical to ensure reproducibility, yet standardized and comprehensive methods to evaluate tissue quality and usability have not been fully established.

However, it is unachievable to perform these analyses in clinical biobanking settings with human tissues due to the limitations, including sample size, genetic variability, a wide disease/lifestyle spectrum, and ethical issues. In this study, we used rat liver tissue which allow us to test a wide variety of conditions in a sequential experimental setting. By evaluating ideal and suboptimal pre-analytical scenarios using liver tissues obtained from one line of Wistar Albino rats, potential bias introduced by biobanked patient samples was minimized.

To find optimized transfer time and conditions for liver samples, we first tested three different cold ischemia durations and three different sample transfer conditions on sample quality. Since transfer at +4 °C has been reported to be critical for maintaining liver tissue stability[24,25] we tested all scenarios at +4 °C, and compared direct transfer, transferring tissues in culture medium, or vacuum sealed bags, to determine whether these conditions further improve sample quality for biomolecular analyses. Although keeping liver tissue samples in vacuum-sealed bags at 4 °C during transfer has been reported to inhibit enzymatic activity and prevent autolysis and mechanical stress,[26] in our experimental setting, vacuum-sealed bags did not produce a statistically significant result in any

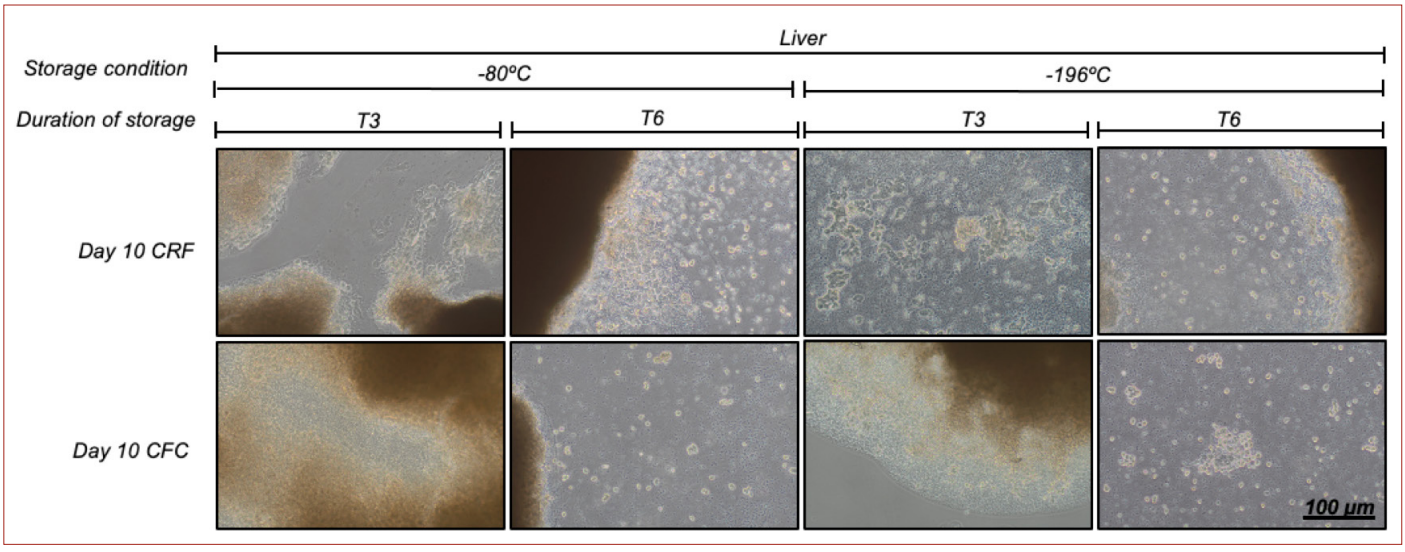

Figure 6. Primary liver cell culture outcomes following different storage durations and conditions: Primary cell cultures were successfully established from liver tissues stored for 3 and 6 months under both freezing methods and storage temperatures.

ischemia duration. Vacuum bags are commonly used to extend the shelf life of food or pharmaceutical products. However, in live tissue samples, particularly in biobanking, methods such as rapid cooling and cryopreservation are more effective. Therefore, the use of vacuum bags cannot compensate for the adverse effects of ischemia time.

Across all ischemia durations tested (2, 8 and 24 h, +4 °C), the total yields of RNA, DNA, and proteins remained stable in liver tissues, with no statistically significant differences between transfer conditions. These findings indicate that, although tissue morphology and RNA integrity showed gradual alterations over time, the overall molecular quantities were preserved regardless of ischemia duration. Data showing primary cell culture initiation capacity up to 8 hours of cold ischemia in all three transfer conditions support keeping cell viability in this time frame. Losing primary culture initiation capacity at longer cold ischemia (24 hours), parallel with the histopathological data showing cell damage.[27,28] Moreover, alterations in protein expression induced by cold ischemia have been found to correlate with concomitant changes at the gene expression level.[24]

The stability of RNA, DNA, and protein yields across different ischemia durations suggests that liver tissue possesses a relatively high resistance to short- and mid-term cold ischemia in terms of molecular quantity. This may be attributed to the dense cellular architecture and high tissue mass, which buffer against rapid degradation, and to the protective effect of storage at +4 °C, which slows enzymatic activity. However, despite similar quantities, RNA integrity was more sensitive to ischemia, highlighting that qualitative parameters rather than total amounts are more critical when evaluating the suitability of liver samples for downstream molecular and cellular applications.[29,30]

While freezing using a controlled-rate freezer (CRF) is commonly recommended in the literature,[31,32] in our study, freezing in isopentane or in a cell freezing container was as effective as using a controlled-rate freezer for preserving liver tissue. Notably, no significant difference was observed between –80 °C and –196 °C storage up to 9 months of storage period, supporting environmentally conscious "green biobanking" approaches.[33] It has been reported that maintaining tissues at –80 °C offers stable long-term preservation with minimal heat output and resource usage.[34,35] Sharing data on alternative preservation conditions, as presented here, can promote the development of more sustainable biobanking practices.

For nucleic acids, the significant decrease in RNA yield observed over time in liver tissues stored at –80 °C reflects the inherent vulnerability of RNA to enzymatic and chemical degradation, even under cold storage conditions. RNA is single-stranded and structurally less stable, making it more sensitive to residual RNase activity and ice crystal-induced damage.[29,36,37] In contrast, DNA is double-stranded and chemically more stable, explaining the lack of significant changes in DNA yields under storage at –80 °C or –196 °C. While ultralow temperatures effectively preserved RNA integrity during the first 3 months, prolonged storage may lead a gradual loss, highlighting the need to consider both storage temperature and duration for RNA-based analyses. The RIN value was 6 at T0, and no significant differences were observed between freezing methods or across storage durations of 3, 6, and 9 months, likely reflecting sample heterogeneity and differential preservation of RNA fragments.

Taken together, our study provides a comprehensive examination of how preanalytical factors, including cold ischemia time, freezing, and storage methods and affect quality parameters of liver tissue and the likelihood of preanalytical errors in a controlled experimental setup. Further studies to assess the impact of long-term storage on the liver tissue quality are needed.

Disclosures

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Original Research

Comparison of Tumour Characteristics and Outcomes in Paediatric Conventional Versus Fibrolamellar Hepatocellular Carcinoma: Tertiary Centre Experience

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Abstract

Objectives: Hepatocellular carcinoma (HCC) in the paediatric age group is a rare and unique disease, with limited evidence to guide treatment decisions. The two main histological subtypes, conventional HCC (cHCC) and fibrolamellar HCC (FL-HCC), differ in their natural history and clinical characteristics. Whether the absence of underlying cirrhosis in FL-HCC confers a survival advantage remains unclear due to inconclusive evidence.

Methods: A retrospective analysis was conducted at a tertiary centre in the United Kingdom, evaluating paediatric patients with HCC referred between 1994 and 2022. Subgroup analysis compared outcomes between cHCC and FL-HCC. Kaplan–Meier analysis was used to compare survival, and Cox regression analysis was performed to identify factors associated with worse survival.

Results: A total of 27 patients were included (cHCC = 17, FL-HCC = 10). The median age was 11 years (cHCC = 9 years, FL-HCC = 14 years), with a male-to-female ratio of 2.5:1 (M = 20, F = 8). Cirrhosis was present in 8 of 17 evaluable cHCC cases and absent in all FL-HCC cases. Surgical treatment was undertaken in 15 cHCC patients (hepatectomy = 3, transplantation = 12) and 8 FL-HCC patients (hepatectomy = 6, transplantation = 2). Median overall survival was 29 months for cHCC and 42 months for FL-HCC (P = 0.580). Median recurrence-free survival was 29 months for cHCC and 31.5 months for FL-HCC (P = 0.395). Cox regression identified PRETEXT stage as an independent prognostic factor for poorer survival.

Conclusion: Although FL-HCC occurs in non-cirrhotic livers and presents in older children, no significant survival advantage was observed compared to conventional HCC. Tumour extent, as reflected by PRETEXT stage, remains a key prognostic factor. Further multicentre studies are needed to better define optimal treatment strategies for paediatric HCC.

Keywords: Paediatric Hepatocellular Carcinoma, Conventional Hepatocellular Carcinoma, Fibrolamellar Hepatoclleular Carcinoma, Liver Transplantation

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Primary liver tumours are rare in children, constituting around 1% of all childhood tumours. The majority are hepatoblastomas (80%), while hepatocellular carcinoma represents only <20% of all cases.[1-3] Although the incidence of hepatoblastoma and mesenchymal tumours have increased over the years, the incidence of HCC remained relatively stable.[4-6]

The treatment pathway for HCC patients is evolving with time. Surgery remains the main stay of any curative intent treatment. Despite the low response rates of HCC tumours to chemotherapy, its role in downstaging advanced tumours is evolving.[7,8] Patients are being increasingly considered in trials, and research is ongoing to dissect the genetic and molecular basis of HCC tumours. Recently, novel vaccinations and immunotherapeutic drugs targeted against tumour specific molecules are being developed.[9,10]

Our understanding of the natural course of HCC in childhood is largely based on analysis of retrospective data extending over a long period of time, while there is limited data from trials or prospective research. Acknowledging the rarity of this disease entity, the latter may prove challenging. The largest ongoing trial is the Paediatric Hepatic International Tumour Trial (PHITT). This is a multi-centre international study evaluating treatment strategies for paediatric liver cancers, including hepatocellular carcinoma. It aims to improve outcomes by tailoring therapy based on risk stratification and tumour biology. Patients with resectable HCC are treated with PLADO (cisplatin + doxorubicin) and may be randomised to receive sorafenib, while patients with unresectable or metastatic HCC receive PLADO alternating with or without GEMOX (gemcitabine +oxaliplatin) and sorafenib.[11]

Similar to adults, conventional HCC (cHCC) and fibrolamellar HCC (FL-HCC) have been distinguished on a histological and clinical basis in paediatric patients.[12,13] Paediatric FL-HCC constitute at least 20-30% of all cases compared to <10% in adults.[14-16] The controversy whether FL-HCC has similar to or better prognosis than cHCC also exists in paediatric patients as in adults.[4,13,17-19]

This study highlights the experience of one of three United Kingdom paediatric hepatobiliary and liver transplant centres in the treatment of paediatric HCC. The treatment pathway and outcomes for paediatric HCC were investigated and presented. We aim to add to the pool of data available and expand our understanding of this rare tumour in the paediatric age group.

Methods

Our study cohort was based in a tertiary paediatric hepatobiliary and liver transplant unit. Patients' records were retrieved and all cases with suspected diagnosis of HCC referred to our unit between 1994 and 2022 were included. All patients were discussed in a multi-disciplinary team meeting, and patients who were considered candidates for curative intent treatment were either offered upfront surgery in the form of liver resection or transplantation, or referred to oncology for consideration of neoadjuvant treatment, possibly in the setting of a clinical trial. Patients without underlying liver parenchymal disease and where two or more contiguous liver segments can be preserved were considered for liver resection after the staging scans confirm absence of metastatic disease. On the other hand, underlying liver cirrhosis or non-metastatic locally unresectable disease (PRETEXT IV) were indications for liver transplantation. Multi-visceral transplantation was only considered in selected cases, mainly extensive thrombosis of the porto-mesenteric venous system.

Inclusion criteria included age of 16 years and below, pre-operative radiologic or histologic diagnosis of HCC and patients with incidental diagnosis of HCC on liver explant histology. Patients with non-HCC diagnosis on final histology or with inconclusive diagnosis due to overlapping features of HCC or hepatoblastoma were excluded. Patients with a minimum of 2 years follow up after diagnosis were included in the study. The following variables were collected: patients' demographics, PRETEXT stage, alpha-feto protein (AFP), extent of surgical intervention, background liver histology, chemotherapy details, enrolment in clinical trials and survival data. Mann-Whitney U test was used to compare numerical variables, and Chi Square test was used for categorical variables.

For survival analysis, overall survival (OS) was calculated from the date of radiological diagnosis to the date of death or last follow up. Disease-free survival (DFS) was calculated from the date of surgery to the date of recurrence or last follow up. Kaplan-Meier analysis was used to compare survival and generate survival curves. Cox regression analysis was performed to investigate factors associated with worse outcomes. SPSS version 26.0 software package (SPSS Inc., Chicago, IL, United States) was used to perform statistical analyses.

Results

Demographics and Clinical Characteristics of Tumours and Patients

Demographics of Whole Cohort

A total of 33 patients with possible diagnosis of HCC were referred over the study period. Six patients were excluded as final histology either confirmed a diagnosis other than HCC or was inconclusive. Twenty-seven patients with HCC

were identified and included. Median age at diagnosis was 11 years (interquartile range (IQR)= 8-14 years). Male to female ratio was 2.5:1 (20 males and 8 females). 17/27 (63%) patients had cHCC based on pre-operative biopsy or histopathological examination of the resected specimen, while 10/27 (37%) patients were diagnosed with FL-HCC.

Comparison Between Patients with cHCC and FL-HCC (Table 1)

Patients with cHCC had a median age of 9 years and were younger compared to FL-HCC patients who had a median age of 14 years, p=0.031. There was no difference in gender distribution between the two entities. Eight out of seventeen (47%) patients with cHCC had underlying liver cirrhosis secondary to: chronic hepatitis B infection (n=1), tyrosinemia (n=1), congenital hepatic fibrosis (n=1), progressive familial intrahepatic cholestasis (n=1), congenital porto-systemic shunt (n=1), mitochondrial disease (n=1), biliary atresia (n=1) and Alagille's disease (n=1). However, none of the patients with FL-HCC showed macroscopic or microscopic features of cirrhosis. Eleven out of seventeen (65%) patients with cHCC had raised AFP levels compared to 2/10 (20%) patients with FL-HCC. Although more advanced PRETEXT stages were noticed in cHCC patients, this was not statistically significant. More patients underwent liver resection than transplantation in the FL-HCC group (resection= 6, transplantation=2), compared to cHCC patients (resection= 3, transplantation= 12).

Table 1. Demographics, tumour characteristics and spectrum of surgical treatment for the study cohort.

	Conventional HCC (n=17)	Fibrolamellar HCC (n=10)	p
Median age at diagnosis (IQR)	9 years (6-14)	14 years (11-15)	0.031
Gender			0.370
Male	13	6	
Female	4	4	
Background liver histology			0.002
Normal	9	10	
Cirrhotic	8	0	
AFP levels			0.013
<=20	4	7	
>20	11	2	
Missing	2	1	
Pre-operative biopsy	12	8	0.562
PRETEXT stage			0.178
Stage I	4	0	
Stage II	3	4	
Stage III	1	3	
Stage IV	8	1	
Missing	1	2	
Neoadjuvant chemotherapy	5	3	0.974
Resected disease	15	8	0.566
Hepatectomy			
Right	-	2	
Extended right	2	-	
Extended left	-	4	
Extended left + ablation	1	-	
Transplant			
Split/reduced OLT	7	1	
Whole graft OLT	5	-	
Multi-visceral transplant	-	1	
Complete resection			0.940
R0	13	6	
R1	2	2	
Missing	2	2	

OLT: Orthotopic Liver Transplant.

Treatment Pathway

Upfront surgery was performed in 17/27 (63%) patients, while 2/27 (7%) patients neither received neoadjuvant treatment nor underwent surgical resection. Of the 8/27 (30%) patients who received neoadjuvant treatment (NAT), curative surgery was performed in 6 patients.

Surgically Treated Patients

A total of 23/27 (85%) patients had curative intent surgery (cHCC= 15/17 patients, FL-HCC= 8/10 patients). Thirteen patients underwent liver transplantation, 9 patients had liver resection, either in the form of a hemihepatectomy or an extended hemihepatectomy, and one patient underwent multi-visceral transplantation due to extensive portal and mesenteric venous thrombosis.

Neoadjuvant Treatment Followed by Surgery

Five patients with cHCC had neoadjuvant treatment, however only four patients underwent surgery; two out of the four patients received peri-operative chemotherapy (neoadjuvant and adjuvant) according to Group D of the PHITT trial (Cisplatin intensive regimen followed by consolidation Carboplatin/Doxorubicin); one of the two patients had lung metastasis that completely responded to treatment and the other patient had partial response. One of the four patients with cHCC had chemotherapy according to Group F (Arm 2) of the trial and received alternating cycles of PLADO/Sorafenib with cycles of Gemcitabine/Oxaliplatin (GEMOX) and sorafenib. One patient had treatment abroad in the form of Cisplatin, 5-FU, Vincristine and Doxorubicin. Both of the latter two patients had stable disease and proceeded to surgical resection.

Three patients with FL-HCC received NAT, but only two patients proceeded to surgery. One patient was enrolled in Group F (Arm 1) and received Cisplatin/Doxorubicin (PLADO) and sorafenib, and one patient had Lenvatinib as

a single agent treatment. Both patients had stable disease post chemotherapy and underwent surgery subsequently.

Surgery Followed by Adjuvant Chemotherapy

Of the 17 patient who underwent upfront surgery, 5 patients received adjuvant treatment. Only one patient with cHCC received chemotherapy with doxorubicin and sorafenib, while four patients with FL-HCC received adjuvant treatment; two patients were enrolled in Group F (Arm 1) of the PHITT trial, one patient had cisplatin and doxorubicin based regimen, while data about type of adjuvant chemotherapy was missing for the last patient.

Unresected Patients

Four patients did not undergo curative resection. Two patients with cHCC and two patients with FL-HCC. Among the two patients in the cHCC group, one patient had chronic hepatitis B cirrhosis and the other had mitochondrial disease. One of them was not fit for neoadjuvant chemotherapy, and the other patient had four cycles of neoadjuvant cisplatin and doxorubicin and showed stable disease. However, both of these patients had extensive disease not allowing for liver resection and significantly high levels of AFP outside the criteria for organ transplantation.

Of the two unresected patients in the FL-HCC group, one patient received alternating cycles of Cisplatin and Carboplatin/doxorubicin (Group D) but showed progressive disease. While the other patient had advanced disease along with extensive portal vein thrombosis that the possibility of disease downstaging to allow resection or transplantation was low, therefore chemotherapy was not offered in favour of better quality of life.

Survival Analysis of Conventional vs Fibrolamellar HCC

Median overall survival (OS) for the whole cohort of patients was 36 months (IQR= 18-86), and the recurrence-free survival (RFS) was 31 months (IQR= 9-57). Median OS for cHCC patients was 29 months (IQR= 15.5-78) and shorter than median OS of FL-HCC patients of 42 months (IQR= 21.3-53.3) though not statistically significant, p= 0.580 (Fig. 1; A). Median RFS was shorter for cHCC compared to FL-HCC patients (29 months (IQR=5-71 months) compared to 31.5 months (IQR= 10-49 months), respectively); however, this also did not differ significantly, p=0.395 (Fig. 1; A).

To eliminate cirrhosis as a cofounding factor in survival analysis, we excluded cHCC patients with underlying cirrhosis. There was no significant difference in the median OS between non-cirrhotic cHCC (18 months) and FL-HCC groups (42 months), p=0.851. However, median RFS for non-cirrhotic cHCC was found to be only 12 months and approached but did not reach statistical significance compared to FL-HCC patients (median RFS= 31.5), p=0.092. (Fig. 1;B).

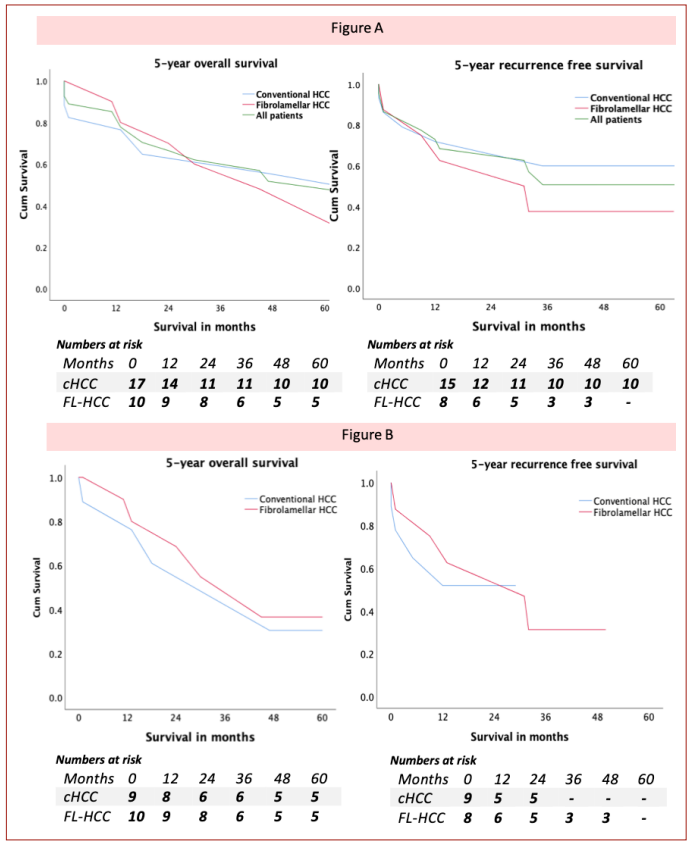

Figure 1. Kaplan-Meier survival curves. **(a)** Comparison of OS and RFS of cHCC and FL-HCC patients who underwent surgery. **(b)** Comparison of OS and RFS of cHCC and FL-HCC patients without cirrhosis.

Recurrence Pattern

A total of ten patients had recurrence following resection (five patients in each group). In the cHCC group, three had recurrence limited to the liver (2 post hepatectomy, 1 post liver transplant) and two patients developed recurrence in the lungs only (both post liver transplant).

Three patients with FL-HCC had isolated lymph node (LN) recurrence (2 in regional LNs, 1 in mediastinal LNs), one patient had recurrence in regional LN and lungs and one patient had liver and lung recurrence.

Factors Predicting Survival

Age, gender, AFP (normal vs high), PRETEXT stage, type of HCC, background liver histology, surgical resection, resection margin status and neoadjuvant treatment (NAT) were entered into a univariate cox regression hazard model. This identified higher PRETEXT stage, absence of surgery and lack of NAT to be associated with worse survival, increasing the risk of mortality by 2.5, 5 and 4.4 times, respectively. These factors were further entered into a multivariate model and this identified higher PRETEXT stage to be independent predictor of poor survival Table 2.

Table 2. Cox regression analysis for overall survival

	Univariable analysis		Multivariable analysis	
Variable	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**
Age	0.787	0.982 (0.86-1.12)	-	-
Gender	0.394	1.77 (0.48-6.57)	-	-
AFP	0.394	1.65 (0.52-5.23)	-	-
PRETEXT stage	0.021	2.54 (1.16-5.61)	0.033	2.44 (1.07-5.55)
Type of HCC	0.816	1.15 (0.36-3.64)	-	-
Cirrhosis	0.545	1.50 (0.40-5.64)	-	-
No surgery	0.013	5.05 (1.41-18.09)	0.107	3.36 (0.77-14.70)
R status	0.640	1.65 (0.20-13.48)	-	-
No NAT	0.038	4.46 (1.09-18.30)	0.326	0.40 (0.07-2.47)

Discussion

This study introduces the experience of a regional paediatric hepatobiliary and transplant centre in the treatment of HCC over a 28-year period. Despite this, only twenty-seven patients were identified after thoroughly scanning data bases and MDT outcomes. This shows the rarity of this tumour and therefore limits our understanding of the disease. Key areas of debate in paediatric HCC include optimal chemotherapy regimen, the role of neoadjuvant treatment, use of adult guidelines, criteria for resectability and indications for liver transplantation. The purpose of this study is to track the treatment pathway of HCC patients including neoadjuvant treatment regimens and extent of surgical treatment provided, and compare outcomes for the two main histologic subtypes of HCC in the paediatric age group, namely conventional and fibrolamellar HCC.

The age distribution and slightly higher incidence in male patients noticed in our cohort correlates with what is reported in literature.[6,20] Patients with paediatric cHCC were younger than FL-HCC, the later being a disease of teens or adolescents. The proportion of FL-HCC in the current study corresponds to the published data.[2] Categorising HCC patients into subgroups is mandated as both diseases have different clinical and histopathological characteristics.[21,22] cHCC in paediatric patients can occur on a background of liver pathology or, more commonly than in adults, de novo. 20-30% of paediatric patients will have underlying liver disease compared to 85% in adults.[2] However, this was noticed to be higher in our cohort (8/17 patients). This may reflect referral bias to a tertiary centre, where children with more complex or pre-existing liver conditions are more likely to be managed, or it could suggest geographical variation in underlying liver disease prevalence. On the other hand, none of the patients with FL-HCC had underlying liver pathology, consistent with its known occurrence in non-cirrhotic livers.

Almost two thirds of cHCC patients in our study had elevated AFP levels, while only two patients with FL-HCC had elevated values. This is likely because AFP is an oncofoetal glycoprotein that is elevated not only in tumour cases, but also a marker of acute and chronic liver disease and cirrhosis.[23] The L3 fraction of AFP has shown greater specificity, especially in early disease, than AFP alone.[24,25] In addition, when combined with another tumour marker, Des-gamma-carboxyprothrombin (DCP), also known as PIVKA-II (Protein Induced by vitamin K absence or antagonist-II), the sensitivity and specificity approach 90%.[23,26] Recently, a novel tumour marker derived from dysregulated RNA processing in HCC tumours; extracellular vesicle-derived long noncoding RNA (lncRNA), has shown promising results in identifying early HCC but is still under investigation.[27]

Less than half of our patients received peri-operative chemotherapy. Hepatocellular carcinomas in general are well known for their chemo-resistance.[7,28,29] However, it is reported that paediatric HCC have higher response rates to chemotherapy.[30] The reported response rate for chemotherapy in paediatric HCC can be up to 50% compared to around 20-25% in adults.[31] This remains unsatisfactory and account for the relatively low rates of chemotherapy administration reported in this group of patients. It also contributes to the fact that the majority of patients with less advanced disease will be offered upfront surgery. Seven out of thirteen patients with PRETEXT stage 3- and 4-disease in our cohort received neoadjuvant chemotherapy, while none of the patients with PRETEXT stages 1 and 2 received neoadjuvant treatment. In addition to low response rates, differences in local practices and expertise have also led to variations in chemotherapy protocols administered. In the majority of patients,

this is usually based on cisplatin and doxorubicin. The addition of immunotherapeutic and molecular targeted agents has made it difficult to standardize regimens and identify associated outcomes.[31,32] The implementation of systematic chemotherapy protocols, within clinical trials, might enable us to explore response rates to different protocols and identify disease patterns for which treatment can be tailored.

Survival In patients with cHCC and FL-HCC was comparable. Survival was initially better for FL-HCC patients in the first two years after diagnosis until survival curves crossed and cHCC patients had survival advantage, though this was not statistically significant. Results from the current literature comparing survival between the two disease entities are mixed.[17-20] Better prognosis in patients with FL-HCC reported by some researchers is thought to be due to the absence of underlying liver parenchymal disease.[12,33] This might explain the better short-term survival noticed in FL-HCC compared to cHCC patients, despite the fact that our subgroup analysis comparing FL-HCC with non-cirrhotic cHCC still showed a survival advantage for the earlier group, though this was not statistically significant. Also, these patients would expectedly tolerate and benefit from more extensive resections and peri-operative chemotherapy. [34,35] On the other hand, research showing similar outcomes for the two categories report that any survival advantage is offset by the higher tendency for lymphatic spread in FL-HCC patients and its role in early disease recurrence,[17,36,37] which may explain why the 5-year survival in FL-HCC patients was lower in the study.

Recurrence pattern for both HCC types is different.[13] In our study, cHCC patients had recurrence in the liver more commonly than FL-HCC, where recurrence in the latter was mainly in lymph nodes and lungs. Median RFS was relatively similar in both groups although only 3 out of 8 resected patients with FL-HCC remained disease free, compared to 10 out of 15 resected cHCC patients over the study period. Building on the observation that 5-year OS was noted to be worse in FL-HCC due to more frequent lymph node metastases, worse long-term RFS was also seen more commonly in FL-HCC. Lymphatic spread is associated with poor tumour biology and high recurrence rates,[38] and immunohistochemistry showed that FL-HCC is derived from cells that can differentiate into hepatocytes or cholangiocytes, with the latter having more potential to metastasize.[39]

Cirrhosis has been inconsistently reported to be associated with worse outcomes.[18,40-42] Cirrhotic patients have two coexisting morbid conditions that are expected to reflect negatively on survival; the tumour itself and the underlying chronic liver disease. However, the caveat here is that patients with cirrhosis are typically under regular clinical follow up and would have interval surveillance scans or laboratory tests (tumour markers) that might lead to early tumour detection.[43] In our cohort, cirrhosis was not associated with worse prognosis on regression analysis. In addition, when cirrhotic patients were excluded from survival analysis, OS and DFS were not significantly different. Eight out of ten patients with cHCC who had underlying liver cirrhosis had resection and all of them underwent liver transplantation. Removing the diseased liver and achieving clearer margins with total hepatectomy and liver transplantation, might explain why cirrhosis was not identified to be associated with worse survival.

Higher PRETEXT stage was identified in univariate and multivariate analysis to be associated with worse prognosis. The PRETEXT staging system was first described by the International Childhood Liver Tumour Strategy Group (SIOPEL) in 1990 to adopt a uniform method to compare the extent and outcome of the disease.[44] It was revised in 2005 to provide more detailed classification of liver tumours to include the local extent of hepatic and vascular involvement, as well as systemic spread.[45] Higher disease stages are expected to reflect poor tumour biology as the tumour involves more liver parenchyma, whether by direct extension of a single lesion or by multiple intrahepatic metastasis. However, the staging system does not take into account the presence or absence of underlying liver cirrhosis, and the association with worse prognosis with higher stages was not consistently reported in the literature.[13,46]

The overall poor prognosis for HCC patients even after surgery and chemotherapy drives the search for different modalities of treatment. The molecular and genetic basis for HCC is a main focus of ongoing clinical research, as genetic mutations identified in such tumours can be targeted. One trial that started in April 2020 investigates the safety and efficacy of a novel vaccine targeting the pathognomonic fusion kinase protein (DNAJB1-PRKACA) along with immunotherapeutic agents in FL-HCC patients; the trial is still in phase 1 and is expected to conclude in 2027. Another phase 2 trial that also started in 2020, investigates the role of an immunologic drug (pembrolizumab) on the outcomes of patients with HCC (conventional and FL), and aims to explore predictors of response to treatment based on tumour biological factors; completion of the study is expected to be at the outset of 2028.[10]

The limitation of our study resides in its retrospective nature, limited number of patients and the span of the study period over which it was conducted. The

variations in chemotherapy treatment and advances in surgical treatment and liver transplantation over time compounded these limitations. Our data showed that there was no significant difference in OS or RFS between cHCC and FL-HCC patients, and that higher PRETEXT stage was independently associated with worse prognosis. Randomised controlled trials would be challenging to perform considering the low incidence of HCC in paediatric age group and its feasibility is uncertain. Combining existing literature with prospective data is the only means to provide strong clinical evidence to help guide treatment pathways.

Disclosures

Ethics Committee Approval: This study received approval from the ethics committee and is registered under CARMS-31035.

Authorship Contributions: Concept – M.A., K.S.; Design – M.A., R.M., K.S.; Supervision – R.M., KS.; Materials – M.A.; Data collection &/or processing – M.A.; Analysis and/or interpretation – M.A., R.M.; Literature search – M.A.; Writing – M.A.; Critical review – D.F.M., D.H., E.O., R.M., K.S.

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Original Research

Three Decades of Laparoscopic Cholecystectomy: Standardized Protocols and Surgical Outcomes

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Abstract

Objectives: The primary aim of this study was to present our 30 years of experience with laparoscopic cholecystectomy (LC) procedures conducted in tertiary care institutions, focusing on patient outcomes, complications, and the efficacy of standardized management protocols.

Methods: This retrospective cohort study analyzed 4,572 LC procedures conducted over a 30-year period in a tertiary medical center. All patients were managed according to a standardized protocol encompassing preoperative, intraoperative, and postoperative care, which was regularly reviewed and updated. Data on demographic characteristics, surgical indications, complications, and patient outcomes were collected and analyzed.

Results: A total of 4,572 patients (3,246 female [71%], 1,326 male [29%]) underwent LC, with a mean age of 41.0 ± 1.3 years (range 14–91). The most common indication for surgery was symptomatic or complicated gallstones, observed in 4,453 patients (97.4%). Of these, 1,966 patients (43%) had gallstone-related complications, including cholecystitis (985 patients [21.5%]), choledocholithiasis (736 patients [16.1%]), and biliary pancreatitis (247 patients [5.4%]). Simultaneous laparoscopic procedures were performed in 342 patients (7.5%), with common surgical interventions such as choledochal exploration (104 patients [2.3%]), hysterectomy (71 patients [1.5%]), and umbilical hernia repair (45 patients [1.0%]). Perioperative morbidity occurred in 361 patients (7.9%), with no reported mortality. According to the Clavien-Dindo classification, 349 patients (96.7%) experienced minor complications (grades I and II), while 12 patients (3.3%) had major complications (grades III and IV), including biliary injury (3 patients [0.07%]), intestinal injury (3 patients [0.07%]), bleeding (3 patients [0.07%]), thromboembolism (2 patients [0.05%]), myocardial infarction (1 patient [0.02%]), and pneumonia (1 patient [0.02%]). Conversion to open surgery was required in 3 patients (0.07%).

Conclusion: The adherence to a unified management protocol for LC, with periodic reviews and updates, significantly reduces postoperative mortality and the incidence of major complications, including biliary injury. Furthermore, this approach enables the safe performance of simultaneous laparoscopic procedures in patients with comorbidities, contributing to improved surgical outcomes in tertiary care settings.

Keywords: Biliary injury, conversion to open surgery, laparoscopic cholecystectomy, surgical outcomes, standardized protocols, perioperative morbidity, simultaneous laparoscopic procedures

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At the beginning of the 21st century, numerous innovations and advancements have profoundly transformed the field of surgery. These include the introduction of minimally invasive surgery, development of high-resolution imaging technologies, advancements in medical soundness, establishment of specialized training programs, and adoption of multidisciplinary approaches. These innovations have collectively reshaped surgical practice, enhanced pre-

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cision, reduced patient recovery times, and improved overall surgical outcomes.

The revolution in laparoscopic surgery began 40 years ago with the introduction of LC, which quickly gained recognition and became the "treatment of choice for patients with symptomatic cholelithiasis" according to the National Institutes of Health (NIH). Despite the absence of empirical or randomized trials, LC has become widely accepted. The safety of the procedure, along with its potential to reduce antibiotic usage and improve outcomes, particularly in cases of acute cholecystitis, has further facilitated its adoption. The introduction of enhanced recovery after surgery (ERAS) protocols also plays a pivotal role in promoting LC as the standard of care among surgeons.

Purpose

The primary aim of this study was to share our 30 years of experience with laparoscopic cholecystectomy performed in tertiary care institutions, highlighting the outcomes, challenges, and evolving techniques associated with this procedure over the past three decades.

Methods

This study encompasses the outcomes of laparoscopic cholecystectomy (LC) procedures performed and documented by the authors over several years. The operations were conducted at multiple institutions, including Van Yuzuncu Yıl University (1996-1998), Emergency Hospital (1999), Central Clinic Hospital (2001-2008), Buraydah Central Hospital (2002-2003), Eurasia Clinic, Central Customs Hospital (2009-2015), Azerbaijan Medical University Educational Surgical Clinic (2014-2024), and the Main Military Medical Department of the State Security Service (2017-2024).

Preoperative, intraoperative, and postoperative management was standardized according to a unified protocol developed by the authors. These guidelines, formulated as comprehensive working articles, have been published in several books.[1-5] The author directly supervised adherence to these protocols, and any deviations or complications noted during patient examinations and treatments were thoroughly discussed during regular audit meetings.

Preoperative Examinations

Standard preoperative assessments were performed for all patients diagnosed with gallstone disease. These evaluations included a thorough clinical assessment, along with laboratory tests, such as hemogram, ALT, AST, GGT, ALP, bilirubin, INR, CRP, HBsAg, anti-HCV, and abdominal ultrasound. Since 2017, liver and spleen elastography have been incorporated into routine preoperative examination protocols. Additionally, MRI and MR cholangiography were performed to assess the bile ducts in patients presenting with elevated liver enzyme levels or signs of cholestasis. In cases whichere elastography readings were elevated (≥7 kPa), comprehensive liver evaluations were conducted to assess liver function and potential fibrosis.

Early laparoscopic cholecystectomy is prioritized in patients with acute cholecystitis. Patients who presented in the morning were typically scheduled for surgery on the same day, whereas those who arrived in the evening were scheduled for surgery the following day. In cases of complicated acute cholecystitis, such as perforation, empyema, or emphysematous cholecystitis, surgery was performed within the first 6-8 hours of hospital admission. Patients with uncomplicated acute cholecystitis underwent surgery within 12-24 hours.

In cases of choledocholithiasis and cholangitis, the approach to surgery is determined by the timing of diagnosis, the clinic's available resources, and patient preferences. For choledocholithiasis that was identified postoperatively, ERCP was performed to remove the stones. In cases of choledocholithiasis diagnosed before or during surgery, one of the two approaches was selected based on technical feasibility and patient preferences. If choledochoscopy and intraoperative cholangiography were available, one-stage laparoscopic cholecystectomy, choledochal exploration, and stone removal were performed. If the stones were extracted transcystically, the procedure was completed by clipping the cystic duct. In cases in which choledochotomy was necessary for stone removal, a T-drain was placed in the choledochus. If stone removal from the choledochus was not possible intraoperatively, choledochal drainage was performed and postoperative ERCP was scheduled. For facilities lacking the ability to perform choledochoscopy or cholangiography, a two-stage approach was used. ERCP was performed first to remove stones from the choledochus, followed by laparoscopic cholecystectomy 1-2 days later, with routine intraoperative cholangiography to confirm duct clearance.[5]

In cases of acute biliary pancreatitis, the timing of cholecystectomy depended on the severity of the condition. For mild to moderate pancreatitis, laparoscopic cholecystectomy was generally performed during the initial hospitalization (within 5 to 14 days). For severe pancreatitis, cholecystectomy was planned once the complications of pancreatitis had been resolved.

Surgical Technique

Our surgical technique for laparoscopic cholecystectomy (LC) has remained largely unchanged over the past 30 years. The procedure begins with a thorough dissection

of Calot's triangle and the proximal third of the gallbladder, exposing the cystic duct and gallbladder artery. Two "windows" are opened to facilitate this dissection, with the artery being clamped, and cut first, followed by the cystic duct. The gallbladder is then carefully separated from the bed and removed. During the first decade of our experience, scissors and clamps were used for dissection, while in the last 20 years, hooks have been employed to enhance precision and minimize trauma.

Intraoperative cholangiography was performed as needed, primarily in cases where choledochal stones had been removed via ERCP prior to surgery, in cases of cholestasis with abnormal liver tests but no identifiable pathology on MRI, and in surgeries where enlargement or abnormalities of the choledochus were suspected during the operation.[6]

In cases where gallbladder cancer was suspected, a biopsy or resection of the gallbladder bed and portal lymphadenectomy was performed.

Liver biopsy was also performed during surgery in patients with fatty liver, cirrhotic changes, or a history of HBV and HCV infections.

In cases of cholecystoduodenal fistula, the fistula tract was surgically closed.

Bile duct injuries were either drained or reconstructed.

Mirizzi syndrome type I, a cholecystectomy, transcystic stone removal, and drainage were performed. In cases of Mirizzi syndrome type II, a partial cholecystectomy with T-drainage was performed laparoscopically.[7]

Perioperative Management

Perioperative management adhered to Enhanced Recovery After Surgery (ERAS) guidelines. A single dose of prophylactic antibiotics was administered during anesthesia, with a second dose administered within 24-48 hours in cases of destructive cholecystitis. To prevent thrombosis, all patients were fitted with elastic stockings, mobilized early postoperatively, and high-risk patients received anticoagulants. Crystalloid solutions were infused during surgery to maintain adequate fluid balance, with a positive fluid balance of approximately 500-1000 ml maintained at the end of the procedure.

In the early postoperative period (6-8 hours after surgery), emphasis was placed on early feeding, mobilization, and minimal use of analgesics. Most patients were discharged within 24 hours, with follow-up appointments scheduled at 1 week, and at 1, 3, 6, and 12 months postoperatively.

Statistical Analysis

All data were collected and analyzed using Microsoft Excel. Quantitative data are presented in the tables.

Results

A total of 4,572 patients who underwent laparoscopic cholecystectomy (LC) were included in the study. The mean age of the patients was 41.0±1.3 years, with the age range spanning from 14 to 91 years. Among the study population, 3,246 (71%) were female, and 1,326 (29%) were male, resulting in a male-to-female ratio of 1:2.4 (see Table 1). The primary indication for surgery in 4,453 (97.4%) patients was symptomatic and complicated gallstone disease (see Table 2).

Gallstone complications were identified in 1,966 (43%) of the patients undergoing laparoscopic cholecystectomy (LC). Among these, acute cholecystitis was found in 985 (21.5%) patients, choledocholithiasis in 736 (16.1%), and biliary pancreatitis in 247 (5.4%). Additionally, asymptomatic gallstones larger than 2 cm, discovered in 34 (0.74%) patients with haemolytic anaemia, were also an indication for surgery.

Although complete cholecystectomy was performed in the vast majority of patients, exceptions were made in 11 cases (0.24%). Among these, 2 patients (0.04%) had cirrhosis, 2 patients (0.04%) had acute cholecystitis, and 7 patients (0.15%) underwent partial cholecystectomy due to Mirizzi syndrome. Furthermore, 342 patients (7.5%) with concomitant surgical pathologies underwent simultaneous laparoscopic procedures. These included 104 patients (2.27%) who underwent choledochal exploration, 71 patients (1.5%) who underwent hysterectomy, and 45 patients (0.98%) who underwent umbilical hernia repair (see Table 3).

Table 1. General Demographics of Patients

Indicator	n	%
Total count	4.572	
Average age	41.0	
Female	3.246	71
Male	1.326	29

Table 2. Indications for Laparoscopic Cholecystectomy

Indicator	n	%
Biliary colic (chronic cholecystitis)	2.599	56.85
Acute calculous cholecystitis	985	21.54
Acute cholecystitis without stones	101	2.21
Asymptomatic gallstones	34	0.74
Gallbladder polyp	106	2.32
Gallbladder cancer	11	0.24
Other complications of gallstones	1.013	22.16
Biliary pancreatitis	247	5.40
Choledocholithiasis	736	16.10
Cholecystio-enteric fistula	4	0.09
Mirizzi syndrome	26	0.57

Table 3. Simultaneous Surgical Operations Performed Laparoscopically

Indicator	n	%
Simultaneous surgeries	342	7.48
Choledochus exploration	104	2.27
Fundoplication	36	0.79
Groin hernia	19	0.42
Umbilical hernia	45	0.98
Postoperative hernia	33	0.72
Hysterectomy	71	1.55
Ovarian cystectomy	24	0.52
Bariatric surgery	7	0.15
Colonic resections	6	0.13
Liver cystectomies	11	0.24
Liver resections	7	0.15
Stomach resections	5	0.11
Pancreatic resections	3	0.07
Splenectomy	4	0.09
Small intestine resection	1	0.02
Nephrectomy	3	0.07

Perioperative Outcomes

Perioperative complication was observed in 361 (7.9%) patients, with no mortaity. According to the Clavien-Dindo classification, 349 (96.7%) of these patients had minor (grade I and II) complications, and 12 (3.3%) had grade III and IV complications: biliary injury in 3 (0.7%), intestinal injuries in 3 (0.07%), bleeding in 3 (0.07%), thromboembolism in 2 (0.05%), myocardial infarction 1(0.02%) and pneumonia 1(0.02%) patient (see Table 4). In the first patient with biliary injury, ligation of the right posterior sectoral duct was performed, and the patient was monitored postoperatively. In the second patient, cystic duct leakage was observed, and 1 day after the operation, a relaparoscopy was performed, during which a transcystic catheter was inserted into the duct. The third patient suffered a lateral choledochal injury, and a T-drain was placed. Bleeding was managed by conversion to open surgery in 2 patients and by relaparoscopy in another. Intestinal injuries occurred in patients during surgery due to trocar insertion, and laparoscopic sutures were applied. Thus, conversion to open surgery was required in 3 (0.07%) patients.

Discussion

In this article, we present the results of our 30-year experience with laparoscopic cholecystectomy (LC) performed in tertiary care institutions, encompassing 4,572 patients. According to our findings, complicated gallstone disease was present in 43% of cases, simultaneous surgeries were performed in 7.5%, and perioperative complications occurred in 7.9%. Importantly, no mortality was reported.

Table 4. Perioperative complications

Indicator	n	%
Perioperative complications	361	7.90
Clavien-Dindo I-II	349	7.63
Clavien-Dindo III	8	0.17
Clavien-Dindo IV	4	0.09
Biliary injury	3	0.07
Intestinal damage	3	0.07
Bleeding	3	0.07
Wound infection	145	3.17
Hernia	105	2.30
Deep vein thrombosis (DVT)	4	0.09
Pulmonary thromboembolism	2	0.04
Conservative treatment	96	2.10
Mortality	0	0.00
Conversion to open surgery	3	0.07
Relaparoscopy	2	0.04

A study by Wong et al., which included 21,706 surgical patients from 57 countries, investigated complications and mortality rates following cholecystectomy for gallbladder pathologies. The 30-day complication rate was 8%, and the mortality rate was 0.4%. These findings are consistent with the general complication rate observed in our experience, although significant differences were observed in the types of complications. In our study, major complications occurred in 3.3% of cases, while major complications accounted for 30% in the Wong study.[8] Additionally, biliary injuries were rarely reported in our experience (0.07%).

Simultaneous surgeries accounted for 7.5% in our experience. The literature shows variability in this figure. For instance, Kadir Y. and colleagues retrospectively analyzed the outcomes of cholecystectomy performed concurrently with bariatric surgery, involving 396 patients. Of these, 72 patients (18.1%) underwent simultaneous laparoscopic surgery.[9]

In our study, choledochal exploration was performed in 104 patients (2.27%). A multicenter study reported a higher rate of 3.5% for choledochal exploration.[10]

A 13-year study reported a mortality rate of 0% and a morbidity rate of 5.08%, with complications primarily due to damage to the bile tree and gallbladder artery.[10] In another study, the mortality rate was found to be 0.24%.[11]

According to the results of our experience, the mortality rate is zero, major complications, including biliary injuries, are low, and the rate of simultaneous operations is relatively high.

It is widely recognized that the organization and management of clinical protocols encompassing the development, adherence, monitoring, and periodic evaluation of perioperative and operative guidelines play a critical role in shaping surgical outcomes. We believe that one of the key factors contributing to the favorable results observed in our laparoscopic cholecystectomy experience is the rigorous adherence to preoperative and postoperative protocols, the use of safe surgical techniques, and the implementation of regular audits and quality control measures.

Conclusion

In conclusion, we emphasize that the systematic organization, implementation, and continuous monitoring of a standardized protocol for preoperative, intraoperative, and postoperative management is essential to minimize mortality, reduce the incidence of major complications, including biliary injuries, and improve the success rate of simultaneous operations in laparoscopic cholecystectomy.

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Review

MASLD and Liver Transplantation: Clinical Challenges, Systemic Complications, and Emerging Role of GLP-1 Receptor Agonists

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most common chronic liver disease worldwide, affecting approximately 30% of the global population, with prevalence reaching up to 50% in certain regions. Its burden is expected to rise in the coming years, primarily due to its potential to progress to liver cirrhosis and ultimately lead to liver transplantation. MASLD has emerged as one of the leading indications for liver transplantation globally, placing its management at the forefront of liver transplant care. Encouraging results from ongoing clinical trials suggest the potential to mitigate the global impact of MASLD in the near future. Glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated promising efficacy in the management of MASLD and are likely to receive approval for its direct treatment. Their beneficial effects on adiposity, along with their ability to reduce cardiovascular and renal burden, further enhance their therapeutic value. Additionally, their potential application in liver transplant settings is gaining increasing attention. In this narrative review, we explore the rising impact of MASLD within transplant medicine, its interplay with metabolic comorbidities, and the emerging utility of GLP-1 receptor agonists in liver transplantation care.

Keywords: MASLD, MASH, cirrhosis, fibrosis, liver transplantation, GLP-1

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most prevalent chronic liver disease worldwide, affecting an estimated 30% of the global population.[1] In the Middle East, the prevalence of MASLD is notably elevated, with rates reaching as high as 40%.[2] In Türkiye, prevalence rates as high as 50% have been previously reported in the general population, with a tendency to increase over the years.[3,4] In Germany, the prevalence of MASLD is currently estimated at around 23%; however, it is projected to double by 2030.[5] Moreover, the economic burden of MASLD continues to grow, largely driven by increasing rates of liver-related complications.[6] It should be noted that in patients with MASLD, cirrhosis is not a prerequisite for the development of hepatocellular carcinoma.[7] Despite this, the disease remains underdiagnosed in countries like Germany, highlighting the urgent need for improved early detection strategies and timely intervention to mitigate associated risks.[6] Moreover, since compensated cirrhosis can remain asymptomatic until decompensation occurs, timely detection of the disease and

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management of it are crucial. A German study from 2023 reported that 16% of patients with cirrhosis experienced decompensation within three years, leading to increased healthcare resource utilization and costs. However, only a small proportion of these patients received definitive treatments such as liver transplantation or transjugular intrahepatic portosystemic shunt.[8]

Beyond its rising prevalence, the burden of MASLD is also increasing. According to the U.S. liver transplantation registry, MASLD is now the leading indication for liver transplantation among patients with hepatocellular carcinoma who are on the waiting list.[9] According to recent analyses, MASLD and alcoholic liver disease have become the predominant indications for liver transplantation in both Europe and the United States, reflecting a rising trend in both regions.[10] Likewise, the number of patients with decompensated cirrhosis due to hepatitis B virus (HBV) on liver transplantation waiting lists is declining, thanks to effective antiviral therapies that achieve sustained viral suppression. In contrast, the number of patients listed for transplantation due to decompensated cirrhosis from MASLD is steadily increasing.[11] In Türkiye, although chronic viral hepatitis remains the leading indication for liver transplantation, the impact of MASLD is steadily increasing, mirroring trends observed in other countries.[12]

Despite the increasing burden of MASLD, until 2024 the only approved therapy was lifestyle intervention aimed at achieving a minimum weight loss of 5% of total body weight. This approach has also been shown to be effective in lean individuals affected by MASLD. However, in the long term, many patients tend to regain weight, raising concerns about the sustainability of lifestyle interventions.[13,14] In 2024, resmetirom was conditionally approved in the USA following the positive results in the MAESTRO-NASH trial.[15] Recently, the ESSENCE trial was published, demonstrating promising results for semaglutide, a glucagon like peptide-1 (GLP-1) agonist, showing beneficial effects on MASLD—partially independent of weight loss—particularly in reducing metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis.[16] In addition, dual agonists such as survodutide are gaining increasing interest due to their combined activity as GLP-1 and glucagon receptor agonists, offering enhanced benefits for liver health.[17] These emerging therapeutic options have the potential to significantly transform clinical practice and improve patient outcomes. However, their effects within the context of liver transplantation remain largely unexplored.

In this review, we aim to discuss the comorbidities associated with MASLD and their impact in the context of liver transplantation. Additionally, we will explore the role of GLP-1 receptor agonists in the management of MASLD, focusing on their potential in preventing chronic liver disease progression and their therapeutic implications within liver transplantation settings.

Liver Transplantation in MASLD

The first liver transplantation was performed in 1963 by Starzl in Denver (Colorado) and is now considered the curative treatment for end-stage liver disease and chronic liver disease complications like hepatic decompensation and HCC. Since then, advancements in areas such as surgical techniques and immunosuppression have led to an increase in liver transplantations since the 1980s.[18,19] Due to that, also long-term outcomes, such as 1-year-survival rates, have improved enormously after transplantation.[20] To date, approximately 34,000 liver transplantations are performed annually worldwide.[21] The number of liver transplants had stagnated due to the limited availability of donor organs. To address this, donation criteria were expanded to include higher-risk donors, such as older individuals or those with comorbidities. However, despite these efforts, the waiting list for liver transplantation remains long, and approximately 15% of patients die while awaiting a new liver. Therefore, indications for liver transplantation must be guided by the need to use the limited supply of donor organs as efficiently as possible.[22]

As previously noted, MASLD is now the leading indication for liver transplantation among patients with hepatocellular carcinoma on transplant waiting lists in both Europe and the United States, reflecting a rising trend across both regions.[9,23] This specific patient group requires particularly cautious management. Careful selection of liver transplant recipients is essential, as patients with MASLD are typically older and frequently present with metabolic risk factors such as obesity, type 2 diabetes, hypertension, and cardiovascular disease — all of which significantly increase perioperative risk. Therefore, the management of MASLD-related liver transplantation must also address a range of cardiometabolic comorbidities, requiring a multidisciplinary approach tailored to this complex patient population.[24]

Comorbidities Associated with MASLD and Their Implications for Liver Transplantation

MASLD is linked to cardiovascular-kidney-metabolic disease, i.e. to metabolic risk factors such as diabetes mellitus, chronic kidney disease, and cardiovascular disease.[25,26] These comorbidities warrant particular attention, especially in the context of risk stratification prior to liver transplan-

tation. Post-transplant, the risk of cardiovascular events and metabolic complications may be further exacerbated by the effects of immunosuppressive therapy.[27] In this section of the review, we will mention metabolic comorbidities in association with the context of MASLD-related liver transplantation.

Impact of Obesity and Type 2 Diabetes Mellitus

Type 2 diabetes mellitus and obesity are the most impactful metabolic comorbidities in MASLD, contributing significantly to its progression to MASH, cirrhosis, and HCC. Indeed, the prevalence of MASLD among patients with type 2 diabetes mellitus is approximately 70%, with MASH occurring in about 66% and advanced fibrosis in 15% of cases, underscoring T2DM as a significant comorbid factor contributing to the severity of MASLD.[28] Moreover, obesity presents a significant clinical challenge in liver transplantation, as more than one-third of liver transplant recipients have been reported to be obese.[36]

Following liver transplantation, the prevalence of type 2 diabetes mellitus (T2DM) ranges from 31% to 38%, while the incidence of new-onset diabetes mellitus within the first three years post-surgery ranges from 13% to 28%.[29] Pre-liver transplantation T2DM is commonly associated with liver diseases such as MASLD, with a reported prevalence ranging from 33% to 66%. Individuals with T2DM prior to liver transplantation are also at increased risk for post-transplant infections, cardiovascular complications, and poorer overall outcomes.[30–32] A study utilizing data from the American Transplant Registry applied a machine learning algorithm to assess the impact of pre- and post-transplant diabetes on outcomes following liver transplantation. The analysis revealed that increasing age (odds ratio [OR]: 1.01), male sex (OR: 1.09), and obesity (OR: 1.13) were significantly associated with the development of new-onset diabetes after transplantation. Notably, patients who developed post-transplant diabetes had significantly lower 10-year survival rates compared to those without diabetes (63.0% vs. 74.9%; $p<0.001$), with survival rates similar to those of patients who had diabetes prior to transplantation (58.9%).[32]

Profound peripheral insulin resistance is a hallmark of liver cirrhosis, occurring in both diabetic and non-diabetic patients, and often emerges in the early stages of liver disease. This might be due to the role of the liver in insulin resistance, which is called hepatogenous diabetes. Interestingly, liver transplantation can potentially resolve type 2 diabetes mellitus by restoring function within the hepato-pancreatic axis.[33] In a large study involving patients with pre-existing type 2 diabetes mellitus who underwent liver transplantation, insulin requirements were found to decrease by 50% within six months post-transplant, highlighting the significant role of the liver in glucose metabolism.[34]

The prevalence of MASLD has increased alongside the rising rates of obesity over the past decade.[35,36] Although BMI is the accepted standard for defining obesity, it has notable limitations, particularly in assessing fat distribution and identifying visceral obesity. Indeed, lean and obese MASLD patients differ in their metabolic profiles and in the prevalence of hypertension, dyslipidemia, insulin resistance, and elevated inflammatory markers. The main consensus indicates that lean MASLD patients have generally a more favorable metabolic profile compared to obese patients.[37,38] On the other hand, evidence suggests that lean MASLD patients may experience worse overall outcomes compared to those with obesity, indicating that alternative pathophysiological mechanisms may be involved. In a recent large-scale study involving 15,155 patients with compensated cirrhosis, obese and non-obese individuals were compared to assess clinical outcomes. The prevalence of type 2 diabetes mellitus (T2DM) was significantly lower among lean patients (47%) compared to their obese counterparts (74%). Interestingly, in multivariable models, lean status was associated with a 64% increased risk of all-cause mortality, despite a lower risk of hepatic decompensation. Moreover, lean individuals exhibited significantly higher rates of cardiovascular-related mortality.[39]

Indeed, pre-transplant obesity is generally considered a risk factor, and many patients are encouraged to lose weight prior to liver transplantation. As a result, obese individuals often remain on the transplant waiting list for longer periods and exhibit a higher model for end stage liver disease (MELD) scores.[40] It has been previously reported that higher BMI and T2DM was associated with adverse post-transplant outcomes.[41] However, paradoxically, some studies have shown that overweight or obese patients may experience lower mortality after transplantation compared to those with normal weight, suggesting the presence of an 'obesity paradox' in this context.[42] Nevertheless, in this single-center study, increased BMI was associated with a significantly higher risk of long-term graft loss. Notably, obese patients did not exhibit longer intensive care unit stays, extended operative times, or increased perioperative complications. However, these findings should be interpreted with caution, as it is likely that obese candidates with the most favorable metabolic profiles were selected for transplantation, potentially contributing to the more favorable short-term outcomes observed.[40] On the other hand, findings on this subject remain conflicting. In another study, obesity was significantly associated with prolonged intensive care unit stays, increased biliary compli-

cations, and a higher incidence of perioperative infections. Moreover, liver transplantation in obese patients is technically more challenging, which may lead some surgeons to be reluctant to operate on this population.[43] Therefore, given the challenges associated with obesity both before and after liver transplantation, it is essential that obesity be appropriately managed within this clinical context.

Cardiovascular Diseases in Liver Transplantation Setting

Cardiovascular disease is the leading cause of mortality in patients with MASLD, followed by extrahepatic malignancies and liver-related complications, highlighting the multisystemic nature of the condition. Therefore, effective management of cardiovascular comorbidities is critically important in this patient population. In fact, cardiology consultation should be considered essential, particularly for patients at high risk of advanced fibrosis.[44] MASLD is also considered an independent risk factor for cardiovascular disease, including myocardial infarction, coronary artery disease, atrial fibrillation, and stroke. In a meta-analysis involving 34,000 individuals with a follow-up period of seven years, advanced MASLD—characterized by increased liver fibrosis—was associated with a 2.5-fold increase in mortality. These findings underscore that not only the presence of MASLD, but also its severity, significantly contributes to cardiovascular morbidity and mortality.[45] In both pre- and post-transplantation settings, cardiovascular events continue to play a critical role in patients with MASLD, representing a major contributor to increased mortality risk.[46,47] Cardiovascular assessment is a critical component of the pre-transplant evaluation for liver transplantation, as cardiovascular disease remains a leading cause of morbidity and mortality in this population. Coronary angiography is considered the gold standard for diagnosing coronary artery disease in transplant candidates. A study demonstrated that guideline-based management of coronary heart disease prior to transplantation does not adversely impact post-transplant survival, suggesting that appropriately treated cardiovascular comorbidities do not compromise transplant outcomes and may, in fact, help optimize candidate selection.[48] In this study, the prevalence of dyslipidemia following liver transplantation at 1, 3, and 5 years was reported as 32.5% (n=146), 46.8% (n=142), and 55.3% (n=115), respectively. Notably, 70% of cases represented new-onset dyslipidemia, for which statin therapy was initiated. The authors also demonstrated that statin use had a beneficial effect on overall survival, highlighting the importance of managing lipid abnormalities in the post-transplant population.[48]

Chronic Kidney Disease in Liver Transplantation Settings

MASLD is known to be associated with an increased risk of chronic kidney disease (CKD), and this risk appears to correlate with disease severity, with more advanced MASLD linked to a higher prevalence of CKD.[49] Even early indicators of CKD, such as microalbuminuria, have been associated with more severe liver histology, suggesting that patients at high risk for MASH should be routinely screened for CKD.[50,51] CKD is also one of the most common post-transplant complications, with reported prevalence rates reaching up to 40% in the post-transplant setting.[52] Moreover, patients with MASLD who undergo combined liver-kidney transplantation have been shown to carry a higher risk of post-transplant renal dysfunction compared to those with other underlying liver diseases, which indicates that MASLD itself can also create a subclinical organ damage on kidney.[24]

The Utility of GLP-1 Agonists in the Liver Transplant Settings

GLP-1 receptor agonists are currently used in clinical practice for the management of type 2 diabetes mellitus (T2DM) and obesity, primarily due to their beneficial effects on glycemic control and weight reduction. The effects of GLP-1 receptor agonists are summarized in Table 1. In the coming years, they are also expected to gain approval for liver-related indications, largely because of their indirect hepatic benefits. Their weight loss effects are primarily mediated through appetite suppression and delayed gastric emptying. Additionally, GLP-1 receptor agonists improve hepatic insulin sensitivity and enhance fatty acid oxidation in the liver, thereby contributing to improved hepatic fat metabolism.[53] Among the GLP-1 receptor agonists, semaglutide has shown particularly promising effects on liver health. The recently completed ESSENCE trial met its primary endpoints, demonstrating significant rates of MASH resolution without worsening of fibrosis, as well as improvement in fibrosis without worsening of MASH.[16] Moreover, the SWITCH-SEMA 1 trial investigated the effects of transitioning patients with T2DM from liraglutide or dulaglutide to semaglutide. The transition demonstrated additional benefits, particularly in improving the Fatty Liver Index, highlighting semaglutide's superior impact on liver health compared to other GLP-1 receptor agonists.[54]

In the transplant setting, the availability of medications for glycemic control in patients with liver cirrhosis is an important consideration. GLP-1 receptor agonists are becoming increasingly attractive in this context due to their additional cardioprotective and renoprotective effects. Consequently, GLP-1 agonists are often favorably selected for

Table 1. Effects of Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists on General Metabolic Health

Organ system	Effect of GLP1-analogs
Digestive system (gastrointestinal tract)	Delayed gastric emptying
	Appetite inhibition
	Increased insulin secretion
	Promotion of insulin-dependent glucose uptak
Pancreas	Promotion of insulin secretion if blood glucose is elevated
	Improved blood glucose control
Liver	Inhibition of glucagon release, especially in the fasting phase
	Improvement of steatosis, inflammation, possibly fibrosis in MASLD
Adipose tissue	Promotion of weight reduction and fat reduction
Kidney	Kidney protection
	Reduction of the risk of diabetic nephropathy
Muscle tissue	Increase in muscle mass and muscle function
	Promotion of fat reduction
	Improving blood glucose and insulin sensitivity
Cardiovascular system	Blood pressure reduction
	Promotion of cardiovascular protective mechanisms
	Reduction in the risk of cardiovascular events in patients with type 2 diabetes mellitus
Central nervous system	Appetite suppression by influencing hypothalamic activity
	Potential neuroprotective effects

patients with type 2 diabetes mellitus, particularly when coexisting cardiovascular or renal comorbidities are present.[55] The strategy for managing MASLD in the context of liver transplantation, including the use of GLP-1 agonists and other medications, is illustrated in Figure 1.

On the other hand, the effects of semaglutide for liver cirrhosis remain controversial. In phase 2 trials involving MASH-related cirrhosis, after 48 weeks of treatment, there was no significant improvement in MASH or fibrosis. Fortunately, no cases of hepatic decompensation or death were reported, although some gastrointestinal

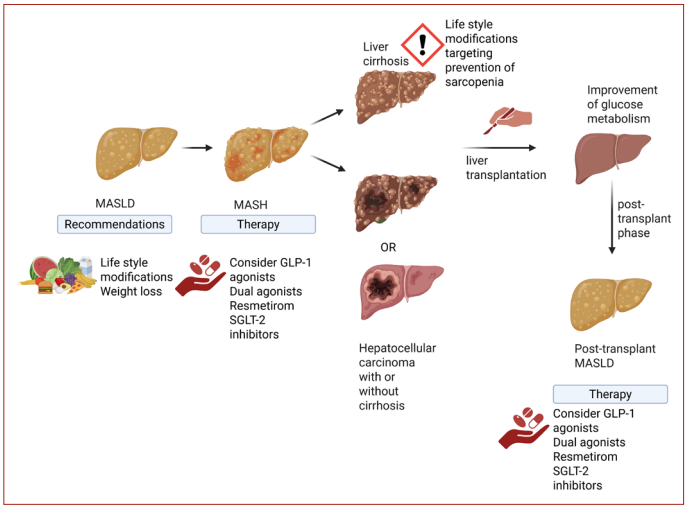

Figure 1. The strategy for managing MASLD in the context of liver transplantation (Created with Biorender.com).

side effects were observed.[56] It is important to note that efruxifermin, a fibroblast growth factor 21 (FGF21) agonist, was recently investigated in a 96-week phase 2b trial (SYMMETRY) involving patients with compensated MASH-related cirrhosis. While no significant effect on liver fibrosis was observed at 36 weeks, by 96 weeks the treatment demonstrated a significant improvement, including evidence of regression from cirrhosis to fibrosis. These findings suggest that, in MASH cirrhosis, trial durations should be extended to capture the potentially delayed therapeutic effects of the drugs.[57] Recently, dual agonists have also gained attention, such as survodutide, which targets both GLP-1 and glucagon receptors. These receptors are directly expressed in the liver, and activation has shown beneficial hepatic effects by increasing hepatic energy expenditure.[17] The effects of survodutide are currently being investigated in the LIVERAGE Cirrhosis Trial (NCT06632457).

On the other hand, data on the use of GLP-1 receptor agonists in the liver transplantation setting remain limited. A recent systematic review analyzed 12 studies examining the efficacy and safety of GLP-1 receptor agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors in liver transplant recipients. Overall, these agents were associated with reductions in hemoglobin A1c levels, improved glucose metabolism, weight loss, and decreased insulin requirements. Moreover, their potential to reduce graft steatosis, enhance renal function, and lower the incidence

of major cardiovascular events highlights their emerging relevance in this patient population.[58]

In a retrospective analysis, liver transplant recipients receiving GLP-1 receptor agonists were compared with those undergoing insulin therapy. Patients treated with GLP-1 receptor agonists experienced an average weight loss of approximately 8%, whereas those on insulin therapy gained around 10% of their body weight. Additionally, GLP-1 agonists demonstrated beneficial effects in reducing graft steatosis. Importantly, neither therapy had a significant impact on the incidence of transplant rejection.[59] In another study conducted among various transplant recipients, GLP-1 receptor agonists were found not to significantly affect tacrolimus levels, further supporting their safety in the liver transplantation setting.[60] Moreover, GLP-1 receptor agonists have been associated with a significant reduction in major adverse cardiovascular events. In various transplant settings, including heart and kidney transplantation, the use of GLP-1 receptor agonists has been linked to a more than 50% reduction in the risk of cardiovascular events.[61] In another study, the use of GLP-1 receptor agonists during the first 12 months post-transplant was associated with a 70% reduction in insulin requirements.[62] Overall, the accumulating evidence supports the beneficial effects of GLP-1 receptor agonists in the liver transplant setting not only in terms of liver health but also a general metabolic health. However, prospective studies are still needed to confirm their safety and efficacy in this specific population.

Conclusion

MASLD represents a significant and growing health burden and is becoming the leading cause of liver transplantation. As a result, the management of MASH cirrhosis, MASH-related liver transplantation, and the post-transplant care of these patients will increasingly become a central focus in liver transplant settings. In this context, GLP-1 receptor agonists appear to be a promising therapeutic option—not only for improving overall metabolic health but also for their potential benefits in reducing graft steatosis. The accumulating evidence supporting the use of GLP-1 receptor agonists in patients with MASH and MASH-related cirrhosis offers promise for more effective disease management in the future. However, further research is needed to clarify the effects and safety of this class of medications in liver transplant recipients.

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Review

Liver Resection and Transplantation for Hepatoblastoma

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Abstract

Hepatoblastoma (HB) is the most common primary malignant liver tumor in children, predominantly affecting those under five years of age. Advances in neonatal care and chemotherapy have improved survival; however, approximately 20% of cases remain unresectable, necessitating liver transplantation (LT). This review outlines current indications, surgical strategies, and outcomes of LT for HB. Transplantation is indicated when complete resection (R0) is unachievable due to multifocal disease, PRETEXT IV involvement, major vascular invasion, or inadequate future liver remnant. Living donor liver transplantation (LDLT), particularly in Japan and other Asian countries, has become a cornerstone of curative therapy, offering timely intervention without waitlist delay. Technical refinements—such as early inflow control, portocaval shunting, and fluorescence-guided surgery—have enhanced operative safety and reduced recurrence risk. Multicenter studies, including the Japanese Liver Transplantation Society and JPLT3 trial, demonstrate 5-year overall survival rates exceeding 80–90% in appropriately selected patients, comparable to resection outcomes in intermediate-risk disease. Prognostic factors influencing recurrence include vascular invasion, high AFP levels, and poor chemotherapy response. Long-term survivors typically achieve normal growth, school attendance, and psychosocial development. The Japanese experience underscores the importance of early multidisciplinary evaluation, central surgical review, and integration of LT into frontline hepatoblastoma management. With continuous advances in surgical technique, molecular profiling, and immunomodulation, liver transplantation represents a definitive and life-saving treatment for children with advanced, unresectable hepatoblastoma.

Keywords: Hepatoblastoma, hepatectomy, liver transplantation, ICG, AFP

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Hepatoblastoma (HB), the most common primary malignant liver tumor in children, represents approximately 1% of all pediatric cancers but accounts for the majority of pediatric liver malignancies, especially in children under five years of age. In recent years, an upward trend in incidence has been observed worldwide, with a current estimated rate of 0.5 to 1.5 cases per million population.[1] This increase has been attributed in part to advances in neonatal care, which have resulted in the increased survival of preterm and very-low-birth-weight infants—a population at significantly elevated risk for developing HB.[2]

HB typically presents in infancy or early childhood, with a median age of diagnosis between 12 and 18 months and shows a male predominance. While the exact etiology remains uncertain in most cases, a number of risk factors have been identified. These include genetic syndromes such as Beckwith-Wiedemann syndrome, familial adenomatous polyposis, trisomy 18, and Li-Fraumeni syndrome, as well as environmental and perinatal factors such as prematurity

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and low birth weight. The increased risk among these populations is thought to result from a combination of epigenetic dysregulation, impaired hepatic differentiation, and DNA repair deficiencies.[3]

Molecularly, HB arises from fetal hepatoblasts and is characterized by frequent activation of the Wnt/β-catenin signaling pathway, particularly through mutations in the CTNNB1 gene. Additional genetic alterations, including TERT promoter mutations and IGF2 overexpression, are found in subsets of tumors and may influence tumor biology and treatment response.[4,5]

The clinical presentation is often nonspecific, with a painless right upper quadrant abdominal mass being the most common initial sign. Other symptoms may include anorexia, vomiting, abdominal distension, and occasionally precocious puberty in males due to ectopic β-hCG production. Laboratory investigation typically reveals markedly elevated serum alpha-fetoprotein (AFP) levels, which are present in over 90% of cases and serve as a useful biomarker for both diagnosis and monitoring of treatment response.[1]

Diagnosis is confirmed through imaging and histological evaluation. Contrast-enhanced CT and MRI are essential for delineating tumor extent, vascular invasion, and the presence of metastatic disease, most commonly to the lungs. Histological subtypes range from well-differentiated fetal types to more aggressive embryonal or small cell undifferentiated variants. The latter subtypes are associated with poorer prognosis and reduced chemosensitivity.

To standardize treatment planning, the International Childhood Liver Tumor Strategy Group (SIOPEL) developed the PRETEXT (Pretreatment Extent of Disease) staging system. This radiologic system divides the liver into four sectors and classifies tumors based on the number of sectors involved and additional annotation factors such as vascular invasion, extrahepatic spread, multifocality, and metastases. The PRETEXT and POSTTEXT (post-chemotherapy) assessments help predict resectability and guide decisions regarding surgical versus transplant approaches.[6] According to PRETEXT staging system, a tumor occupying 1, 2, 3 or 4 adjacent liver sector is defined as PRETEXT I, II, III or IV, respectively. Historically, survival for HB was poor, particularly in unresectable cases. The introduction of cisplatin-based chemotherapy regimens dramatically improved outcomes by increasing the rate of complete surgical resection. In modern protocols, neoadjuvant chemotherapy enables resection in more than 60% of cases. However, approximately 20% of tumors remain anatomically unresectable after chemotherapy, necessitating consideration for liver transplantation.[7]

Indication of Liver Transplantation

Higher survival rates have been achieved through combined improvements in imaging, surgical resection and systemic chemotherapy. Although cisplatin chemotherapy regimens have dramatically improved disease-free survival rates, liver transplantation remains an alternative curative treatment for patients whose liver tumor is unresectable following systemic chemotherapy or radical hepatectomy.[8,9] Initial studies of liver transplantation in children with unresectable hepatoblastoma report a 50% survival rate.[10]

The indication for liver transplantation centers on the inability to achieve complete resection (R0 resection) due to tumor burden, vascular invasion, multifocality, or insufficient future liver remnant. Patients with PRETEXT IV tumors, which involve all four liver sectors, or with tumor thrombus extending into the main portal vein or the confluence of all three hepatic veins, are typically considered for transplantation. In such cases, extended hepatectomy may carry unacceptable risk or lead to incomplete tumor removal (Fig. 1 A, B).[11]

Biologic factors, including high AFP levels at diagnosis (>500,000 ng/mL) and at the time of surgery (>4,000 ng/mL), and poor chemotherapy response, also predict recurrence and are considered relative indications for liver transplantation. Patients whose tumors exhibit minimal radiologic or serologic response to neoadjuvant therapy may benefit from early transplant evaluation to avoid tumor progression beyond transplantable limits.[12, 13]

Previously, the presence of extrahepatic disease, especially pulmonary metastases, was considered a contraindication to liver transplantation. However, more recent data have shown that long-term survival is achievable in patients with lung metastases who undergo complete remission after chemotherapy or metastasectomy prior to transplantation. Studies from the Japanese Liver Transplantation Society and the JPLT3 trial indicate that survival in such patients is comparable to those without metastatic disease, provided that all extrahepatic foci are resolved at the time of liver transplantation.[14, 15]

Salvage transplantation may be considered for patients with isolated intrahepatic recurrence after prior hepatectomy. While survival is slightly lower than in primary transplantation, outcomes are acceptable if disease is limited to the liver and responsive to chemotherapy.[16]

The integration of real-time central surgical review, as implemented in the JPLT3 study, has significantly improved appropriate and timely referral to transplant centers. This centralized approach allows for expert assessment of resectability and facilitates coordinated

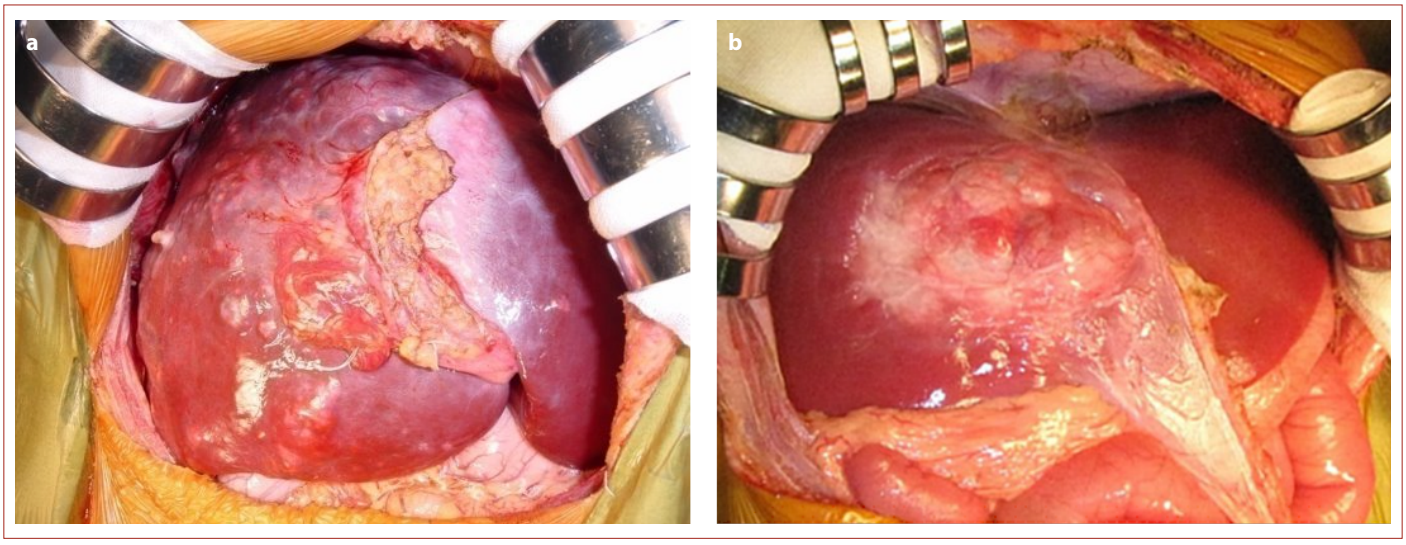

Figure 1. Lacroscopic findings of liver transplantation for hepatoblastoma. **(a)** Multifocal. **(b)** Centrally located.

planning between oncologists, hepatobiliary surgeons, and transplant teams.[15]

Timing of transplantation is crucial. Delays beyond the chemotherapy window may allow tumor progression, while early transplantation in the setting of chemotherapy-induced myelosuppression increases the risk of infectious complications. Most centers perform liver transplantation 4–6 weeks after the final chemotherapy cycle. Living donor liver transplantation (LDLT), in particular, allows optimal timing by eliminating waitlist uncertainty, which is particularly beneficial in regions with low deceased donor organ availability, such as Japan.[12, 17]

LDLT has become the dominant modality for pediatric liver transplantation in Asia and has demonstrated excellent long-term outcomes. In a multicenter Japanese study of 100 children with hepatoblastoma who underwent LDLT, the five-year overall survival exceeded 80%, and recurrence rates were low in patients without vascular invasion or extrahepatic disease. Moreover, the use of preoperative inflow exclusion techniques and portocaval shunting has been shown to minimize blood loss, improve surgical safety, and potentially reduce recurrence risk by preventing intraoperative tumor dissemination (Fig. 2).[18]

Liver transplantation has emerged as a standard and life-saving therapy for children with unresectable hepatoblastoma. Careful assessment of tumor resectability, vascular involvement, biological behavior, and treatment response is essential in determining candidacy. Early referral, multidisciplinary evaluation, and consideration of individualized surgical risk all contribute to successful outcomes. As the global experience with pediatric liver transplantation continues to expand, so too does the imperative to refine patient selection and integrate transplant strategies into frontline hepatoblastoma care.

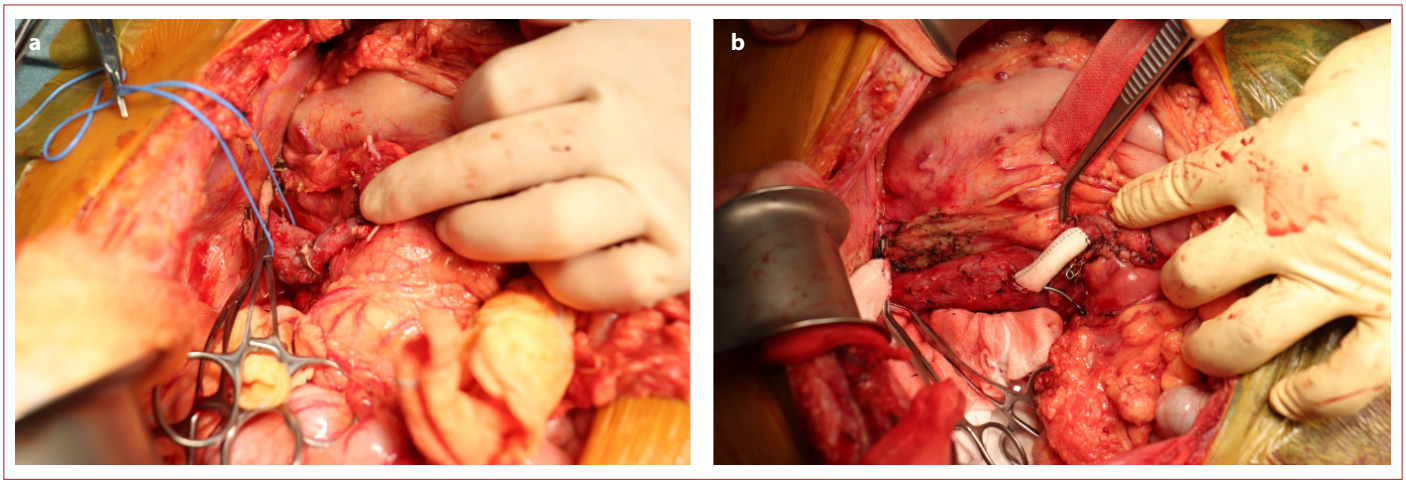

Figure 2. Portosystemic shunt. **(a)** With native portal vein. **(b)** With EPTFE graft.

Surgical Procedure

Surgical intervention remains the cornerstone of curative treatment for hepatoblastoma. Whether through partial hepatectomy or liver transplantation (LT), complete tumor removal with negative histologic margins (R0 resection) is essential to long-term survival. While cisplatin-based chemotherapy has dramatically improved tumor shrinkage and operability, about 20% of cases remain unresectable by conventional means, requiring transplant-based strategies. The surgical approach to hepatoblastoma is therefore highly nuanced, demanding meticulous planning, technical precision, and intraoperative adaptability. This section details the operative considerations, techniques, and challenges encountered in both hepatectomy and liver transplantation for hepatoblastoma.

General Principles and Preoperative Planning

Preoperative preparation begins with careful imaging review to define tumor boundaries, vascular involvement, and segmental liver anatomy. Modern protocols rely heavily on high-resolution contrast-enhanced CT or MRI to assess the post-chemotherapy tumor status (POSTTEXT classification). Multidisciplinary surgical conferences with transplant surgeons, hepatobiliary surgeons, pediatric oncologists, and radiologists are essential to determine whether a resection is feasible or a transplant is required (Fig. 3).

In patients considered for liver resection, the size, location, and degree of vascular involvement are evaluated alongside the anticipated future liver remnant by CT volumetry (FLR).[19] The widely accepted minimum remnant liver volume in living liver donors is generally around 30~35% of the donor's total liver volume to ensure donor safety and avoid postoperative liver failure.[20] This threshold is considered safe to maintain adequate liver function and regeneration capacity after donation. Pediatric patients typically tolerate resection better than adults due to a larger hepatic reserve relative to body mass. Nonetheless, extensive resections involving three or more segments may require portal vein embolization, or the associating liver partition and portal vein ligation for staged hepatectomy or FLR volumetry to ensure postoperative hepatic sufficiency.[21] In pediatric patients, an FLR as low as 18–20% is generally safe, and the standard adult thresholds are too conservative for children. The most critical factor in pediatric liver resection is not merely the FLR volume, but the precise balance between hepatic inflow and outflow. If the tumor cannot be removed with adequate margins without sacrificing critical vascular inflow or outflow, liver transplantation is considered. One of the most significant innovations is central surgical review and real-time consultation, as implemented in the JPLT3 protocol, which has improved resectability assessment and surgical outcomes. These systems enable early identification of transplant candidates, standardize surgical criteria, and reduce interinstitutional variation.[15]

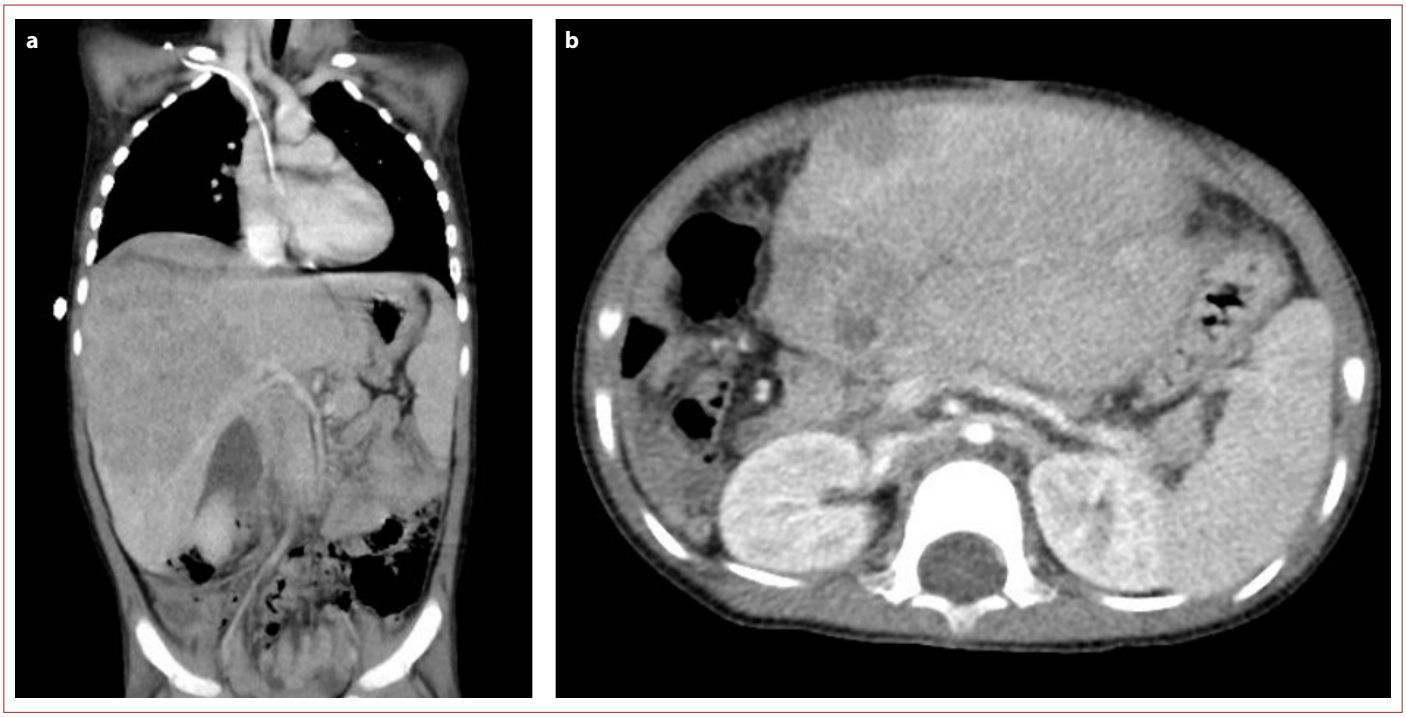

Figure 3. Preoperative imaging study. **(a)** 1y8m baby, multifocal with main PV invasion. **(b)** 2y10m baby, post right hepatectomy, multiple recurrence in the remnant left lobe.

The importance of timing cannot be overstated. For patients who will undergo liver transplantation, surgery is optimally scheduled 4 to 6 weeks after completion of neoadjuvant chemotherapy.[17] This interval allows recovery from myelosuppression while minimizing the risk of tumor progression. In LDLT, coordination between recipient and donor teams is critical to align operative schedules. In DDLT, timely listing and allocation are often complicated by organ availability and competition with other indications, particularly in regions with low donation rates.[22]

Liver Resection for Hepatoblastoma

For tumors classified as POSTTEXT II or III, resection may be possible. Depending on tumor location and liver anatomy, surgical options include left lateral segmentectomy (segments II and III), left hepatectomy (segments II–IV), right hepatectomy (segments V–VIII), or extended resections. The decision to pursue resection rather than transplantation must be guided by the ability to achieve complete tumor clearance without risking hepatic insufficiency.[23]

Intraoperatively, a subcostal or extended Chevron or reverse T incision is typically used. The liver is mobilized by dividing the triangular and coronary ligaments. Cholecystectomy is routinely performed, and the hepatic hilum is dissected to expose and control the hepatic artery, portal vein, and bile duct as a Glissonian approach.[24] Intraoperative ultrasound is critical for evaluating tumor margins, satellite nodules, and vascular anatomy, particularly after chemotherapy-induced changes. Fluorescence-guided surgery for hepatoblastoma with indocyanine green will be effective to define the tumor boundaries, and it allows for the more sensitive identification of lesions that may go undetected by conventional imaging or be invisible macroscopically (Fig. 4).[24]

Parenchymal transection is performed using a combination of techniques, including ultrasonic dissection (CUSA), bipolar sealing, and stapling devices. Bleeding control is paramount. In selected cases, low central venous pressure anesthesia and intermittent inflow occlusion (Pringle maneuver) are used to reduce blood loss. If the tumor abuts major hepatic veins or the inferior vena cava (IVC), vascular resection and reconstruction may be necessary (Fig. 5). In some institutions, advanced techniques such as extracorporeal circulation or ex vivo liver resection with autotransplantation have been attempted, although these are technically demanding and carry higher morbidity.[25, 26]

While resection offers a shorter operative time and obviates the need for lifelong immunosuppression, incomplete resection or positive margins are associated with high recurrence rates. Therefore, borderline resectable cases are increasingly managed with transplant-first strategies, particularly in centers with transplant expertise.

Liver Transplantation for Hepatoblastoma

In patients with unresectable hepatoblastoma, liver transplantation is the definitive treatment. Indications for transplantation include tumors involving all four sectors of the liver (PRETEXT IV), invasion of all three hepatic veins or main portal vein, multifocal lesions, or inadequate FLR. Living donor and deceased donor transplants are both employed depending on regional practices and organ availability.

Pre-transplant evaluation includes thorough assessment of extrahepatic disease. Pulmonary metastases must be treated and cleared before proceeding with LT. Repeat imaging and, if necessary, metastasectomy are performed prior to LT. AFP normalization or significant decline is

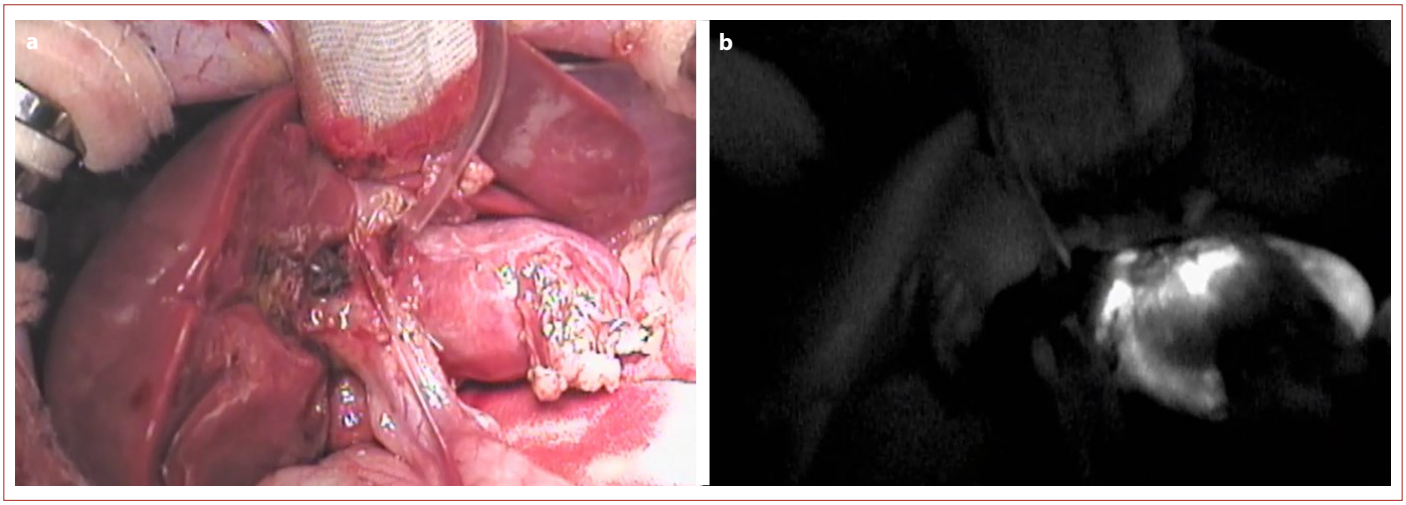

Figure 4. Fluorescence-Guided Surgery for Hepatoblastoma with Indocyanine Green. **(a)** Hepatoblastoma originated the Caudate lobe. **(b)** Fluorescence-guided surgery allows for the more sensitive identification of lesions that may go undetected by conventional imaging or be invisible macroscopically.

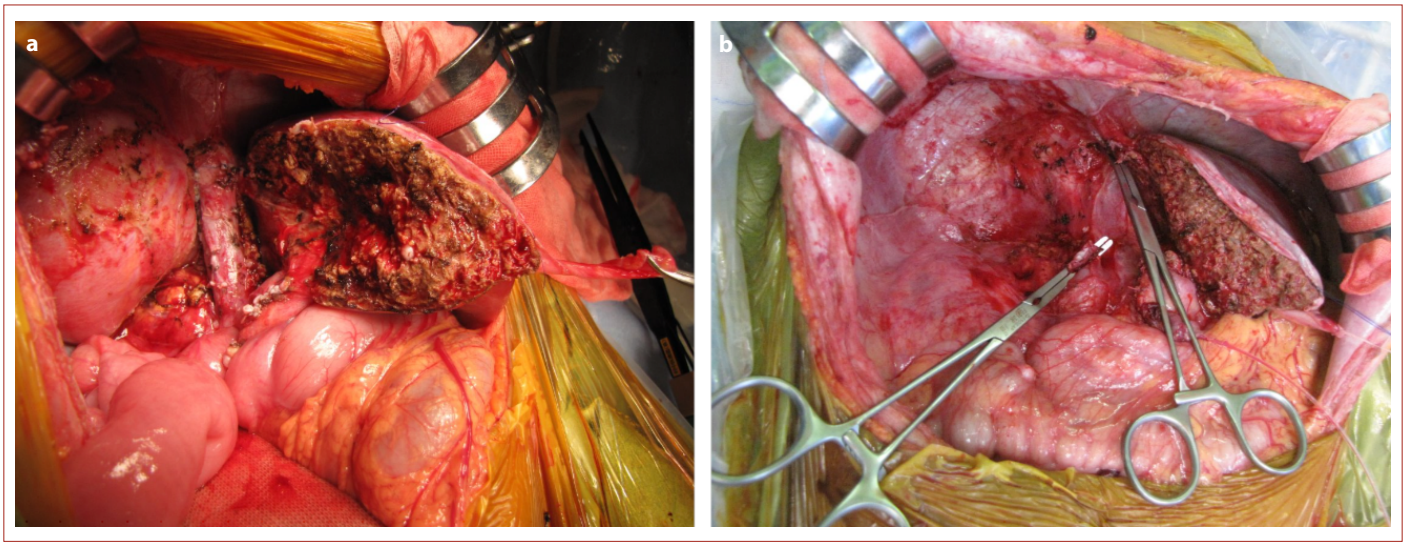

Figure 5. Extended hepatic resection in Hepatoblastoma. **(a)** 3y9m Boy, right trisectionectomy. **(b)** 10y7m boy, right trisectionectomy + IVC resection.

a favorable prognostic sign. In patients with previous hepatectomy or abdominal surgery, adhesions and altered anatomy may complicate transplant surgery.

LDLT is particularly advantageous in HB due to the ability to schedule transplantation electively and avoid waiting-list mortality. In most pediatric LDLT cases, the donor is a parent who donates the left lateral segment (segments II and III), which provides sufficient volume for infants and small children. For older children or larger recipients, a left lobe or extended left lobe graft may be required.[17]

The donor operation is performed under general anesthesia, and careful anatomical dissection of hepatic vasculature and bile ducts is performed to ensure minimal morbidity. After graft removal, the graft is flushed and preserved in HTK solution before transplantation.

The recipient operation begins with total hepatectomy. One of the significant challenges is managing large tumor burden with potential vascular invasion. To reduce the risk of intraoperative tumor dissemination, our team pioneered the strategy of early inflow control, which involves ligation of the hepatic artery and portal vein before liver mobilization.[13] This is often followed by the creation of a temporary portocaval shunt to decompress the portal system and maintain hemodynamic stability during the anhepatic phase. The native liver is then removed en bloc.

Vascular reconstruction includes anastomosis of the portal vein, hepatic artery, and hepatic veins (often via a venoplasty to the IVC). Biliary reconstruction is typically performed using a Roux-en-Y hepaticojejunostomy in small children. In LDLT, the smaller graft size facilitates easier placement in the abdominal cavity but may increase the risk of small-for-size syndrome. Graft-to-recipient weight ratio (GRWR) >1.0% is generally targeted.[27]

DDLT is more common in North America and Europe. It eliminates donor risk and may provide full-size or reduced-size grafts, depending on recipient needs. However, access is limited by donor availability, and patients with HB are often lower priority compared to those with end-stage liver disease due to MELD/PELD-based allocation.

DDLT for HB follows the same technical principles as LDLT. The use of reduced-size or split liver grafts is increasing, particularly in pediatric recipients. Cold ischemia times must be minimized to prevent primary graft dysfunction. In some series, DDLT has shown similar survival to LDLT when performed in experienced centers.[28]

Postoperative care includes intensive monitoring, immunosuppression initiation (often with tacrolimus monotherapy or combined with low-dose steroids), and early resumption of adjuvant chemotherapy when indicated. It has been reported that hepatoblastoma recipients trended to have fewer rejections than other recipients which may allow less immunosuppression due to the preoperative chemotherapy.[29,30]

Postoperative Management and Complications

Following surgery, patients are monitored in the pediatric intensive care unit for hemodynamic stability, graft function, and early detection of complications. Common issues include biliary leakage, vascular thrombosis (especially of the hepatic artery), and infection. In transplant recipients, immunosuppression is carefully balanced against infection and tumor recurrence risk.

Adjuvant chemotherapy (cisplatin or CPT-11) is resumed postoperatively in high-risk patients, typically within 3 to 5 weeks of transplantation, once hepatic and hematologic parameters permit.[14] The timing and regimen are based

on pretransplant protocols and pathology findings. In a large Japanese cohort, early postoperative chemotherapy was associated with improved recurrence-free survival. Rejection, both acute and chronic, is managed with immunosuppression adjustments. In the context of pediatric transplantation for malignancy, tacrolimus-based regimens with or without steroids are standard. ABO-incompatible transplants are increasingly successful due to chemotherapy-induced immunologic modulation.

Outcomes

The outcomes of liver transplantation for hepatoblastoma have improved dramatically over the past two decades, establishing LT as a curative treatment modality for patients with unresectable disease. Long-term survival now exceeds 80% in properly selected pediatric patients, a figure that rivals, and in many cases surpasses, outcomes following conventional resection for high-risk tumors. This success is a result of advances in surgical technique, improved perioperative management, timely referral, and integration of chemotherapy and surgical strategies in a multidisciplinary context.[12]

Numerous retrospective and prospective studies have demonstrated high overall survival (OS) and event-free survival (EFS) following liver transplantation for hepatoblastoma. In the Japanese national survey of 100 children who underwent LDLT for hepatoblastoma, the 5-year OS was reported as 87.5%, with a recurrence-free survival (RFS) of 84.2%.[14] These outcomes were comparable to, or even better than, those achieved with primary liver resection in intermediate-risk patients. A separate report from the National Center for Child Health and Development (NCCHD) demonstrated a 10-year overall survival of 85.7% and recurrence-free survival of 81.0% among 35 consecutive patients who underwent LDLT for advanced HB.[17]

International data from centers in Europe and North America similarly support these excellent outcomes. In a multi-institutional analysis of patients treated within the SIOPEL and COG (Children's Oncology Group) frameworks, transplant candidates had 5-year survival rates approaching 80–90% when disease was confined to the liver and metastases, if present, had resolved prior to LT. These results reinforce the utility of transplant in the treatment paradigm of high-risk and PRETEXT IV hepatoblastoma.[31,32]

While recurrence after LT for hepatoblastoma is relatively uncommon, when it occurs, it is typically within the first two years post-transplant and often portends a poor prognosis. In the Japanese LDLT cohort, recurrence was noted in 13.5% of patients. Sites of recurrence included the lungs, brain, adrenal gland, and peritoneum. Lung metastasis remains the most common form of relapse, consistent with the natural history of HB.[17]

Prognostic factors associated with recurrence include high pretransplant AFP levels, poor chemotherapy response, presence of vascular invasion, and positive surgical margins in explant pathology. In particular, persistent elevation of AFP at the time of transplant, or failure to achieve radiologic remission of pulmonary metastases, has been shown to significantly increase the likelihood of relapse.

Tumor recurrence after LT poses a difficult therapeutic dilemma. While re-resection or metastasectomy may be feasible in isolated pulmonary relapse, systemic chemotherapy is often the only option for disseminated disease. The role of immunosuppression reduction or conversion to mTOR inhibitors in the context of recurrence remains under investigation.

Factors Influencing Survival

Survival outcomes are strongly influenced by tumor biology, disease extent at diagnosis, and response to chemotherapy. In multivariate analyses, several factors have emerged as independent predictors of poor outcome:[14, 33,34]

- Vascular Invasion: Tumor thrombus in the portal vein or hepatic veins significantly increases recurrence risk. Even when removed en bloc during transplantation, vascular invasion may reflect aggressive biology.
- High AFP Levels: AFP levels >500,000 ng/mL at diagnosis and >4,000 ng/mL at transplant have both been associated with worse survival.
- Extrahepatic Disease: Although controlled pulmonary metastases do not preclude good outcomes, persistent or recurrent metastases before or after transplant are linked to poor survival.
- Histological Subtypes: Small cell undifferentiated HB and tumors with mesenchymal elements tend to behave more aggressively and respond poorly to chemotherapy.
- Explanted Liver Pathology: Microscopic residual tumor at margins, lymphovascular invasion, and multifocality are associated with recurrence.

Impact of Graft Type and Center Experience on Liver Transplantation Outcomes

Both living donor and deceased donor liver transplantation have demonstrated excellent outcomes in experienced hands. In Japan and other parts of Asia, where LDLT predominates due to donor scarcity, survival has been outstanding owing to meticulous donor selection, surgical technique, and perioperative care. Notably, LDLT offers the

benefit of timely, scheduled surgery without the delays associated with deceased donor allocation.[14]

Center experience plays a critical role. High-volume pediatric transplant centers with integrated oncology and surgical teams have consistently reported superior outcomes. Central surgical review and adherence to standardized protocols, such as those implemented in the JPLT3 trial, have been associated with reduced recurrence and improved survival.[36]

Long-Term Complications and Quality of Life

Survivors of pediatric LT for HB generally report good quality of life. However, they remain at risk for long-term complications, including:

- Chronic Rejection: Rare, especially in the era of tacrolimus-based regimens.
- Biliary Complications: Bile leaks and strictures are more common in LDLT but can usually be managed with endoscopic or surgical revision.
- Infection: Immunosuppression predisposes recipients to opportunistic infections, though rates have declined with modern prophylaxis.
- Growth and Development: Most children exhibit normal growth and neurocognitive development post-transplant, although those with comorbid syndromes or prematurity may be at higher risk of delays.
- Renal Dysfunction and Hypertension: Nephrotoxicity from calcineurin inhibitors remains a concern and requires careful long-term monitoring.

Recent studies have reported that survivors have excellent school attendance, social integration, and psychological well-being, particularly when they have minimal postoperative complications and no disease recurrence.[35, 36]

Institutional Experiences and Recommendations

In Japan, the standardized evaluation of FLR using three-dimensional imaging and intraoperative strategies has been adopted in centers of excellence such as NCCHD. The JPLT3 protocol includes volumetric thresholds and central review mechanisms to guide surgical planning and ensure safe margin acquisition without compromising hepatic function. Uchida et al. have emphasized that early identification of inadequate FLR—and referral to transplantation—contributes significantly to the high survival seen in Japanese LDLT series.[13] These results support the growing consensus that FLR assessment in HB should not merely be based on volumetry but must integrate patient age, chemotherapy effects, functional studies, and institutional surgical expertise.

Choosing between radical hepatectomy and liver transplantation (LT) remains the pivotal surgical decision in the management of hepatoblastoma, one that determines not only short-term perioperative risk but also long-term survival, quality of life, and exposure to lifelong immunosuppression. Although complete resection with negative margins is universally recognised as the most powerful predictor of cure, the path to achieving this goal differs profoundly between partial hepatectomy and total hepatectomy with graft replacement. Over the past two decades, accumulated experience—particularly from large Japanese series in which living-donor liver transplantation (LDLT) is commonplace—has clarified the indications, advantages, and limitations of each strategy and has highlighted the importance of tailoring the operative plan to individual tumour biology, hepatic anatomy, chemotherapy response, and institutional capability.[14]

Historically, hepatectomy was considered first-line treatment for virtually all patients, largely because early transplantation programmes reported modest survival and substantial perioperative mortality. The advent of cisplatin-based neoadjuvant chemotherapy in the 1980s and 1990s transformed resectability; tumours once deemed inoperable shrank sufficiently to permit margin-negative excision, and five-year survival for children with PRETEXT II–III disease who underwent successful resection rose into the 70–80 % range.[6,10,37] Nevertheless, approximately one fifth of tumours remained unresectable after chemotherapy, and outcomes for these children were dismal until transplantation emerged as a viable alternative. Kasahara and colleagues were among the first to demonstrate that LDLT could be performed safely in this setting, reporting five-year survival of 65 % in their initial series and >90 % in patients without macroscopic vascular invasion or extrahepatic disease.[12] These results, corroborated by multicentre surveys, shifted the paradigm: the question was no longer whether transplantation could cure hepatoblastoma but rather which patients should receive it and when.

The decision framework that has since evolved is anchored on two overarching considerations: technical resectability and oncological soundness. Technical resectability encompasses the ability to remove all gross tumour while preserving an adequate FRL with intact inflow, outflow, and biliary drainage. Oncological soundness refers to the probability that complete resection will eradicate microscopic disease and deliver durable remission. A child with a solitary tumour confined to the left lateral sector, for example, meets both criteria and is offered an anatomic

left lateral segmentectomy. Conversely, a child whose tumour involves all four Couinaud sections (PRETEXT IV) fails the technical criterion—any resection would leave an insufficient FLR—and is therefore routed to transplantation. Between these extremes lie tumours with borderline characteristics—partial vascular encasement, multifocal satellitosis, poor chemotherapy response, or histologic subtypes associated with high relapse risk—which require nuanced appraisal.

Vascular involvement remains the dominant anatomical barrier to safe resection. Magnetic resonance angiography and contrast-enhanced CT permit high-resolution mapping of the hepatic veins, inferior vena cava (IVC), and portal structures. Invasion of all three hepatic veins or the retro-hepatic IVC, circumferential encasement of the main portal bifurcation, or tumour thrombus extending into central vessels dramatically increases operative complexity and the likelihood of residual disease. Uchida and co-workers showed that such involvement predicts recurrence after hepatectomy even when margins appear negative, whereas transplantation that removes the entire hepatic venous outflow tract can yield excellent disease-free survival.[13] Similarly, the Japanese nationwide survey identified macroscopic venous invasion and extrahepatic spread as the principal determinants of post-transplant relapse, underscoring the need for meticulous vascular assessment before choosing resection over LT.[14]

Chemotherapy response provides a complementary biological lens. Alpha-fetoprotein (AFP) kinetics and radiologic shrinkage after two to three cycles are powerful surrogates of chemosensitivity. Children whose AFP falls precipitously and whose tumours shrink to half or less of pretreatment volume frequently achieve long-term remission after partial hepatectomy. In contrast, tumours that remain bulky or in which AFP remains above 4,000 ng mL^{-1} despite adequate dosing behave aggressively; these children experience high relapse rates if treated with extended resection, prompting many centres to recommend primary transplantation. Such biologically driven decision-making avoids the morbidity of futile hepatectomy and the subsequent need for salvage LT, which, although feasible, is associated with increased operative difficulty, adhesions, and slightly lower survival.

FLR evaluation also shapes strategy. In adults a threshold of 25–30 % of standard liver volume is generally accepted, whereas paediatric livers regenerate faster, and an FLR as low as 20 % of total volume can sometimes suffice.[23] However, chemotherapy-induced sinusoidal injury, small body size, and potential hepatic steatosis in syndromic children argue for caution. When projected FLR falls near institutional cut-offs—often 30–40 % after intensive chemotherapy—transplantation offers a safer oncological and physiological solution, avoiding postoperative hepatic failure.

LDLT adds an additional dimension. Because a parental left-lateral-segment graft can be procured electively, LDLT abolishes the uncertainty of deceased-donor waiting times and permits synchronous planning with chemotherapy completion. Early inflow exclusion and temporary portocaval shunting, pioneered in NCCHD, have further reduced blood loss and preserved renal function during LDLT, translating into low perioperative mortality and facilitating prompt resumption of adjuvant chemotherapy. These technical refinements, together with proactive central surgical review in the JPLT3 trial, have driven Japanese five-year survival beyond 85 %, a benchmark now influencing Western practice.[14]

Notwithstanding these advances, partial hepatectomy retains important advantages. It avoids lifelong immunosuppression, eliminates donor morbidity, and preserves future transplant options should late recurrence occur. For tumours clearly amenable to R0 resection—typically PRETEXT I–II or favourable POSTTEXT III lesions—hepatectomy remains the preferred route. Moreover, innovations such as intraoperative indocyanine-green fluorescence imaging have enhanced the surgeon's ability to detect occult nodules and secure wider margins, further improving oncologic safety.

Ultimately, the decision between hepatectomy and transplantation hinges on an integrated appraisal of anatomical feasibility, biological aggressiveness, chemotherapy response, and institutional expertise. Centres with robust transplant programmes lean toward earlier LT for borderline cases, whereas those with limited access to grafts may push the envelope of resection. What is universally accepted, however, is that delayed referral to transplant units after failed or marginal resections compromises survival. Multidisciplinary evaluation early in the treatment algorithm, preferably after the second chemotherapy cycle, ensures that each child receives the operation most likely to achieve durable cure with acceptable risk.

As the field advances, molecular profiling and real-time predictive analytics may refine selection further, identifying tumours whose intrinsic biology favours transplantation despite anatomical resectability, and vice versa. For now, the art of choosing between hepatectomy and liver transplantation lies in marrying objective radiological criteria with nuanced clinical judgement, always in service of the child's long-term well-being.

Conclusion

Liver transplantation has emerged as a definitive, life-saving intervention for children with advanced hepatoblastoma who candidates for safe or curative hepatic resection are not. What was once considered a last resort for patients with inoperable tumors has, over the past two decades, evolved into a proactive first-line strategy for carefully selected children. This evolution has been driven by key clinical insights: the inadequacy of aggressive resection in cases of major vascular invasion or insufficient liver remnant; the consistently high cure rates achieved with transplantation; and the cumulative experience of expert centers, particularly in Japan, where living donor liver transplantation (LDLT) has been refined to an exceptional degree of safety and efficacy.

At the heart of successful hepatoblastoma management is the principle of complete tumor clearance—achievable either through surgical resection or through total hepatectomy with liver replacement. The decision between these options is nuanced, requiring detailed assessment of tumor burden, anatomical complexity, vascular involvement, chemotherapy response, and the future liver remnant. While partial hepatectomy remains appropriate and effective for low- to intermediate-risk disease, transplantation offers the best oncologic outcome for patients with PRETEXT IV tumors, multifocal lesions, central vascular invasion, or those with poor response to chemotherapy. In these cases, LT avoids the risks of residual microscopic disease, inadequate liver regeneration, and postoperative hepatic failure.

The survival rates now routinely reported after LT for hepatoblastoma—ranging from 80% to 90%—are a testament to multidisciplinary coordination. This includes careful patient selection, precise surgical planning, intraoperative strategies to minimize blood loss and preserve hemodynamics, and meticulous postoperative care including timely chemotherapy when needed. The Japanese experience, especially from institutions like the National Center for Child Health and Development, has illustrated the advantages of coordinated LDLT, central surgical review, and national consensus protocols such as JPLT3. These elements have collectively helped establish a new standard of care.

Importantly, the decision to pursue transplantation must not be delayed. Patients who undergo futile or marginal resections, only to relapse and require salvage transplantation, have worse outcomes than those who undergo LT as their primary surgical treatment. Early referral to transplant centers, ideally after the second or third cycle of chemotherapy when the tumor biology is clearer, allows for appropriate evaluation and scheduling. With the increasing availability of living donors and the growing use of split or reduced-size deceased donor grafts, timely transplantation is feasible in a majority of healthcare settings.

Despite these successes, challenges remain. The risk of tumor recurrence, particularly in patients with vascular invasion or persistent metastases, underscores the need for continued refinement of selection criteria and adjuvant treatment protocols. Furthermore, the lifelong need for immunosuppression raises concerns about infection, metabolic complications, and long-term graft survival. In the coming years, greater integration of molecular diagnostics may allow for better risk stratification and treatment personalization. Novel strategies such as immunotherapy, targeted molecular agents, and refinements in preoperative imaging may further reduce relapse rates and expand transplant indications.

In conclusion, liver transplantation has solidified its role as a curative modality for hepatoblastoma in children with otherwise unresectable disease. When applied judiciously and within an integrated treatment framework, LT offers excellent survival, minimal recurrence, and a pathway to normal growth and development. Continued progress in surgical technique, transplant immunology, and cancer biology will further enhance outcomes for this uniquely curable childhood liver cancer.

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Review

Serum Albumin in Relation to Hepatocellular Carcinoma: A Review

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Abstract

The known factors that are associated with the development of HCC are chronic inflammation by hepatitis viruses B and C, alcoholism, metabolic dysfunction-associated steatotic liver disease (such as obesity) and chronic dietary intake of hepatocarcinogens such as aflatoxin B1. They cause chronic inflammation, which can lead to cirrhosis, a precursor of HCC, which in turn is often associated with serum hypoalbuminemia. Interventions can be used at any of these stages for the prevention and possible treatment of HCC. This article reviews the normal physiology of albumin and the use of its serum levels in survival prognostication in HCC patients, as well as the known actions of albumin in normal and diseased liver, especially in the context of hepatocarcinogenesis and its relationship to the HCC biomarker alpha-fetoprotein.

Keywords: Aggressiveness, HCC, survival

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The introduction into clinical practice of the Glasgow nutrition-systemic inflammation prognostic score (Albumin plus C-reactive protein serum levels) for prognosis of gastrointestinal cancers and the ALBI index (Albumin plus Bilirubin serum levels) for assessment of both liver cirrhosis and for prognosis of patients with hepatocellular carcinoma (HCC), prompted this review of the normal control and function of serum albumin (normal concentration range 3.4-5.4 g/dL) and what its role and significance might be in patients with HCC, to help understand why its serum levels are such a useful prognosis marker.

Albumin Structure, Function and Uses

Human serum albumin (HSA) is a 66.5 kDa negatively charged protein with high solubility and stability, encoded on chromosome 4. It has a single polypeptide sequence formed by 585 amino acids[1] and a secondary structure consisting of 55% α-helix and 45% β-structure. Its tertiary structure is heart-like shaped, possessing three homologous domains, I-III. Albumin accounts for roughly 50% of total plasma proteins and its 2 major functions are to maintain plasma osmolality and to protect cells from damage by free radicals and various toxic chemicals.[2] The presence of negative charges on albumin enhances its solubility and facilitates stable binding with diverse drug molecules via electrostatic interactions. These allow it to act as a drug-transport system in vivo. It also has a variety of enzymatic activities such as esterase function, which can convert pre-drugs to active drugs. It is already in clinical use for its property of binding nano-particle paclitaxel (nab-paclitaxel) in medical oncology practice,[3] as well as for binding and delivery of doxorubicin and cisplatin.

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Albumin is also a major antioxidant in the bloodstream, closely linked to its structure. Its cysteine residues which contain thiol groups account for 80% of all thiol groups in the blood and are key antioxidants within blood vessels. Human serum albumin (HSA) utilizes these cysteine residues to neutralize free radicals and exhibits antioxidant functions by binding with various ligands. Furthermore, it has anti-inflammatory properties, by binding mediators such as TNF- α or indirectly by regulating cellular glutathione levels. It can undergo post-translational modifications in diseases such as cirrhosis, the commonest of which is oxidation of cysteine residue 34, leading to both structural and functional changes in the albumin molecule.[4] Albumin can protect healthy cells during treatment by radiotherapy and free radical-generating chemotherapies. Albumin can also be used in clinical diagnostics, such as in hepatic arterial perfusion scintigraphy using 99mTc-labelled albumin macroaggregates (MAA) to identify potential pulmonary or digestive shunts in preparation for hepatic artery radioembolization.[5] Interestingly, most human albumin is not in circulation, since 60% is stored in the interstitial space. Although the half-life of albumin is about 17-20 days, it only lasts 16-18 hours in circulation owing to transcapillary escape.

Albumin (from Latin albus, white) is predominantly synthesized in the liver, although extra-hepatic albumin mRNA has been detected. Hepatic albumin synthesis can increase several-fold in response to hypoalbuminemia and stimulation by insulin, glucocorticoids, or growth hormone.

In contrast, proinflammatory cytokines inhibit albumin synthesis. Degradation of albumin can occur in any tissue, but mostly in the liver, kidney and muscle. Plasma albumin concentration is the result of the balance between albumin synthesis, exchange between intravascular and interstitial compartments, albumin degradation by catabolism, and renal or intestinal loss.[1]

Causes of Hypoalbuminemia

Hypoalbuminemia is present in about 20% of hospital patients and has many causes, mostly associated with acute and chronic inflammation. Associated conditions include liver cirrhosis, cardiac failure, malnutrition (deficient amino acid intake), nephrotic syndrome and increased losses from the gut and kidneys. It is a very important prognostic factor for death, but it is unclear if this is a direct effect of hypoalbuminemia, or a secondary consequence of its manifold causes, such as inflammation or malnutrition. Albumin infusion has been used for many years for treating the consequences of cirrhosis and has been recommended for large volume depletion after paracentesis, for spontaneous bacterial peritonitis and for acute liver injury of cirrhosis.[6] However, its use for many other indications in clinical practice is largely controversial.[7]

Hypoalbuminemia in Cancer

Several mechanisms seem to be involved in the hypoalbinemia of cancer. Most important is the inflammation-mediated reduction in synthesis.[8] In addition, both changes in its secretion[9] and increased vascular permeability, contribute to a redistribution of albumin from the intravascular to the interstitial spaces. Furthermore, malnutrition, especially in patients with cancer of the GI tract, as well as cancer cachexia are also involved in the hypoalbuminemia of cancer.

Tissue Albumin and Alpha-Fetoprotein in HCC

The structures of albumin and alpha-fetoprotein are similar and they are from closely related gene families. Several quantitative studies in HCC patient tissues, particularly of tumor tissue, show decreased albumin and often increased in alpha-fetoprotein (AFP), usually in the same tumor. Albumin amounts are often related to the degree of HCC differentiation , with sparser albumin being found in more poorly differentiated HCCs.[10-12]

Cancer Cachexia and HCC

Cancer cachexia, meaning the weakness, loss of body mass and tumor-produced catabolic factors occurs in many advanced cancer patients, including those with HCC.[13-16] A prominent associated feature is hypoalbuminemia.[17] The main treatments are nutritional support and control of the underlying cancer.

Inflammation and HCC

Most HCCs arise in the setting of a chronically inflamed liver, due mainly to infections with chronic hepatitis B or C, toxic free radicals from alcoholism or dietary hepatocarcinogens (Aflatoxin B1), and increasingly from metabolic dysfunction-associated steatotic liver disease (formerly, non-alcoholic fatty liver disease).[18] However, genome instability and non-resolving inflammation are well-described hallmark of many cancers including HCC.[19] This is a 2-way process in which the HCC can recruit inflammatory cells and thereby change its microenvironment.[20] This inflammation then promotes tumor cell growth, angiogenesis, tumor invasion and the evasion of immune surveillance.[20] Targeting inflammation can thus be seen as a reasonable and biology-based approach to HCC therapy.

Liver Function and HCC

Hypoalbuminemia has been shown to be linearly and inversely related to risk of development of cancers, including HCC.[21-23] Furthermore, both albumin and other liver function tests relate to parameters of HCC aggressiveness.[24-32] Thus, which comes first? An HCC of increasing size that invades and destroys hepatic parenchyma? Or, hepatic inflammatory signals that provide support and drive increasing HCC growth?

Albumin Levels and HCC Survival

Serum albumin levels have been shown to correlate with HCC survival in association with a variety of treatments.[33-38] Again, does low albumin cause worse survival, or does aggressive HCC cause worse survival and worse albumin and other liver parameters? The situation has not been clearly resolved.

Glasgow Index and ALBI Score in HCC

Both scores have 2 serum parameters, one of which is serum albumin. Glasgow score also includes an inflammation marker, serum C-reactive protein (CRP), whereas ALBI includes total serum bilirubin levels as a second parameter of liver function. Both albumin and total bilirubin are 2 important objectively measurable components of the Child-Pugh score. There is considerable literature on the Glasgow score (and its updated variants) as an HCC prognosticator.[39-46] An even larger literature has emerged and continues to grow on the value of the ALBI score both for treatment-based prognosis as well as for liver toxicities post therapy.[47-55] An easy Web-based method for calculating ALBI score and grade is now available at www.mdcalc.com. However, it has been suggested that prognosis in HCC depends more on albumin levels that ALBI.[56]

The Mechanisms for Albumin Actions on Tumor Growth

Is hypoalbuminemia a passive index of poor survival, or is it telling us something important about the function of serum albumin in controlling HCC growth or development?

There is increasing direct evidence that albumin can control HCC growth and invasion. When added directly at physiological concentrations to HCC cells growing in culture, albumin can cause inhibition of both cell growth and migration and a decrease in alpha-fetoprotein levels.[57-59] Albumin in also associated with growth inhibition of other cancer cells in vitro.[60] Since albumin can bind and transport many drugs, the interaction with drugs and HCC cells may be complex, as it has also been shown to antagonize the cytostatic actions of sorafenib.[6] Furthermore, there may be a reciprocal effect on AFP as albumin can also inhibit AFP levels, and levels of albumin and AFP seem to be inverse, both in tumors and in HCC patients.[10, 33, 58, 61, 62]

Therapeutic Manipulation of Albumin Levels for HCC Therapy

There is a great deal of nutritional literature concerning various foods in relation to both protein levels and to cancer. However, it is mainly speculative and contradictory, with little practical science or experimentation behind it.[63-68] Nevertheless, albumin synthesis is influenced by both nutritional status and growth hormone stimulation;[69, 70] and conversely it is inhibited by inflammation. Albumin infusions have been evaluated for treating the hypoalbuminemia of cirrhosis, as well as for cirrhotic complications. However, at the time of this writing, the national liver societies have approved its use only for a few specific complications of cirrhosis[1, 6, 7] as noted in the first section of this review. This seems also applicable to treatment of liver dysfunction in HCC patients.[71]

We are thus left with the overall idea that hypoalbuminemia is a response to inflammation, rather than a consequence of cancer growth,[72] although both are plausible. The evidence supporting nutritional treatment for cancer is weak, mainly owing to the absence of robust clinical trials.

Is there a case for a pilot study of albumin infusion, or of other means of suppressing the inflammation as the cause of hypoalbuminemia, such as salicylates, as shown in Figure 1, or the use of non-steroidal anti-inflammatory drugs (NSAIDs) to increase serum albumin levels and possibly decrease AFP levels, given the experimental evidence of suppression of HCC growth and reduction in high AFP levels by albumin? There is epidemiological evidence for lower HCC incidence in patients taking these agents,[73,74] but whether they act through control of albumin or other pathways is unclear.

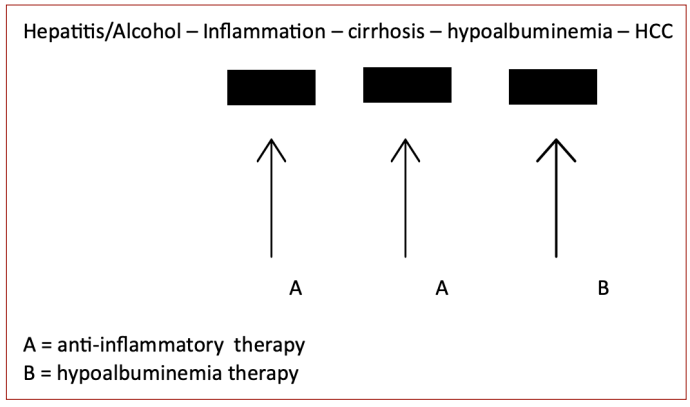

Figure 1. Summary of the ideas in this review.

One other use for serum albumin or ALBI (Albumin Bilirubin) levels is as an early marker for tumor responses to anti-HCC therapy. This has already been incorporated as an ALBI-sarcopenia score[75] and is being used as a prognostic indicator for survival in patients being treated with radioembolization,[55, 76] although albumin-only levels seem to be sufficient for prognosis in transarterial radioembolization (TARE).[55] It seems to be similarly useful in assessing tumor responses to chemoembolization in HCC patients[49, 77] as well as in HCC patients being treated with immune checkpoint inhibitors.[78, 79] Low baseline ALBI grade may even predict response to this class of agents.[80] ALBI also predicted response to both regorafenib and lenvatinib therapy and to transarterial chemoembolization (TACE) therapy in HCC patients.[81-85] There are multiple factors involved in both HCC development and in HCC aggressiveness, which have recently been integrated into a single multifactorial prognostic web tool[86] at: https://apkatos.github.io/webpage_ nps. The use of ALBI in non-cirrhotic HCC patients is unclear,[87] although conversely, hypoalbuminemia is a prognostic factor even in patients with small size HCCs.[88]

Conclusion

Albumin is a critically important blood component with many biochemical functions in addition to the control of oncotic pressure. There is a strong relationship between hypoalbinemia and poor prognosis in patients with HCC and with many other tumor types. It also has known activities in experimental HCC growth and migration control. Whether it is only a passive predictor of HCC survival and responses to therapy or is actively involved in HCC biology remains to be determined.

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Review

Phenotypic Plasticity of Hepatocytes and Cholangiocytes in Chronic Liver Disease

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Abstract

The hepatic epithelial system, composed of hepatocytes and bile duct cells, exhibits remarkable phenotypic plasticity despite its highly differentiated state. During acute liver injury, hepatocytes rapidly regenerate through self-duplication; however, chronic or repetitive injury induces incomplete regeneration, fibrotic remodeling, and ductular reactions. Historically, a liver progenitor cell (LPC) population was proposed to mediate regeneration when hepatocyte proliferation is impaired, but recent lineage-tracing and single-cell analyses indicate that LPCs contribute minimally, and that most new hepatocytes arise from pre-existing hepatocytes. Ductular reactions, frequently observed in chronic liver diseases, primarily result from proliferation and remodeling of existing bile ducts, with a subset derived from hepatocyte transdifferentiation. Such hepatocyte-to-ductular transitions may help re-establish bile canalicular continuity in damaged tissue. Oncogenic activation in hepatocytes further reveals their plastic potential, producing diverse tumor phenotypes—ranging from hepatocellular carcinoma to cholangiocarcinoma and hepatoblastoma—through transdifferentiation or dedifferentiation programs reminiscent of liver development. These findings suggest that liver regeneration and carcinogenesis share common mechanisms of epithelial reprogramming. Future research should aim to identify subsets of hepatocytes capable of sustained replication and to elucidate how the injured microenvironment governs epithelial cell fate through processes such as paligenosis. Understanding and modulating hepatic epithelial plasticity may provide new strategies for treating chronic liver diseases and liver cancer.

Keywords: Cholangiocytes, dedifferentiation, ductular reaction, hepatocytes, liver progenitor cells, phenotypic plasticity, primary liver cancers, transdifferentiation

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The hepatic epithelial system, composed of hepatocytes and bile ducts, plays a central role in the liver's complex metabolic, synthetic, and secretory functions, supported by non-epithelial cells such as sinusoidal endothelial cells, hepatic stellate cells, myofibroblasts, and a variety of immune cells. Despite being highly differentiated and specialized, the liver is well known for its robust regenerative capacity following acute parenchymal injury, as demonstrated in rodent partial hepatectomy experiments and in the rapid recovery observed in several human acute liver diseases.[1] However, when parenchymal injury is prolonged or repetitive, regeneration becomes incomplete, leading to fibrotic remodeling and ultimately cirrhosis, which is characterized by regenerative nodules surrounded by fibrous septa.[2]

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Although hepatocyte phenotypes were long assumed to be fixed once maturation was complete, accumulating evidence indicates that the hepatic epithelial system retains substantial phenotypic plasticity, particularly under conditions of chronic injury, when the hepatic microenvironment is altered.[2] Hepatocytes can undergo transdifferentiation toward bile duct cells or dedifferentiation toward liver progenitor cells (LPCs), which are thought to represent bipotential intermediate hepatobiliary cells similar to hepatoblasts. Recent studies have also proposed that bile duct cells themselves may exhibit plasticity and transdifferentiate into hepatocytes. Nevertheless, the extent of this epithelial plasticity and its precise contribution to liver regeneration and hepatocarcinogenesis remain unclear, as experimental findings are often conflicting.

In this short review, I aim to synthesize recent data on hepatic epithelial plasticity and propose a more unified framework for understanding these processes.

Development of the Hepatic Epithelial System

The epithelial cells of the liver are derived from hepatoblasts, which emerge from the hepatic diverticulum of the foregut at 3–4 weeks post-coitum in humans and at embryonic day 8.5–9.0 in mice.[3] During the early stages of hepatogenesis, immature hepatoblasts strongly express Myc and delta-like 1 (DLK1), but the expression of these markers declines rapidly before birth (Fig. 1).[4,5] Although hepatoblasts specifically express a variety of proteins and mRNAs—including α-fetoprotein (AFP), insulin-like growth factor 2, and H19 mRNA—that are absent in mature hepatocytes, their expression continues during the early postnatal period.[4,5]

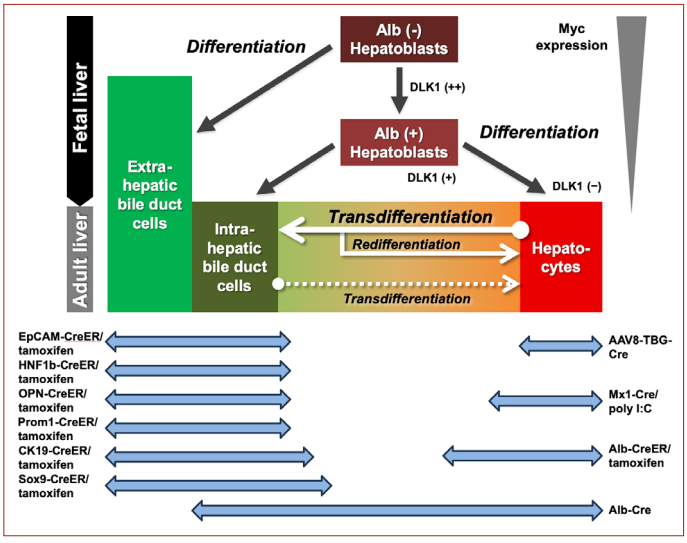

Figure 1. The lineage of hepatic epithelial cells.

Hepatocytes and bile duct cells (cholangiocytes) are derived from hepatoblasts. Although hepatocytes and intrahepatic bile duct cells can mutually transdifferentiate, hepatocytes are generally more malleable. The potential cellular spectrum labeled by various lineage-tracing systems is illustrated below.

While immature hepatoblasts proliferate and form the liver bud, they also give rise to the extrahepatic bile ducts, which connect the liver to the intestinal lumen (Fig. 1).[6] As hepatoblasts differentiate into hepatocytes and begin to express albumin, they simultaneously generate nascent intrahepatic bile ducts, appearing as ductal plates along the developing portal veins (Fig. 1).[6] Differentiation of the intrahepatic bile ducts is initiated by collagen deposition along the developing portal vein and activation of the Notch signaling pathway.[7] Development of the intrahepatic bile ducts continues during the postnatal period, ultimately giving rise to bile ductules—the terminal branches of the biliary tree, which abut periportal hepatocytes—and to interlobular bile ducts embedded within the portal connective tissue.

Liver Progenitor Cell Hypothesis

It has been proposed that a small population of hepatoblast-like cells resides in the adult liver, serving as liver progenitor cells (LPCs) that are bipotential and contribute to regeneration when hepatocyte proliferation is impaired during chronic liver injury.[8] The most likely LPC candidates are intermediate hepatobiliary cells located in the canal of Hering, the junction between the hepatocyte canalicular system and bile ductules. Research on LPCs has long been hampered by the absence of specific markers. Nevertheless, Sox9 and osteopontin—both also expressed in bile duct cells—have been utilized for lineage-tracing experiments in mice.

Periportal Sox9-positive cells were once reported to contribute to liver homeostasis and regeneration,[9] but subsequent studies failed to reproduce these findings.[10] Lineage tracing of osteopontin-positive cells has yielded variable results; however, the generation of new hepatocytes from osteopontin-positive cells appears limited (at most a few percent).[11-13] Similarly, Axin2-positive cells, which were once proposed as unique centrilobular LPC candidates, were later shown not to significantly contribute to liver regeneration.[14]

Cholangiocytes have also been suggested to act as LPC-like cells in mice, particularly when hepatocyte proliferation is suppressed by chronic injury induced by Mdm2 deletion.[15] Subsequent studies demonstrated that reactive cholangiocytes may serve as important sources of hepatocytes following chronic injury induced by a methionine- and choline-deficient diet,

3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC), or CCl_4.[13,16,17] Notably, these conclusions were largely based on the observation that clusters of unlabeled hepatocytes appeared in regenerating livers in experiments using the AAV8-Tbg-Cre system. Although this is currently the most efficient hepatocyte-lineage tracing method, unlabeled hepatocytes can sporadically arise anywhere in the hepatic lobule, gradually forming clusters and even regenerative nodules during chronic injury.[2]

Taken together, it is now evident that the small pool of intermediate hepatobiliary cells in the adult liver does not possess robust proliferative activity in chronic injury. Instead, new hepatocytes are generated primarily through self-duplication.[18,19] Thus, the liver may not require a dedicated stem cell system for its regeneration.

Ductular Reaction: Cells of Origin and Significance

In various chronic liver diseases, abnormal proliferation of bile ductules occurs in association with progressive fibrosis. This phenomenon, termed the ductular reaction, has long been the subject of debate regarding its cellular origin, underlying mechanisms, and biological significance.[20] The presence of intermediate hepatobiliary cells around ductular reactions suggests that hepatocyte transdifferentiation into ductular cells may contribute to this process. Indeed, we have demonstrated ductular transdifferentiation of mature hepatocytes in three-dimensional cultures and transplantation experiments.[21-23] This transdifferentiation is not accompanied by reactivation of hepatoblastic proteins such as DLK1, is markedly enhanced by tumor necrosis factor-α, and is at least partially reversible.[22] Furthermore, ductular transdifferentiation of chronically injured hepatocytes has been reported to play a significant role in liver regeneration.[24,25]

Multiple groups have employed hepatocyte lineage-tracing systems in mice to assess the extent of ductular transdifferentiation in ductular reactions.[23,26-29] Using the Mx1-Cre/ROSA26R system, we estimated that hepatocyte transdifferentiation contributes to approximately 10% of ductular reactions during chronic injury.[23] Recent single-cell analyses have revealed substantial heterogeneity in the adult liver, including various hybrid hepatobiliary cell populations.[30-32] Depending on which subpopulation is labeled in a given lineage-tracing system, results may vary considerably (Fig. 1). When cholangiocyte lineage-tracing data are also considered,[26,33] it appears that most ductular reactions primarily reflect proliferation of pre-existing bile ducts and ductules.

Ductular reactions are also associated with extensive remodeling of the biliary system. In centrilobular ductular reactions induced by CCl_4, thioacetamide, or a 0.1% methionine/choline-deficient L-amino acid-defined high-fat diet, bile ductules emerge within the damaged centrilobular zones. Importantly, these remodeled ductular networks maintain communication with the common bile duct. The transdifferentiation of injured hepatocytes into ductular cells may therefore be critical for re-establishing junctions with the bile canalicular system.[23,34]

The Histological Diversity of Hepatocytic Tumors: Transdifferentiation and Dedifferentiation Induced by Oncogenic Processes

Primary liver epithelial cancers are histologically diverse, including hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), combined hepatocellular-cholangiocarcinoma (cHCC-CCA), hepatoblastoma (HB), and other rare entities. The phenotypic plasticity of liver epithelial cells has important implications for understanding the diversity of these tumor types. Using somatic gene transfer via hydrodynamic tail vein injection of oncogene-harboring transposons into mouse hepatocytes, we have shown that a wide spectrum of liver tumors—including HCC, CCA, cHCC-CCA, and HB-like tumors—can be generated from transformed hepatocytes.[4,35–37] This hepatocarcinogenesis model is robust, enabling the induction of multiple liver tumors with defined oncogenic mechanisms, dependent on the introduced oncogene(s), within a few weeks.[38]

CCA was first generated by Fan et al.[39] from mouse hepatocytes through activation of the Notch pathway, which is critical for bile duct differentiation in the fetal liver, in combination with AKT pathway activation. Activation of AKT together with YAP also induces CCA,[37] consistent with the known reciprocal interaction between the Notch and YAP signaling pathways. cHCC-CCA can be induced by combinations of activated YAP (or Notch) with Myc, mutant HRAS with p53 knockout, or mutant HRAS, Myc, and p53 knockout.[36,37] Notably, some human intrahepatic CCAs may arise from hepatocytes via transdifferentiation, as recent evidence suggests.[40]

Although hepatocytes exhibit an intermediate hepatobiliary phenotype during chronic injury, they do not activate the hepatoblastic gene and protein expression program, including DLK1 and AFP. Interestingly, the combination of mutant HRAS and Myc generates HB-like tumors expressing DLK1, AFP, and stem cell markers.[4] Similar dedifferentiation occurs in tumors induced by YAP and Myc.[37] These findings suggest that Myc activation, which occurs during early liver development (Fig. 1), is essential for hepatocyte dedifferentiation.

Conclusions and Future Directions

In chronic liver injury, hepatocytes and cholangiocytes exhibit considerable phenotypic plasticity, contributing to liver regeneration and the ductular reaction. The ductular reaction is primarily a consequence of biliary remodeling triggered by microenvironmental changes—including fibrotic matrix deposition and inflammatory cell infiltration—rather than activation of LPC. The ductular transdifferentiation of hepatocytes also plays an important role in maintaining the continuity of the biliary network.

Recent single-nucleus RNA sequencing studies have revealed significant epithelial plasticity in human chronic liver disease.[41] Interestingly, intermediate hepatobiliary cells identified in metabolic dysfunction-associated steatotic liver disease lack LPC-like properties and are largely non-proliferative.[41] These findings suggest that regeneration in chronic liver disease may depend on the selective proliferation of a subset of hepatocytes rather than on LPCs or intermediate hepatobiliary cells. Identifying hepatocytes capable of repeated replication will be an important goal for future research.

Tissue remodeling in chronic liver disease may be governed by paligenosis,[42] a process in which mature hepatocytes and cholangiocytes re-enter the cell cycle and regenerate damaged tissue without relying on professional stem cells. For hepatic epithelial cells to properly restore damaged tissue through their phenotypic plasticity, it is crucial to normalize the abnormal microenvironment in which they reside.

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Review

Pushing the Boundaries for Liver Transplantation in Hepatocellular Carcinoma

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Abstract

Liver transplantation (LT) is the only curative treatment for unresectable or decompensated cirrhotic patients with hepatocellular carcinoma (HCC). Currently, the transplantable window for HCC patients is defined by meeting the extended transplant criteria. Notably, 20-30% of patients who beyond all established transplant criteria have demonstrated survival more than 10 years post-transplant, indicating that current selection criteria may exclude individuals who could significantly benefit from LT. Therefore, there is no perfect criteria currently, as these patients are excluded from the possibility of transplantation. Limits should be pushed to make LT possible for these patients.

Patients meeting the Expanded Malatya Criteria had a 78.4% 5-year overall survival (OS), a 4.7% recurrence rate, and a 35% Milan Criteria expansion rate, suggesting that the Expanded Malatya Criteria provide a reasonable approach for expanding transplant candidacy.

In cases of LT for patients with macroscopic portal vein tumor thrombus (Macro-PVTT), limited data from the Malatya experience indicate encouraging outcomes using living donor liver transplantation (LDLT): Macro-PVTT patients categorized as Vp1-3 with low alpha-fetoprotein (AFP ≤200) and gamma-glutamyl transferase (GGT ≤104) levels demonstrated five-year OS and disease-free survival (DFS) rates of 100% and 68.6%, respectively.

Another challenging cohort includes BCLC stage D patients, typically offered only supportive care with an expected median survival of three months. However, selected patients aged 18 to 65, CHILD class C, without extrahepatic spread and beyond Expanded Malatya Criteria, achieved a three-year survival rate of 50% following salvage LDLT.

In conclusion, during the era of LDLT, it is recommended that all HCC patients be evaluated in a multidisciplinary tumor board, irrespective of transplant criteria.

Keywords: Advanced HCC, live donor, macrovascular, macroscopic portal vein tumor thrombus, salvage liver transplantation, best supportive care

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Hepatocellular carcinoma (HCC) remains a global health concern. It is estimated that there will be 1.41 million new cases and 1.26 million deaths in 2045.[1] The Milan criteria (MC),[2] defined almost 30 years ago as patient selection criteria for liver transplantation (LT), which is the curative treatment for HCC because it eliminates both the underlying liver disease and the tumor, are not sufficient today and even the creators of the Milan criteria have expanded the MC three times.[3-5] How far can the MC be extended, reasonably? According to the EASL Clinical Practice Guidelines on the management of HCC 2025, If the patient within or slightly beyond MC is not suitable for downstaging due to the poor liver function, transplant listing may be considered which means MC can be expanded slightly.[6] On the other hand, according to the 2024 ILTS-ILCA consensus

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recommendations for LT for HCC, transplantation can be performed without downstaging if outcome measures are preserved.[7] The minimum acceptable 5-year survival rate after LT should be greater than 50%[7] or 60%.[6] Since all transplant criteria achieve this target survival,[8] we can say that the current transplantation limits are expanded criteria.

These criteria use parameters to predict the tumor's biological behavior. Predictors of tumor recurrence can be grouped into four main categories:

- **Morphological:** tumor number, largest tumor diameter, total tumor volume, sum of tumor diameters and tumor number.
- **Biological:** AFP, PIVKA-II (DCP), GGT, LRT response, PET/CT uptake.
- **Inflammatory:** neutrophil-to-lymphocyte ratio (NLR).
- **Histopathological:** microvascular invasion, poor differentiation.

Pushing the Boundaries for Liver Transplantation in Hepatocellular Carcinoma

Extended Transplant Criteria (Current limits for LT for HCC)

A chronological summary of the transplant criteria and scoring systems described in the literature is given in the Table 1 and 2.[9-35]

Our center in Türkiye established two transplant criteria—Malatya and Expanded Malatya Criteria—and published outcomes based on them.[36]

The expanded Malatya criteria had a 78.4% 5-year overall survival (OS), a 4.7% recurrence rate, and a 35% Milan criteria expansion rate, which would reasonably broaden transplantation boundaries (Fig. 1). However, regardless of the criteria used, 20-30% of patients who beyond any

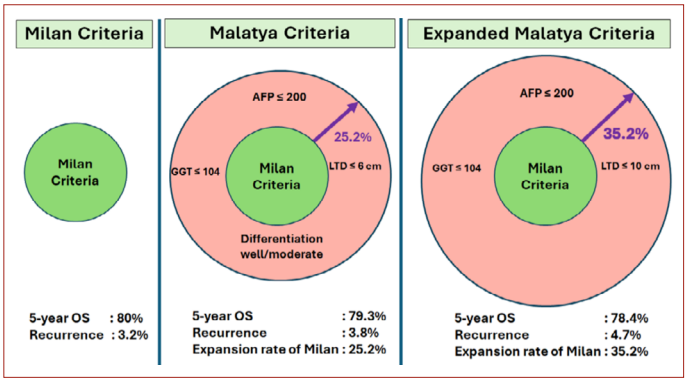

Figure 1. Summary of OS and DFS, recurrence rates, and Milan criteria expansion rates of patients within the criteria.

criteria have a 10-year survival with liver transplantation (Fig. 2). Therefore, there is no perfect criteria yet that would select patients who beyond these criteria but have a long survival rate. Therefore, all HCC patients should be discussed in a multidisciplinary tumor board, regardless of the criteria.

Liver Transplantation in Patients with Macroscopic Portal Vein Tumor Thrombus (Macro-PVTT)

Macroscopic portal vein invasion was previously a contraindication for liver transplantation, and all defined transplant criteria exclude these patients. Over time, studies have shown that patients with Macro-PVTT who respond well to downstaging and whose AFP levels are lower have acceptable liver transplantation outcomes.[37-41]

Therefore, it is no longer an absolute contraindication because liver transplantation outcomes are acceptable in selected patients with Macro-PVTT. Select patients with macrovascular invasion (Vp1 or Vp2) may be considered for LT if able to be successfully downstaged to local criteria (based on radiographic response, decrease in serum AFP). A minimum observation time of 12 months post-Downstaging may allow for assessment of tumor biology.[7]

In a study in which we retrospectively analyzed the liver transplantation results for patients with Macro-PVTT, after excluding those classified as Vp4 Macro-PVTT, the remaining 33 patients presenting with Vp1, Vp2, and Vp3 Macro-PVTT underwent liver transplantation. When we divided these 33 patients into two groups based on their final pre-transplant AFP and GGT blood levels (Group 1: low AFP + low GGT; Group 2: other combinations of AFP and GGT), the 5-year OS for patients with low AFP + low GGT (AFP ≤ 200 + GGT ≤ 104) (n=10) was 100% and the 5-year disease-free survival (DFS) was 68.6%.[43] (Fig. 3a and 3b). Although the sample size is small, the results are promising and LT boundaries can be extended even for patients with Macro-PVTT (AFP ≤200 + GGT ≤ 104).[42] Therefore, patients with PVTT should also be discussed in a multidisciplinary tumor board.

Pushing the limits by LDLT in HCC

Mazzafero et al.'s revised figure at the "Transplant Oncology Book" demonstrates the correlation between oncological acuity, organ allocation, and patient prioritization across various etiologies, it is noted that the transplantable window for cancer patients should be within the transplant criteria. Patients beyond the criteria are un-

Table 1. A summary of transplant criteria features as defined in the literature, presented in chronological order

Criteria	Single Tumor LTD, cm	Multiple Tumor (NN)	Multiple Tumor LTD, cm	TTD, cm	AFP, ng/mL	PIVKA -II	Differentiation	MiVi	LTD+ NN	TTV, cm^3	GGT, IU/L	5-year DFS, criteria in, %	5-year OS, criteria in, %	5-yr Recurrence, criteria in, %
Paul Brousse[9]	3	1-2	3	-	-	-	-	-	-	-	-	83	83	
Milan[2]	≤ 5	2-3	≤ 3	-	-	-	-	-	-	-	-	82 (4yr)	85 (4yr)	8
UCSF[10]	≤ 6.5	2-3	≤ 4.5	≤ 8	-	-	-	-	-	-	-		75.2	
BCLC[11]	≤ 7	2-3	≤ 5	-	-	-	-	-	-	-	-		80.2	23.8
		4-5	≤ 7											
Extended Criteria[12]	≤ 7.5	2-3	≤ 5	-	-	-	(>5 cm with poor diff also excluded)	-	-	-		76.8 (4yr)	82.9 (4yr)	
Berlin[13]	≤ 6	No limit	≤ 6	≤ 15	-	-	-	-	-	-	-	64 (3yr)	68 (3yr)	
Kyoto[14]	≤ 5	2-10	≤ 5	-	-	≤ 400	-	-	-	-	-		86.7	4.9
Tokyo[15]	≤ 5	2-5	≤ 5	-	-	-	-	-	-	-	-	94 (3yr)	75	
Onaca[16]	≤ 6	2-4	≤ 5	-	-	-	-	-	-	-	-	64.6		
Hangzhou[17]	≤ 8	-	-	≤ 8	-	-	-	-	-	-	-	70.7	62.4	
	>8	-	-	>8	≤ 400	-	Well/moderate				-			
Asan[18]	≤ 5	2-6	≤ 5	-	-	-	-	-	-	-	-		76.3	13.6 (3yr)
CUN[19]	≤ 6	2-3	≤ 5	-	-	-	-	-	-	-	-		73	
Valencia[20]	≤ 5	2-3	≤ 5	≤ 10	-	-	-	-	-	-	-		67	9
Shangai[21]	≤ 9	2-3	≤ 5	≤ 9	-	-	-	-	-	-	-	52.6	78.1	10.7
Kyushu[22]	≤ 5	No limit	≤ 5	-	-	≤ 300	-	-	-	-	-	87	82.7	
UpToSeven[4]	≤ 6	-	-	-	-	-	-	negative	≤ 7	-	-		71.2	39.9
TTV/AFP[23]	-	-	-	-	≤ 400	-	-	-	-	≤ 115	-		≈60 (4yr)	
Ext Toronto[24]	No limit	No limit	No limit	-	-	-	Well/moderate	-	-	-	-		68	25.6
AFP-TTD[25]	≤ 8	-	-	≤ 8	≤ 400	-	-	-	-	-	-	74.4		4.9
Samsung[26]	≤ 6	2-7	≤ 6	-	≤ 1000	-	-	-	-	-	-	89.6		
5-5-500[27]	≤ 5	2-5	≤ 5	-	≤ 500	-	-	-	-	-	-	73.2	75.8	7.3
Malatya[28]	≤ 6	No limit	≤ 6	-	≤ 200	-	Well/moderate	-	-	-	≤ 104		79.7	
Exp Malatya[29]	≤ 10	No limit	≤ 10	-	≤ 200	-	-	-	-	-	≤ 104		77.6	

AFP: alpha fetoprotein; GGT: Gamma glutamyl transferase; LTD: Largest tumor diameter; MiVi: Microvascular invasion; NN: Number of nodules; TTD: Total tumor diameter; TTV: Total tumor volume; PIVKA II: Protein induced vitamin K antagonist II.

Table 2. A summary of the scoring systems features as defined in the literature, presented in chronological order

Scoring System	Scores of the parameters					Posttransplant Recurrence Risk	5-year DFS in low risk	5-year OS in low risk	Recurrence in low risk, at 5-yr
AFP Model[30], 2012	LTD point	NN point	AFP point			Total point = score (0-9)		67.8	8.8
	≤ 3 cm = 0	1-3 nodule = 0	≤ 100 = 0			Score ≤ 2, low risk		47.5	50.6
	3-6cm = 1	>4 nodule = 2	100-1000 = 2			Score > 2, high risk			
	>6cm = 4		>1000 = 3						
RETREAT[31], 2017	LTD+NVT point	MiVi point	AFP at Tx point			Total point = score (0-8)			2.9
	0 = 0	Positive = 2	0-20 = 0			Score = 0,			75.2
	1.1-4.9 = 1		21-99 = 1			Score < 5, low risk			
	5.0-9.9 = 2		100-999 = 2			Score ≥ 5, high risk (RR)			
	≥10 = 3		≥1000 = 3						
MoRAL[32], 2017	Pre-Tx-MoRAL point		Post-Tx-MoRAL point			Total point = score (0-13)	97.4		
	LTD > 3cm = 3		LTD>3cm = 3			Score 0-2, low risk	75.1		
	NLR > 5 = 6		NN>3 nodules = 2			Score 3-6, medium risk	49.9		
	AFP > 200 = 4		Grade 4 tumor = 6			Score 7-10, high risk	22.1		
			MiVi positive = 2			Score > 10, very high risk			
NYCA[33], 2018	LTD at diagnosis Point	NN at diagnosis Point	AFP response Point			Total point = score (0-14)	90		cumulative
	0-3 cm = 0	1 nodule = 0	AFP always < 200 = 0			Score 0-2, low risk	70		7
	>3-6 cm = 2	2-3 = 2	Responders			Score 3-6, acceptable risk	42		27.5
	>6 cm = 4	≥4 = 4	Max > 200-1000 to final < 200 = 2			Score ≥7, high risk			62.5
			Max >1000 to final<1000 (must be 50% drop) = 2						
			Nonresponders						
			Max > 200-400 to final >200 = 3						
			Max > 400-1000 to final >200 = 4						
			Max > 1000 to final >1000 = 6						
Metroticket 2.05, 2018	LTD + NN ≤ 7 and AFP ≤ 200 or					Low risk	87.4	78	
	LTD + NN ≤ 5 and AFP 200-400 or								
	LTD + NN ≤ 4 and AFP 400-1000								
SNAPP[34], 2020	LTD point	NN point	AFP and PIVKA point	PET-CT point		Total point = score (0-8)	97		3
	≤ 3 cm = 0	1 nodule = 0	AFP≤150 + PIVKA≤100 = 0	Isometabolic = 0		Score ≤ 2, low risk	71		29
	3-6 cm = 1	2-3 nodule = 1	AFP≤150 + PIVKA>100 = 1	Hypermetabolic = 1		Score 3-4, medium risk	31		69
	>6 cm = 2	≥4 nodule = 2	AFP>150 + PIVKA≤100 = 2			Score > 5, high risk			
			AFP>150 + PIVKA>100 = 3						
R3-AFP Score[35],	LTD point	NN point	MiVi point	Nuclear Grade point	AFP point	Total point = score (0-11)		77.2	5.5
2022	≤ 3cm = 0	1-3 nodule = 0	Negative = 0	Well / Moderate = 0	≤ 100 = 0	Score 0, very low risk		67.8	15.1
	3-6cm = 1	>4 nodule = 1	Positive = 2	Poor = 1	100-1000 = 1	Score 1 - 2, low risk		57.2	39.1
	>6cm = 5				>1000 = 2	Score 3 - 6, high risk		19.8	73.6
						Score >6, very high risk			

AFP: alpha fetoprotein; LTD: Largest tumor diameter; MiVi: Microvascular invasion; MoRAL: Model Of Recurrence After Liver transplant; NLR: Neutrophile to lymphocyte ratio; NN: Number of nodules; NVT: Number of Viable Tumor, PIVKA II: Protein induced vitamin K antagonist II.

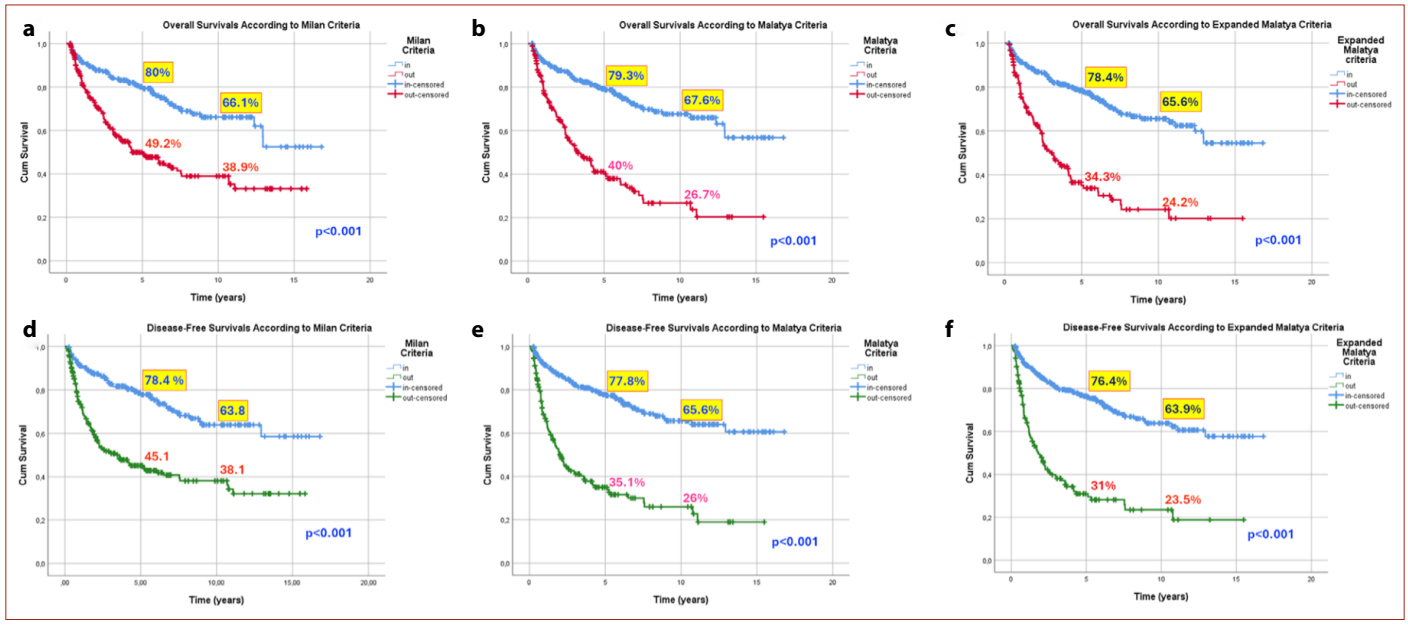

Figure 2. (a) Overall survivals according to Milan Criteria, **(b)** Overall survivals according to Malatya Criteria, **(c)** Overall survivals according to Expanded Malatya Criteria. **(d)** Disease-free survivals according to Milan Criteria, **(e)** Disease-free survivals according to Malatya Criteria, **(f)** Disease-free survivals according to Expanded Malatya Criteria.

likely to benefit from transplantation (Fig. 4a).[43] Setting these limits is justified when there is competition for deceased organs, as HCC patients beyond the criteria have only a 30% 10-year overall survival rate. Allocating the donated organ to the patient who is expected to benefit the most may be considered equitable; however, it is important to note that there are patients beyond the criteria who have a 30% 10-year overall survival rate by LT (Fig. 2). There is currently no perfect criteria that will select these patients beyond the criteria with longer survival by liver transplantation, and there will never be one. Because HCC is a highly heterogeneous tumor, and no single criteria can be applied to all HCC patients. "One size does not fit all" principle applies to HCC.

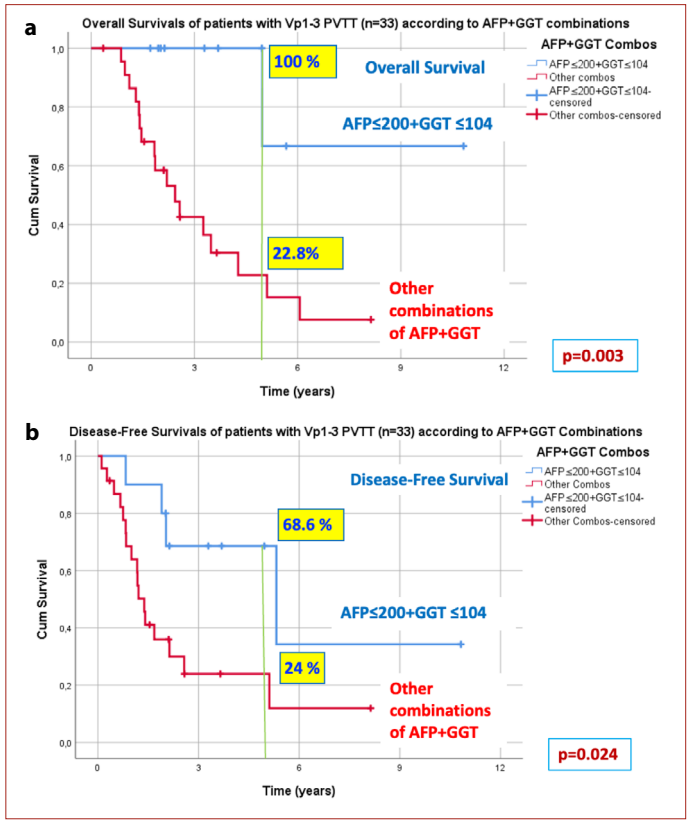

Figure 3. (a) Overall survivals of patients with Vp1-3 macro-PVTT according to AFP+GGT combinations. **(b)** Disease-free survivals of patients with Vp1-3 macro-PVTT according to AFP+GGT combinations.

However, living donor liver transplantation may allow us to push and even expand these limits. Because there is no competition for organs in LDLT, the rights of other patients on the cadaveric waiting list are protected, and it has the potential to provide an unlimited organ source. The expanded criteria above have been developed based on the outcomes of LDLT centers, and macroscopic PVTT is no longer an absolute contraindication. Therefore, this figure should be updated for LDLT. The transplantable window should also cover a subset of cancer patients beyond the criteria (Fig. 4b). It is important to note that patients who do not meet the established criteria have a 30% ten-year survival rate. The assessment of these patients' eligibility for liver transplantation should be conducted by multidisciplinary tumor boards, with careful consideration of individual patient and tumor characteristics.

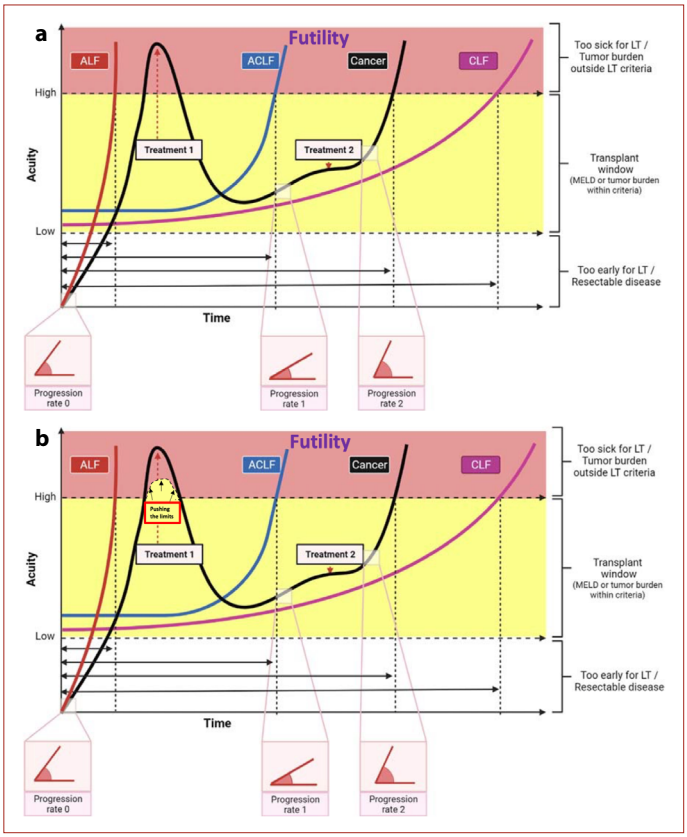

Figure 4. (a) The oncological acuity, organ allocation, and patient prioritization across various etiologies. Transplantable window is yellow area. **(b)** The oncological acuity, organ allocation, and patient prioritization across various etiologies. Updated Transplantable window is yellow area, in the LDLT era for cancer patients.

Salvage LDLT for Best Supportive Care Patients with Advanced HCC

Patients with advanced HCC and liver decompensation are classified as Stage D according to BCLC staging, and for these patients, only best supportive care is recommended because their impaired liver function does not allow downstaging procedures.

Patients with BCLC stage D have a median survival of three months. Young patients with decompensated cirrhosis and portal vein tumor thrombus often cannot receive LRT or systemic therapy due to poor liver function and typically receive only palliative care.

We conducted a retrospective study[44] to determine whether LDLT could benefit these patients by improving liver function (salvage LDLT=sLDLT). If tumor recurrence occurs after transplantation, preserved liver function enables further treatment—such as surgery, LRT, or systemic therapy—potentially leading to longer survival and improved quality of life.

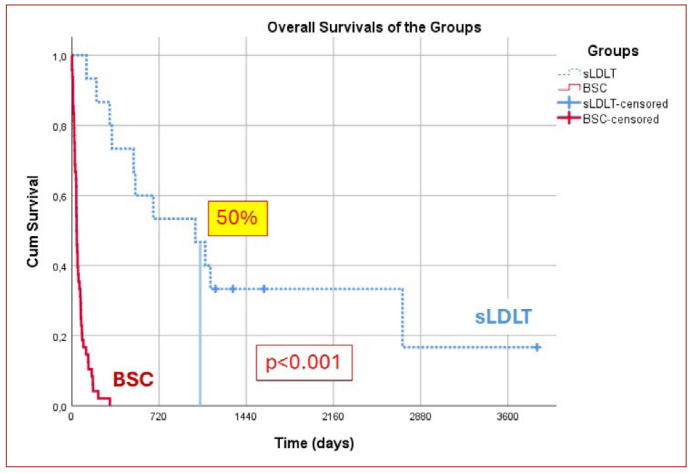

Figure 5. Overall survivals of the sLDLT vs BSC groups.

In this study, a 50% 3-year overall survival rate was observed following liver transplantation in patients aged 18 to 65 with CHILD class C, beyond expanded Malatya criteria, and without extrahepatic spread (Salvage LDLT Group n=17). For the BSC group (n=48), the median survival was 40 days. A 50% 3-year survival rate with LDLT, compared to a 40-day survival rate with BSC, is a remarkable result (Fig. 5).[44] Ongoing developments in systemic treatments may extend these survival rates.

In Conclusion, in the LDLT era, LT margins may need to be wider, but live donor hepatectomy complications should remain acceptable.

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Review

Integration of Comprehensive Genomic Profiling into Clinical Settings for Gastrointestinal System Cancer Enhancing Diagnosis, Molecular Classification, and Therapeutic Precision

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Abstract

The advent of comprehensive genomic profiling (CGP) has revolutionized cancer diagnosis and personalized treatment and has become increasingly standard in oncology for advanced solid tumors. In gastrointestinal (GI) cancers, which include colorectal, gastric, pancreatic, esophageal, biliary tract cancers, and hepatocellular carcinomas, genomic insights have increasingly informed clinical decision-making. This review provides an overview of the current landscape of CGP integration into clinical practice for GI cancers, highlighting clinical applications, challenges, and future perspectives.

Keywords: Comprehensive genomic profiling, gastrointestinal cancers, liquid biopsy, molecular classification, precision medicine, targeted therapy

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Gastrointestinal cancers are among the leading causes of cancer-related morbidity and mortality globally. Traditional diagnostic approaches—relying on histopathology and imaging—fail to fully capture the molecular heterogeneity that influences tumor behavior and treatment response. The integration of comprehensive genomic profiling (CGP) via next-generation sequencing (NGS) and complementary techniques like immunohistochemistry (IHC) has transformed this landscape, enabling more precise tumor classification and personalized therap.[1]

In solid tumor analysis, CGP detects a broad spectrum of genetic alterations—including single nucleotide variants, insertions-deletions, copy number changes, gene fusions, and key signatures like microsatellite instability (MSI), tumor mutational burden (TMB), and homologous recombination deficiency (HRD). Liquid biopsy techniques, analyzing circulating tumor DNA (ctDNA), further enable non-invasive, real-time tumor profiling, monitoring resistance mechanisms, and detecting minimal residual disease.[2]

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By providing detailed molecular insights, CGP uncovers actionable mutations and molecular subtypes across GI cancers, thereby guiding targeted therapies and immunotherapies. Numerous studies report that molecular profiling identifies actionable mutations in over one-third of patients with solid tumors, leading to improved treatment outcomes and survival. Incorporating CGP and liquid biopsy into routine practice is now a pivotal step toward achieving true precision oncology, revolutionizing diagnosis, prognosis, and personalized management of GI cancers in many leading medical centers worldwide.[3,4]

Role of CGP in Colorectal Cancer Diagnosis, Classification and Managment

Vogelstein's multistep model of colorectal cancer (CRC) development elucidates how CRC evolves through a series of accumulating genetic alterations, transforming normal epithelium into invasive carcinoma.[5] This understanding of disease progression provides a crucial foundation for the therapeutic application of CGP. By identifying specific genetic mutations at various stages; such as APC, KRAS, BRAF, p53, or mismatch repair deficiencies, CGP enables clinicians to tailor targeted therapies and immunotherapies accordingly.

The model also helps in prognostication, as certain mutations like BRAF, TP53 or MSI status correlate with tumor aggressiveness, aiding risk stratification and treatment planning. Overall, integrating CGP into clinical practice based on the principles outlined by Vogelstein's model fosters personalized treatment approaches, improves outcomes, and guides the development of novel targeted interventions by highlighting critical molecular pathways involved in gastrointestinal cancers.[6]

The first predictive genomic biomarker incorporated into the standard of care for metastatic colorectal cancer (mCRC) was the KRAS gene; mutations in specific codons of KRAS were found to negate the effectiveness of anti-EGFR therapies such as cetuximab and panitumumab.[7] In addition to KRAS, the mutation statuses of NRAS and BRAF are also essential for guiding treatment decisions. Patients with wild-type (non-mutated) KRAS, NRAS and BRAF are considered suitable candidates for anti-EGFR therapies, as mutations in these genes confer resistance. However, additional resistance mechanisms—both primary (innate) and acquired—limit the benefits for many patients. Increasing evidence demonstrates that resistance arises from a complex network of molecular alterations that promote tumor growth independently of EGFR signaling. These include amplification of ERBB2 (HER2) and MET, activation of the PI3K and AKT pathways, extracellular domain mutations of EGFR, and rare kinase fusions. Moreover, the BRAF V600E mutation is associated with a poorer prognosis and often necessitates combination therapies or alternative treatment strategies to improve outcomes.[8, 9]

NCCN recommends testing for RET and NTRK1, 2, and 3 translocations; ERBB2 (HER2) amplification; as well as PIK-3CA, BRAF V600E, and KRAS G12C mutations. Additionally, testing for microsatellite instability-high (MSI-H), tumor mutational burden-high (TMB-H), POLE, and POLD mutations is advised in patients with colorectal cancer.[10]

Circulating tumor DNA (ctDNA) testing has emerged as a revolutionary tool in the personalized management of colorectal cancer (CRC), offering a minimally invasive method to access tumor-specific genetic information through a simple blood draw.[11]

ctDNA testing can be broadly categorized into tumor-informed and tumor-agnostic approaches. This approach involves first performing comprehensive genomic profiling of the patient's tumor tissue to identify specific tumor mutations, structural variants, or alterations. Subsequently, personalized assays are designed targeting these known mutations to detect ctDNA in the patient's blood.[12]

Although still investigational, ctDNA has potential in screening high-risk populations for early detection of CRC. It can identify tumor-derived mutations before clinical symptoms or radiological evidence emerge, potentially enabling earlier intervention and improving outcomes.[13]

Monitoring ctDNA levels during therapy provides a dynamic measure of tumor burden. Decreasing ctDNA correlates with response, while rising levels may indicate treatment failure or progression, often before imaging detects changes. This real-time feedback allows for more timely adjustments to therapy.[14]

Postoperative ctDNA analysis can identify residual microscopic disease that may not be visible on imaging. The presence of ctDNA after surgical resection signifies a higher risk of recurrence, supporting decisions for adjuvant chemotherapy. Several studies have shown that ctDNA positivity post-surgery predicts relapse with high sensitivity and specificity.[15, 16]

During targeted treatments—for example, anti-EGFR therapy—ctDNA can detect emergent mutations (such as RAS or BRAF mutations) associated with resistance. Early detection of these mutations enables clinicians to modify treatment strategies before clinical progression occurs.[14, 16] Regular ctDNA testing during follow-up can detect molecular signs of recurrence months before radiological evidence appears, allowing for earlier intervention and potentially improved survival.[17]

In summary, ctDNA testing enhances the precision of CRC management by providing real-time, minimally invasive insights into tumor dynamics, resistance mechanisms, and residual disease. Its integration into clinical practice supports personalized treatment, timely decision-making, and improved patient outcomes.

Role of CGP in Gastric Cancer Diagnosis, Classification and Managment

Gastric cancer exhibits substantial molecular heterogeneity, which has important implications for prognosis and treatment. Different molecular subtypes demonstrate diverse genetic alterations, signaling pathway activations, and clinical behaviors.

Recent advances have led to the development of molecular classification systems based on genomic alterations identified through next generation sequencing (NGS) of gastric cancer samples. Notable among these are The Cancer Genome Atlas (TCGA) and Asian Cancer Research Group (ACRG) classifications, which categorize gastric cancers into distinct molecular subtypes:

Chromosomal instability (CIN): Characterized by aneuploidy, amplifications of receptor tyrosine kinases (e.g., HER2, EGFR), and TP53 mutations. These tumors often present with intestinal histology and respond to targeted therapies against HER2 or EGFR.

Genomically stable (GS): Frequently associated with diffuse histology and mutations affecting cell adhesion, such as CDH1 and RHOA mutations. These tumors tend to be more aggressive and less amenable to targeted therapy.

MSI-high: Marked by microsatellite instability and mismatch repair deficiency. These tumors tend to have a high mutational burden and are more likely to respond to immunotherapy.

Epstein-Barr virus (EBV)-positive: Characterized by frequent PIK3CA mutations, amplification of immune-related genes, and PD-L1 overexpression. These tumors may also benefit from immunotherapy.[18-20]

CGP provides the molecular signatures necessary for this classification, informing prognosis and guiding personalized therapy. The molecular insights derived from CGP have paved the way for targeted therapies, transforming gastric cancer management:

HER2 Amplification: Approximately 15-20% of gastric cancers overexpress HER2. CGP identifies HER2 gene amplifications or mutations, directing the use of HER2-targeted agents like trastuzumab, pertuzumab, and trastuzumab emtansine, which improve survival in HER2-positive tumors.

PIK3CA Mutations: Common in EBV-positive tumors, these mutations may be targeted through PI3K inhibitors, though clinical efficacy is under ongoing investigation.

FGFR2 Amplification: Several gastric tumors exhibit FGFR2 gene amplification. FGFR inhibitors are being evaluated in clinical trials as targeted options for these tumors.

MET Pathway Alterations: Amplifications or overexpression of MET are other potential targets, with some MET inhibitors in clinical trials or limited clinical use.

MSI-High Tumors and Immunotherapy: Tumors with high microsatellite instability or high tumor mutational burden (TMB) identified through CGP are more responsive to immune checkpoint inhibitors like pembrolizumab and nivolumab.

Claudin 18.2 (CLDN18.2) is gaining attention as an emerging marker because of its selective expression in gastric cancer cells. Novel therapeutic agents targeting CLDN18.2, such as monoclonal antibodies and bispecific constructs, are under development and showing promising clinical activity.

Other Emerging Targets: CGP continues to reveal novel alterations such as mutations in ERBB2 (HER2), MET, and other signaling pathways, expanding the repertoire of actionable targets.[20, 21]

The Role of Comprehensive Genomic Profiling in Esophageal and Esophagogastric Junction Cancers Diagnosis, Classification and Managment

Esophageal and esophagogastric cancers present significant clinical challenges due to their aggressive nature and late-stage diagnosis, with limited effective treatment options for advanced disease. Recent advances in high-throughput genomic technologies have transformed our understanding of their biology, offering new avenues for personalized medicine. CGP provides an invaluable tool to dissect tumor heterogeneity, refine diagnosis, classify tumors at a molecular level, and uncover actionable targets, all geared toward improving clinical outcomes.

Distinguishing between esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) is crucial given their distinct clinical behaviors and therapeutic responses. CGP significantly improves diagnostic precision by revealing subtype-specific genetic signatures, especially in cases where histopathology is ambiguous or when metastatic lesions obscure primary classification. Next-generation sequencing (NGS) platforms analyze an extensive array of gene mutations, amplifications, deletions, and rearrangements, often uncovering clinically relevant alter-

ations that confirm or refine the diagnosis of esophageal cancer subtypes.[22, 23]

While traditional classifications relied primarily on histological features, CGP delineates esophageal tumors into biologically and therapeutically relevant molecular subgroups:

EAC: Characterized by a higher frequency of mutations in KRAS and ERBB2 (HER2) amplification, alongside alterations in RAS/MEK/MAPK and TGF-β signaling pathways. These genomic signatures support targeted therapy approaches, such as HER2 inhibitors, and provide prognostic insights.[22, 23]

ESCC: Demonstrates a distinctive landscape with frequent alterations in PI3K/AKT/mTOR, NOTCH1, PTEN, FGFR1, and KEAP1/NRF2, alongside aberrant cell cycle regulation. Hierarchical clustering based on copy number alterations (CNAs) further stratifies ESCC into molecular subgroups, which correlate with clinical outcomes and guide personalized treatment decision-making.[22, 23]

This detailed molecular taxonomy offers prognostic utility and helps identify patients who might benefit from emerging targeted and immune-based therapies. The power of CGP lies in uncovering actionable genetic alterations:

HER2 Amplification: Present in a subset of EACs, HER2 overexpression can be targeted with trastuzumab or pertuzumab, offering survival benefits.

FGFR Alterations: FGFR2 gene amplifications and fusions are emerging targets, with several FGFR inhibitors under clinical evaluation.

EGFR and PI3K/AKT/mTOR Pathways: Amplifications and mutations in these pathways suggest potential for targeted inhibition, with ongoing trials testing relevant agents.

Emerging Targets in Immunotherapy: Alterations such as high tumor mutational burden (TMB) and PD-L1 expression, identified via CGP, identify patients who may respond to immune checkpoint blockade. Although less common than in other cancers, these biomarkers are gaining relevance in esophageal cancer.

NCCN currently recommends immunohistochemistry (IHC) for CLDN18.2 and/or molecular testing for HER2/ERBB2 status, microsatellite instability (MSI) or mismatch repair (MMR) deficiency, programmed death ligand-1 (PD-L1) expression, tumor mutational burden-high (TMB-H), neurotrophic tropomyosin-related kinase (NTRK) gene fusions, rearranged during transfection (RET) gene fusions, and BRAF V600E mutations in the clinical management of advanced esophageal and esophagogastric junction (EGJ) cancers. When tissue samples are limited or when patients are unable to undergo a traditional biopsy, testing with a validated next-generation sequencing (NGS) assay—performed in a CLIA-certified laboratory—may be considered to provide comprehensive molecular profiling. This approach allows for molecular insights that can guide targeted therapies and immunotherapy choices, especially in cases where obtaining sufficient tissue is challenging.[24]

As ongoing research continues to uncover novel targets and develop tailored therapies, integrating CGP into clinical practice will be pivotal in transforming esophageal cancer from a largely incurable disease to one amenable to precision medicine.

Role of CGP in Hepatocellular Carcinoma Diagnosis, Classification and Managment

Hepatocellular carcinoma (HCC) is characterized by diverse molecular alterations, including activation of oncogenic signaling pathways such as Wnt-TGFβ, PI3K-AKT-mTOR, RAS-MAPK, MET, IGF, and Wnt-β-catenin. Additionally, mutations in TP53 and the TERT promoter are commonly observed.[25]

Despite this molecular complexity, targeted therapies with proven differential benefit for specific molecularly defined HCC subgroups have yet to be developed or approved. Although numerous targetable genetic alterations have been identified in HCC patient samples, their overall prevalence remains relatively low compared to other cancers. While detecting these mutations can inform and guide targeted treatment strategies, their limited frequency means only a subset of HCC patients are likely to benefit from such therapies.[26]

While biomarkers like MSI, TMB, and HRD are important in cancer immunotherapy broadly, their roles in HCC are limited due to low prevalence, lack of standardized thresholds, and inconsistent predictive value. Notably, the emerging role of liquid biopsy—particularly circulating tumor DNA (ctDNA)—offers promising implications for early detection of hepatocellular carcinoma, especially in high-risk populations such as cirrhotic patients. Additionally, liquid biopsy techniques are showing potential in the early detection of recurrence post-liver transplantation, enabling minimally invasive, real-time monitoring of tumor dynamics and residual disease that may not be captured through conventional imaging. These innovations could revolutionize surveillance strategies, allowing for timely intervention and personalized management.[25,27]

According to recent NCCN guidelines, there is no established indication for routine molecular profiling in all HCC cases; however, it should be considered on a case-by-case basis. Clinical trials exploring molecular profiling and targeted therapies are strongly encouraged for this patient

population. Tumor molecular testing may be warranted in cases with atypical histology, combined hepatocellular-cholangiocarcinoma (cHCC-CCA), unusual clinical presentations, or when enrolling in clinical trials.[28]

The Role of Comprehensive Genomic Profiling in Biliary Tract Cancer: Diagnosis, Molecular Classification, and Targeted Therapy

Biliary tract cancers (BTCs) represent a spectrum of malignancies arising from epithelial cells of the bile ducts, including cholangiocarcinoma (CCA) arising in the intrahepatic, perihilar or distal biliary tree, and gallbladder carcinoma. CGP is transforming the diagnosis, molecular classification, and targeted therapy of BTCs, including intrahepatic and extrahepatic cholangiocarcinoma as well as gallbladder cancer.

BTCs are rich in clinically actionable molecular alterations and CGP enables identification of specific genomic mutations and fusions (such as FGFR2, IDH1/2, ERBB2/HER2, BRAF, and KRAS), improving the accuracy of diagnosis and detection of rare but actionable alterations in BTC.[29] This molecular insight complements histologic and radiologic findings, especially in cases with ambiguous pathology or atypical clinical presentations. Approximately 40% of BTCs harbor potential druggable genetic alterations. For this reason, molecular analysis should be carried out before or during first-line treatment to timely establish the best therapeutic option for second or subsequent lines.[30]

The NCCN recommends biomarker testing in BTCs, including CGP with broad gene panels to identify actionable alterations such as IDH1/2, FGFR2, BRAF, HER2, MSI status, and tumor mutational burden (TMB). Testing is particularly advised for patients with unresectable, locally advanced, or metastatic disease to inform targeted therapy options and clinical trial enrollment.[31]

Because BTCs demonstrate high inter- and intra-tumoral heterogeneity with respect to tumor stroma content, appropriate FFPE block selection under the microscope is critical for reliable NGS analysis.[32] If a FFPE sample does not meet quality requirements for NGS, a tissue re-biopsy is recommended; if this is not feasible, then liquid biopsy–based NGS is recommended (Table 1).[31]

The Role of Comprehensive Genomic Profiling in Pancreatic Cancer: Diagnosis, Molecular Classification, and Targeted Therapy

Pancreatic cancer, especially pancreatic ductal adenocarcinoma (PDAC), is characterized by remarkable molecular heterogeneity that influences tumor progression, treatment response, and patient outcomes. Approximately 90% of PDAC cases harbor mutations in key driver genes, including KRAS, TP53, SMAD4, and CDKN2A. Although

Table 1. NCCN-recommended genes, incidence of therapeutic targets and targeted therapies in advanced biliary tract cancers

Recommended Molecular Testing	Anatomic Subsite				
	Frequency	Targeted Therapy	Gallbladder	Intrahepatic CCA	Extrahepatic CCA
NTRK gene fusion	X	X	X	<1%	Entrectinib, Larotrectinib, Repotrectinib
MSI-H/dMMR	X	X	X	1%–3%	Pembrolizumab
TMB-H	X	X	X	<5%	Nivolumab + Ipilimumab
BRAF V600E mutation	X	X	X	1%–5%	Dabrafenib + Trametinib
FGFR2 fusion or rearrangement	-	X	X	9%–15% of intrahepatic CCAs and rare in other subsites	Futibatinib, Pemigatinib Erdafitinib
IDH1 Mutation	-	X	X	10%–20% of intrahepatic CCAs and rare in other subsites	Ivosidenib
HER2 (ERBB2) overexpression and/or amplification	X	X	X	5%–20% of CCAs, 15%–30% of gallbladder cancer	Fam-trastuzumab deruxtecan-nxki Trastuzumab + pertuzumab Tucatinib + trastuzumab Zanidatamab-hrii
RET gene fusion	X	X	X	<1%	Pralsetinib Selpercatinib
KRAS G12C mutation	X	X	X	1%	Adagrasib

KRAS mutations are nearly ubiquitous and considered a hallmark of PDAC, alterations in TP53, SMAD4, and CDKN2A provide critical insights into tumor biology, aggressiveness, and prognosis.[33]

Currently, the standard-of-care approach for most patients with metastatic pancreatic cancer remains cytotoxic chemotherapy. However, for patients with metastatic pancreatic cancer, both germline and somatic sequencing should be performed in an expeditious manner as up to a quarter of patients with advanced pancreatic cancer might have a potentially actionable mutation and may be eligible for biomarker-directed therapies or clinical trials.[34,35]

Notably, it can identify rare but therapeutically relevant targets such as NTRK gene fusions, PIK3CA mutations, and microsatellite instability-high (MSI-H) status—findings that are increasingly pertinent for guiding targeted therapies or immunotherapy. For instance, tumors with MSI-H may respond favorably to immune checkpoint inhibitors, offering hope for a subset of patients. Furthermore, integrating CGP with other advanced diagnostic modalities, such as circulating tumor DNA (ctDNA) analysis, enhances early detection of tumor-derived genetic alterations, facilitates real-time monitoring of tumor burden, and provides insights into tumor evolution and resistance mechanisms over time.

Emerging molecular classifications of PDAC, derived from comprehensive genomic profiling (CGP) and transcriptomic data, have stratified tumors into distinct subtypes with important clinical implications:

Stable/KRAS-driven subtype: This is the predominant PDAC subtype, characterized by the presence of classic KRAS mutations, most commonly in codons G12D, G12V, and G12R. It generally exhibits relative genomic stability. Therapeutic options remain limited, except for the rare KRAS G12C mutation, which can be targeted with specific inhibitors. This subtype often displays a less invasive profile but has a variable prognosis.

Squamous or basal-like subtype: Marked by high rates of TP53 mutations and the loss of differentiation markers, this subtype is associated with aggressive tumor behavior, early metastasis, and poor survival outcomes. It aligns with features of epithelial-mesenchymal transition (EMT) and squamous differentiation, suggesting potential sensitivity to therapies targeting EMT pathways and basal-like features.

Immunogenic subtype: Defined by substantial immune cell infiltration, high tumor mutational burden (TMB), and in some cases, microsatellite instability-high (MSI-H), the immunogenic subtype exhibits the most promising therapeutic opportunities. These tumors may respond well to immune checkpoint inhibitors, highlighting the importance of molecular stratification for immunotherapy eligibility.

DNA damage repair deficient (DDR) subtype: This subtype includes tumors harboring deficiencies in homologous recombination repair mechanisms, often linked to mutations in BRCA1/2, PALB2, or other DNA repair genes. Such tumors tend to be more sensitive to platinum-based chemotherapy and PARP inhibitors, offering targeted options for this subgroup.

This molecular taxonomy aids in prognostic stratification and guides personalized therapy selection. However, the clinical implementation of these classifications is still evolving, with ongoing efforts to refine subtype definitions and integrate molecular profiles with treatment decision-making (Table 2).[36,37]

Table 2. Summary of NCCN-Recommended Genes, Diagnostic, and Molecular Testing for Gastrointestinal Cancers. Comprehensive genomic profiling tests

Type of GI Cancer	Genes to Test (according to NCCN)	Guideline-Required Tests	Recommended Tests
Colorectal Cancer	KRAS, NRAS, BRAF, MSI/MMR, HER2, PIK3CA, G12C, POLE, POLD	RAS (KRAS, NRAS) mutation testing before anti-EGFR therapy; MSI/MMR status; BRAF V600E	NGS panels covering RAS, BRAF, MSI, TMB, HER2; POLE/POLD mutation testing
Gastric Cancer	HER2, MSI, PD-L1, PIK3CA, TP53, FGFR2, ERBB2, CLDN18.2	HER2 testing (IHC/FISH); MSI testing; PD-L1 testing; PIK3CA mutations	NGS panels for MSI, TMB; HER2 amplification by FISH/IHC; PD-L1 expression
Pancreatic Cancer	BRCA1/2, KRAS, TP53, CDKN2A, MSI, NTRK, HER2	BRCA testing (for PARP inhibitors); MSI/MMR testing; NTRK fusion testing	Germline and somatic BRCA testing; NGS panels including MSI and NTRK
Esophageal Cancer	HER2, PD-L1, EGFR, MSI, TP53, CDKN2A	HER2 amplification; PD-L1 expression; MSI testing	IHC or FISH for HER2; MSI testing; NGS for PD-L1, EGFR mutations
Biliary Tract Cancer	IDH1/2, FGFR2, HER2, MSI, BRAF, KRAS, NTRK	IDH1/2 mutations; FGFR2 fusions; MSI status; HER2 amplification	NGS panels targeting FGFR, IDH, MSI; FISH/IHC for HER2
Hepatocellular Carcinoma	CTNNB1, TP53, TERT, MSI, NTRK, BRAF	TERT promoter mutations; MSI testing; NTRK fusion testing	NGS for TERT, TP53; MSI testing; NTRK fusion assays

Advancements in comprehensive genomic profiling (CGP) have profoundly transformed the landscape of gastrointestinal (GI) cancers, enabling more precise diagnosis, refined molecular classification, and tailored targeted therapies. Through detailed genomic and transcriptomic analysis, clinicians can now delineate distinct tumor subtypes with unique biological and clinical behaviors, guiding personalized treatment strategies that improve patient outcomes. The integration of CGP into routine clinical practice, supported by guidelines from organizations such as NCCN, facilitates identification of actionable mutations—such as HER2, FGFR2, IDH1/2, BRAF, and MSI-H—broadening therapeutic options beyond standard chemotherapies and embracing immunotherapy, targeted agents, and clinical trial inclusion.

Currently, certain cancers, such as HCCs, have limited applications for CGP. However, the landscape is evolving. In HCC, common mutations include TP53 and CTNNB1 (beta-catenin). Advances in targeted approaches, such as synthetic lethality strategies, may soon enable TP53 mutations to be exploited therapeutically—comparable to treatments targeting BRCA mutations. Additionally, oncogenic mutations like KRAS G12C, which can drive tumor growth, are increasingly recognized as potential therapeutic targets. As our understanding deepens and new targeted therapies emerge, CGP is expected to play a more significant role in the diagnosis and treatment planning of HCC, expanding its application in this challenging malignancy.

Despite these significant advances, challenges remain in fully translating molecular classifications into standard care, including issues related to tumor heterogeneity, sample availability, and evolving biomarker validation. Ongoing clinical trials and global sequencing initiatives continue to refine our understanding of disease subtypes, promising a future where molecular diagnostics are central to decision-making in GI oncology. Ultimately, harnessing CGP promises to not only improve survival rates but also herald an era of truly personalized medicine in the management of gastroenterological malignancies, transforming prognosis and quality of life for patients worldwide.

Disclosures

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Review

A to Z of Imaging Modalities for the Diagnosis and Quantification of Hepatic Steatosis

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Abstract

Steatotic liver disease (SLD), marked by triglyceride accumulation in over 5% of hepatocytes, affects around a quarter of the global population. A key subtype, Metabolic dysfunction-associated steatotic liver disease (MASLD), is closely associated with obesity, type 2 diabetes, and metabolic syndrome, with rising prevalence worldwide. MASLD can lead to severe hepatic complications such as cirrhosis, liver failure, and hepatocellular carcinoma if left untreated. While liver biopsy remains the diagnostic gold standard for assessing hepatic steatosis, its invasive nature and sampling variability underscore the need for reliable non-invasive alternatives. Advances in imaging have enabled the development of modalities such as ultrasonography (US), computed tomography, and magnetic resonance imaging (MRI) for non-invasive steatosis assessment. Conventional US, though widely used, is limited by observer dependency and poor sensitivity for detecting mild steatosis. Quantitative US techniques, particularly attenuation coefficient-based algorithms, have shown improved diagnostic accuracy. The controlled attenuation parameter, often used with transient elastography, offers quick and cost-effective assessment, albeit with reduced sensitivity in obese individuals and limited grading accuracy. CT enables steatosis evaluation via liver attenuation values and liver-spleen attenuation ratios. Dual-energy CT enhances tissue differentiation and correlates moderately well with magnetic resonance imaging proton density fat fraction (MRI-PDFF) and histopathology but is constrained by radiation exposure and limited sensitivity for mild steatosis. MRI techniques—especially PDFF-based imaging—provide superior accuracy and reproducibility in liver fat quantification. PDFF allows for non-invasive, radiation-free measurement across the full steatosis spectrum, with established diagnostic thresholds. Additionally, MR spectroscopy offers the most precise quantification but remains primarily research-based due to logistical constraints. In summary, non-invasive imaging modalities, particularly MRI-PDFF, are increasingly favored for diagnosing and monitoring hepatic steatosis. Future research should focus on optimizing and standardizing these techniques to enhance clinical integration and management of SLD.

Keywords: Steatosis, Liver, Ultrasonography, Computed tomography, Magnetic resonance imaging

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Steatotic liver disease, which is characterised by the accumulation of >5% triglycerides in hepatocytes, is a common liver disease affecting approximately 25% of the world's population.[1] This condition encompasses a wide range of conditions, from simple fatty liver disease (metabolic dysfunction-associated steatotic liver disease, MASLD) to alcoholic, drug-induced and monogenic disease-related hepatic steatosis and steatohepatitis, the latter of which is characterised by more severe inflammation and hepatocyte damage.[2] MASLD is strongly associated with obesity, type 2 diabetes and metabolic syndrome, and its prevalence is increasing worldwide.[3] If left untreated, MASLD can lead to serious liver-related complications such as cirrhosis, liver failure and hepatocellular carcinoma. Cirrhosis due to MASLD is

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the second most common reason for liver transplantation after hepatitis.[4] Therefore, early diagnosis and accurate quantification of hepatic steatosis are critical to preventing disease progression and determining appropriate treatment strategies.

A liver biopsy has long been considered the gold standard for diagnosing and grading hepatic steatosis. Histologically, the percentage of fat in hepatocytes is categorised as follows: <5% (normal); 5%–33% (mild); 34%–66% (moderate); and >66% (severe).[5] However, a biopsy is an invasive procedure with significant disadvantages, including sampling error, variability in interpretation, cost and morbidity.[6] Furthermore, the infrequent need for repeat biopsies to monitor treatment responses has increased the demand for non-invasive methods. In recent years, advances in imaging technologies have enabled the development of various methods for non-invasively detecting and quantifying hepatic steatosis. Table 1 summarizes the diagnostic features of hepatic steatosis across imaging modalities. This review aims to provide a comprehensive examination of the major imaging modalities used in the diagnosis and quantification of hepatic steatosis: ultrasound, computed tomography and magnetic resonance imaging. It discusses their respective advantages and limitations, as well as their clinical applications. It also discusses recent developments and future trends in this field.

Ultrasonography

Ultrasonography (US) is generally the primary imaging technique used to evaluate hepatic steatosis.[7] It is widely used because it is non-invasive, widely available and capable of real-time imaging, as well as being relatively low cost. Liver steatosis is graded on US based on liver echogenicity compared to surrounding organs (such as the kidneys or diaphragm) and the visibility of vascular structures. Mild (Grade 1): There is a slight increase in liver echogenicity and the vascular structures and diaphragm are still clearly visible. Moderate (Grade 2): A marked increase in liver echogenicity and slight obscuration of vascular structures and the diaphragm. Severe (Grade 3): A very marked increase in liver echogenicity; the vascular structures and diaphragm are barely or completely obscured.[8] Ultrasound (US) is effective in detecting moderate to severe fatty infiltration and may be suitable as a screening method for abnormal liver morphology.[9] However, conventional ultrasound has some limitations. These include a lack of interobserver and intraobserver reliability and reproducibility, subjective and operator-dependent inter-

Table 1. Comparison of imaging modalities for the detection and quantification of hepatic steatosis.[38,40-44]

Modality	Sub-techniques	Steatosis Threshold	Sensitivity (%)	Specificity (%)	Advantages	Limitations	Clinical Use
Conventional Ultrasound (B-mode US)	- B-mode - Echogenicity grading	Moderate–severe (≥30%). Mild (≥5%)	84–94 50–65	85–95 60–85	Widely available, inexpensive, bedside tool	Operator-dependent, limited accuracy in mild steatosis and obesity	First-line screening tool
Quantitative Ultrasound	-Attenuation coefficient based -Elastography	Mild (≥5%) Moderate–severe (≥15–30%)	80–90 92–97	80–92 85–95	Objective, quantifiable, improved reproducibility, simultaneous fibrosis evaluation	Requires compatible equipment and trained personnel	Diagnosis, staging, treatment monitoring
Controlled Attenuation Parameter (CAP)	-CAP via FibroScan -Elastography	Mild steatosis (≥5%)	70–89	80–95	Quantitative, rapid, simultaneous fibrosis evaluation	Decreased accuracy in obese or ascitic patients, limited spatial resolution	Screening, diagnosis, and longitudinal follow-up
Computed Tomography (CT)	- Non-contrast CT - Dual-energy CT	Moderate–severe (≥30%)	43–77	88–100	Rapid, objective attenuation (HU) measurement, often incidental	Ionizing radiation, poor sensitivity for mild steatosis	Opportunistic diagnosis during unrelated imaging
Magnetic Resonance Imaging (MRI)	- In-phase/Out-of-phase (Chemical shift) - PDFF (Proton Density Fat Fraction) - MR Spectroscopy (MRS) -MR Elastography	Mild (≥5%), All stages	PDFF: 90–98 MRS: 95–99	PDFF: 90–95 MRS: 90–98	Gold standard for noninvasive fat quantification; excellent for both steatosis and fibrosis assessment	High cost, limited availability, MRS requires expertise	Diagnostic reference standard, research and follow-up

pretation, low accuracy in detecting mild hepatic steatosis and an inability to quantify liver fat.[10]

Recently developed quantitative ultrasound-based imaging techniques show significant promise in transforming the qualitative assessment of hepatic steatosis with conventional ultrasound into objective, quantitative measurements.[11] This new technology is based on the premise that fatty liver disease may accelerate US energy loss, which is associated with increased sound attenuation. Among the various commercially available algorithms, attenuation coefficient (AC) algorithms are the most widely used.[12] This method has yielded good to excellent results in the detection and grading of hepatic steatosis.[13] Additionally, it can be used in conjunction with elastography to simultaneously assess fibrosis. In addition to having similar advantages to traditional US, they are less operator-dependent.[14] Nevertheless, the variability observed across different imaging platforms necessitates the use of vendor-specific cutoff thresholds for accurate fat quantification, which are still under refinement and standardization. Figures 1 shows examples of conventional grey-scale and quantitative US.

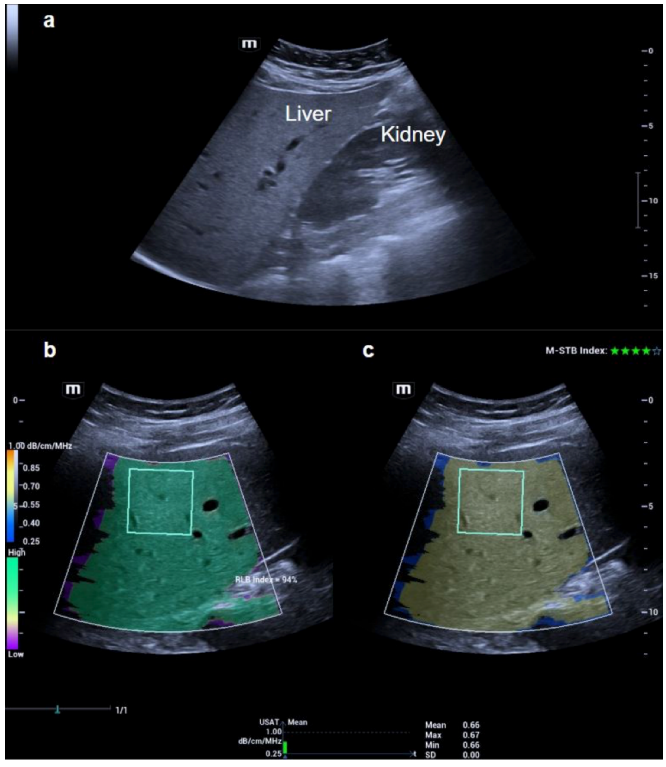

Figure 1. Conventional grayscale ultrasonography **(a)**, increased hepatic echogenicity relative to the renal cortex is observed. Despite this elevation, vascular structures within the liver and the posterior diaphragm remain clearly visualized, which is characteristic of Grade I hepatic steatosis. In quantitative ultrasonography, a reliability map is displayed alongside the B-mode image to evaluate the accuracy of measurements **(b)**. Green areas indicate regions where data was acquired optimally. An attenuation index is also displayed, with values exceeding 90% reliability being recommended for diagnostic confidence. Measurements are taken from the hepatic parenchyma using a region of interest measuring around 3 cm. In this case, the observed mean attenuation value of 0.66 dB/cm/MHz is consistent with Grade I hepatic steatosis **(c)**.

Controlled Attenuation Parameter

The Controlled Attenuation Parameter (CAP) is a widely used method for the rapid, non-invasive assessment of fatty liver that is also cost-effective. It can be used alongside transient elastography to measure fibrosis simultaneously.[15] CAP cut-off values vary between studies, with initial values between 219 and 248 dB/m generally indicating mild steatosis (S1).[16] However, its accuracy may be reduced in obese individuals. Furthermore, CAP is less sensitive than quantitative ultrasound (US) and magnetic resonance imaging (MRI) in detecting and classifying hepatic steatosis. Although current guidelines still recommend CAP, AC-based ultrasound and MRI-PDFF are increasingly favoured for diagnosing steatosis.[11]

Computed Tomography

The diagnosis of hepatic steatosis using computed tomography (CT) is based on the X-ray absorption properties of liver parenchyma. Fat has a lower density than water or tissue, and therefore appears less dense (in Hounsfield units, or HU) on CT images.[17] There are two main methods of estimating hepatic steatosis using CT: measuring liver attenuation alone, or comparing liver attenuation with spleen attenuation.[18] The attenuation of a healthy liver is generally 8–10 HU higher than that of the spleen, at around 50–57 HU. A liver HU value below 40 has been reported to indicate 30% steatosis. A liver-to-spleen HU ratio below 1.0 is another method of suggesting steatosis.[19,20] Figure 2a presents an example of a CT liver steatosis measurement. The linear relationship between HU units on CT and PDFF enables CT-based liver fat content to be expressed as the PDFF equivalent [PDFF(%) = -0.58 x (CT HU) + 38.2].[21] Dual-energy computed tomography (DECT) enables hepatic fat to be quantified by acquiring images at two different energy levels (typically 80 and 140 kVp), allowing tissue components to be distinguished based on their atomic number.[22] In cases of hepatic steatosis, DECT enhances fat detection by amplifying the contrast between lipid-rich and lipid-poor tissues, offering superior sensitivity compared to conventional single-energy CT.[23] Recent studies have found that DECT-derived fat quantification correlates moderately well with MRI-PDFF and histopathology.[24,25]

The main advantages of CT scanning are its widespread availability, short acquisition time and ability to rapidly assess the entire abdomen. CT has made one-stop assessment possible, integrating vascular, parenchymal, volume and steatosis assessment, particularly in the evaluation of liver transplant donors.[17] However, CT has several significant disadvantages when it comes to detecting fatty liver. The most notable of these is the use of ionising radiation, which is particularly concerning in the case of repeated scans or when scanning young patients. Furthermore, CT is less sensitive than more advanced methods (e.g. MRI-PDFF) for detecting mild steatosis; it may miss cases where the liver fat content is below 10–20%. HU values can also be affected by factors such as hepatic iron deposition, glycogen storage diseases or recent contrast medium administration, which makes it difficult to accurately quantify the amount of steatosis.[18]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is considered a superior method to ultrasonography and computed tomography (CT) for comprehensively assessing hepatic steatosis.[26,27] The ability of MRI to detect and quantify liver fat is based on the difference in resonance frequencies between hydrogen protons bound to water and triglycerides — a phenomenon known as the chemical shift effect. Some MRI techniques can calculate this frequency difference, which can also be directly observed in the spectrum with MR spectroscopy. Thus, the amount of liver fat can be reliably assessed.[28] The fact that MRI provides detailed data without the need for contrast material enables it to be used safely in children and patients with renal failure.[29] Furthermore, MRI elastography can provide a simultaneous assessment of fibrosis.

Chemical shift imaging (in-phase/opposed-phase MRI) is

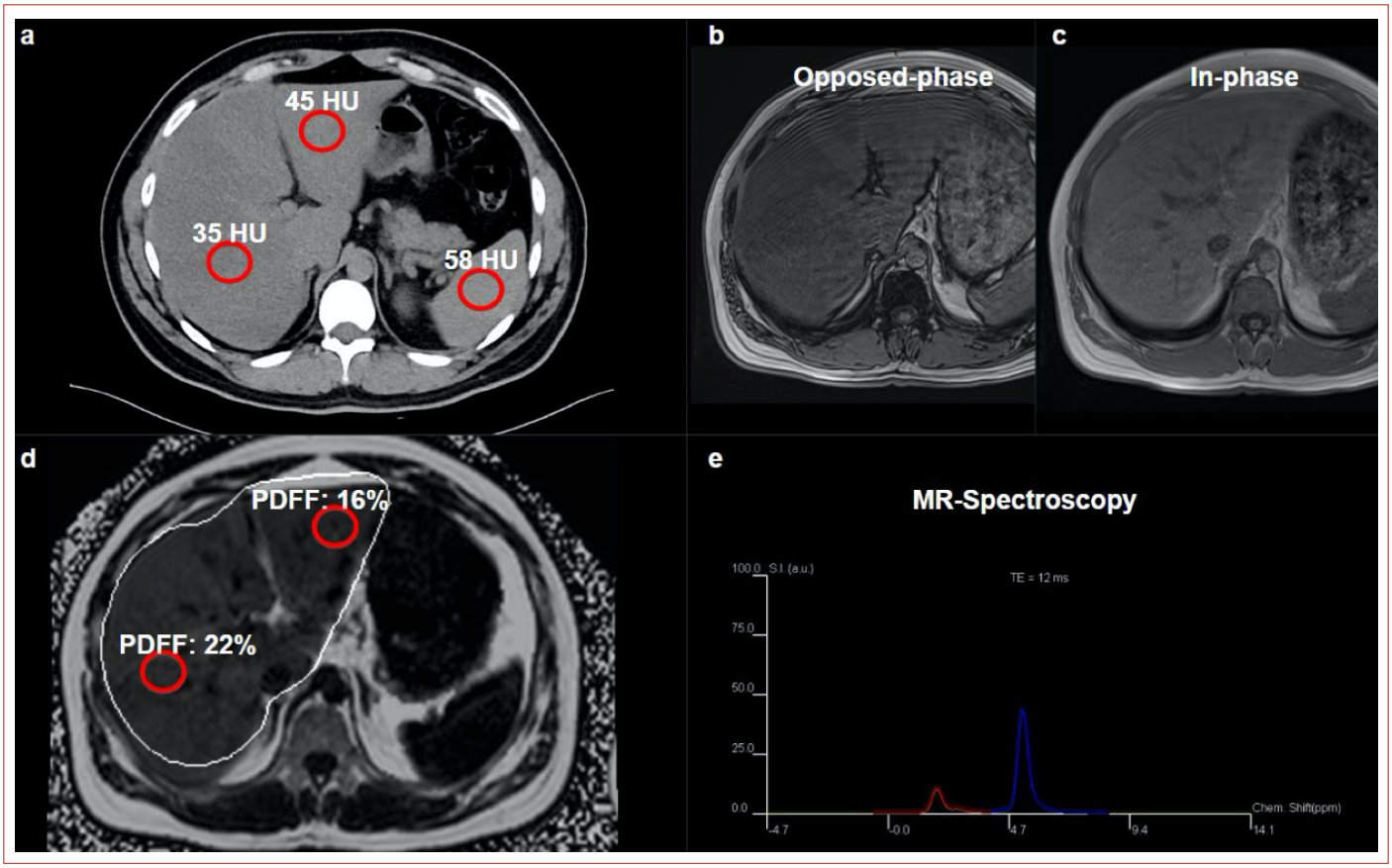

Figure 2. In a 42-year-old male living liver donor candidate, non-contrast computed tomography **(a)** demonstrates hepatic and splenic attenuation values, with lower Hounsfield Unit (HU) measurements in the liver compared to the spleen. Steatosis appears more pronounced in the right hepatic lobe. On magnetic resonance imaging, the opposed-phase images show a marked signal drop compared to in-phase sequences, supporting the visual, qualitative diagnosis of hepatic steatosis. On MRI-PDFF **(d)** images, quantitative fat fraction measurements are displayed for both hepatic lobes using regions of interest, revealing objective fat quantification. Additionally, magnetic resonance spectroscopy **(e)** demonstrates two prominent spectral peaks at 4.7 ppm (water) and 1.3 ppm (fat). The ratio of the signal intensities of the fat peaks to the sum of the fat and water peaks is used to calculate liver fat content. Based on the quantitative assessment, severe steatosis is identified in the right lobe, while the left lobe shows moderate steatosis.

based on the different resonance frequencies of hydrogen protons in water and fat molecules.[30] By using in-phase (IP, water + fat) and opposed-phase (OP, water – fat) sequences, it is possible to observe the tendency for signals from fat and water protons to either sum up or cancel each other out.[31] When there is little or no fat in the liver parenchyma, the signal intensity on in-phase and out-of-phase images is similar. However, when fat accumulates in the liver, the signal intensity decreases on out-of-phase images; this decrease is proportional to the degree of steatosis. A fat signal fraction image can be generated by combining IP and OP images (IP-OP/2IP).[32] Chemical shift imaging is widely used for the qualitative detection of macrovesicular steatosis, and its radiation-free nature and relatively short acquisition time make it valuable in clinical practice.[33] Figure 2b-c present an example of a IP/OP liver steatosis measurement.

Proton density fat fraction (PDFF), as measured by MRI, provides a quantitative and verifiable measure of liver steatosis and is considered the non-invasive gold standard due to its high correlation with histological fat content.[34] PDFF is obtained using multi-echo gradient echo (GRE) sequences. These sequences capture signals from fat and water at different echo times (TE) and use mathematical models to calculate the percentage fat fraction in the liver. Cut-off values for MRI PDFF liver steatosis grades are <6% for normal (S0), 6–17% for mild (S1), 17–22% for moderate (S2), and >22% for severe (S3) steatosis.[35] PDFF measurements provide high accuracy and reproducibility in fat quantification by correcting for the influence of other biological factors, such as iron accumulation, on the signal (T2* correction). This feature offers a significant advantage in the detection of mild steatosis and sensitive monitoring of treatment response, playing an increasingly important role in clinical research and individualised patient management.[36] Figure 2d presents an example of a MRI-PDFF liver steatosis measurement.

Magnetic resonance spectroscopy (MRS) is an MRI technique that provides highly accurate quantitative measurements of liver steatosis, but it is primarily used for research purposes in clinical practice.[37] By analysing the frequency spectrum of signals from a specific volume (voxel), MRS can quantify individual fat and water protons. This method provides an absolute percentage of fat content with a high level of accuracy and is more resistant to artefacts than other imaging technique.[38] However, MRS has several practical limitations, including long acquisition times, relatively small sample sizes and more complex data processing requirements. Due to these limitations, MRS is generally used as a reference tool for scientific studies and the validation of new imaging methods, rather than in clinical practice.[39] Figure 2e presents an example of a MRS liver steatosis measurement.

Conclusion

Hepatic steatosis is a growing global health problem that requires accurate, non-invasive diagnostic tools for early detection and monitoring. Although liver biopsy remains the reference standard, its invasiveness limits its widespread use. However, advances in imaging modalities, particularly quantitative AC-based US and MRI-PDFF techniques, have significantly improved the noninvasive assessment of liver fat content. MRI techniques offer the highest diagnostic accuracy among imaging modalities and are becoming increasingly important in clinical management. Future research should focus on optimising these methods for broader clinical integration and standardization.

Disclosures

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Review

Perioperative Medicine in Oncologic Hepato-Pancreato-Biliary Surgery – An Evidence- Based Narrative Review of Perioperative Concepts

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Abstract

Optimizing perioperative care in oncologic hepato-pancreato-biliary (HPB) surgery is critical to improving surgical outcomes and long-term prognosis. This narrative review provides a comprehensive synthesis of current concepts in perioperative medicine, including risk stratification, prehabilitation, enhanced recovery after surgery (ERAS) pathways, neoadjuvant therapy, and the management of procedure-specific complications in pancreatic and hepato- biliary surgery.

In pancreatic cancer surgery, advances in neoadjuvant strategies for borderline resectable disease, individualized antibiotic prophylaxis, and structured ERAS pathways have significantly influenced clinical outcomes. Similarly, in hepato-biliary surgery, neoadjuvant concepts are evolving for hepatocellular and cholangiocarcinoma, while prehabilitation and risk-based ERAS implementation are gaining importance. Special attention is given to complications such as postoperative pancreatic fistula, bile leakage, portal vein thrombosis, small-for-size syndrome, and liver failure.

Drainage strategies are discussed in light of recent guideline-based recommendations, emphasizing the importance of avoiding prophylactic drainage in uncomplicated liver and pancreatic resections. Novel concepts such as staged hepatectomy with ALPPS, combined vein embolization, and minimally invasive liver surgery, including robotic approaches, expand the surgical toolbox but demand strict patient selection and high expertise.

Taken together, perioperative care in HPB oncology is transitioning toward a multimodal, individualized approach. Future directions include the integration of precision medicine in surgical oncology and perioperative care into standard pathways to further reduce complication-related failure-to-rescue and improve oncological outcomes.

Keywords: HPB surgery, Neoadjuvant therapy, Oncologic surgery, Perioperative medicine, Prehabilitation, Preoperative optimization

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Oncologic hepato-pancreato-biliary (HPB) surgery comprises some of the most complex and high-risk procedures in surgical oncology. Patients undergoing liver, bile duct, pancreatic surgery or combined resections in the HPB system frequently present with advanced disease stages, impaired organ function, and systemic comorbidities. These characteristics, combined with the invasiveness of the surgical procedures themselves, render the periop-

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erative period particularly vulnerable to severe and potentially life-threatening complications. Despite centralization and improvements in surgical techniques, anesthetic and intensive care medicine, morbidity after major HPB procedures remains high.

The field of perioperative medicine aims to optimize the entire surgical pathway – before, during, and after the operation – through evidence-based interventions designed to reduce complication rates and improve short- as well as long-term outcomes. In the HPB setting, where postoperative liver failure, pancreatic fistula, cholangitis, bile leaks, and hemorrhage may lead to life-threatening complications, a structured, multidisciplinary perioperative strategy implemented in experienced high-volume centers is essential to minimize major morbidity and reduce failure-to-rescue rates.[1–4] This includes precise patient selection, individualized risk stratification, and targeted prehabilitation as well as tailored intraoperative techniques and postoperative complication management. Thereby, perioperative medicine in HPB oncology should be understood as a dynamic, evidence-based framework that integrates surgical, anesthetic, oncologic, infectious disease, and interventional perspectives. Its goal is not only to improve recovery from major resection but also to facilitate access to curative therapies and improve long-term survival.

Over the past decade, the concept of perioperative medicine has evolved beyond anesthesiology and is increasingly recognized as a multidisciplinary responsibility. Particularly in HPB oncology, recent years have seen growing evidence supporting the use of structured preoperative conditioning ("prehabilitation"), neoadjuvant or induction and conversion therapies, selective use of drainage procedures, and patient-specific antimicrobial prophylaxis [4–6]. These interventions not only reduce surgical risk but may also improve oncologic outcomes by faster recovery and consecutively avoiding delays in adjuvant or additive oncologic treatment protocols, reducing recurrence, or enabling secondary resectability.

Preoperative optimization encompasses several domains: nutritional and functional conditioning; management of jaundice, cholangitis, and biliary drainage; tailored antibiotic prophylaxis; and, in select cases, augmentation of liver volume to avoid small-for-size syndrome and postoperative liver insufficiency. Each component requires careful balance between oncologic urgency and physiological stabilization. In patients with borderline resectable tumors, neoadjuvant chemotherapy or chemoradiotherapy is increasingly used to improve R0 resection rates and reduce systemic dissemination. At the same time, minimally invasive techniques, including robotic surgery, are being integrated into HPB practice with the goal of reducing surgical trauma and accelerating recovery.

A major challenge in the implementation of perioperative strategies lies in the heterogeneity of disease patterns and treatment algorithms across the hepato-biliary and pancreatic spectrum. This review narratively summarizes the current evidence and emerging concepts in perioperative medicine for oncologic HPB surgery. The review is organized by organ system and follows the patient pathway: from neoadjuvant therapy and preoperative optimization, through intraoperative considerations, to postoperative (complication) management (Table 1 illustrates common post-pancreatectomy and post-hepatectomy specific complications). In the hepato-biliary section, key focus areas include neoadjuvant approaches in hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCC), management of malignant biliary obstruction, drainage strategies, antibiotic treatment, and techniques to avoid small-for-size syndrome. In the pancreatic section, we address neoadjuvant therapy in borderline resectable pancreatic cancer, prehabilitation, the role of biliary drainage, antimicrobial prophylaxis, drain management, and post-pancreatectomy specific complications.

Evidence in Perioperative Medicine of Pancreatic Surgery

Neoadjuvant Concepts Against Pancreatic Carcinoma

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most aggressive malignancies in gastrointestinal oncology and contribute significantly to the population-based cancer burden. In 2022, the incidence in Germany alone was over 18,000 new cases.[5] The mortality in the same year was around 19,000, underlining the aggressive nature of PDAC.[5]

Most patients present at advanced stages, and the five-year survival rate remains dismal. Curative treatment requires complete surgical resection with tumor-free margins (R0 resection), meaning that the tumor-free surgical margin is at least at 1 mm.[6] Formal resections are intended to achieve this including partial pancreaticoduodenectomy, distal pancreatectomy or total pancreatectomy. However, whether these standard procedures should be expanded by more radical surgical concepts – such as the TRIANGLE operation or anterior/ posterior RAMPS (radical antegrade modular pancreatosplenectomy) in left-sided tumors (depicted in Fig. 1) – is currently under investigation in ongoing clinical trials. Nevertheless, surgical resection is usually followed by adjuvant chemotherapy.[7]

Standard therapy naturally depends on the location and lo-

Table 1. Specific complications in hepato-pancreato-biliary surgery

	Complication	Grade A	Grade B	Grade C
ISGPS	**Postoperative pancreatic fistula**			
	Increased amylase activity >3 times upper limit institutional normal serum value	Biochemical leak without clinical consequence	Clinically relevant change in management, drainage >3 weeks, intervention without surgery	Clinically relevant change in management of POPF with angiographic procedures for POPF- related bleeding, signs of POPF- related infection with organ failure, POPF-related reoperation, POPF-related death
	Delayed gastric emptying with			
	Nasogastric tube needed	4-7 d or reinsertion after POD 3	8-14 d or reinsertion after POD 7	>14 d or reinsertion after POD 14
	Post-pancreatectomy hemorrhage			
	Time of onset, location, severity and clinical impact of bleeding	Early (≤24 hours after the surgery), intra- or extraluminal, mild	Early, intra- or extraluminal, severe or Later (>24 hours after the surgery), intra- or extraluminal, mild	Late, intra- or extraluminal, severe
	Clinical condition	Well	Often well/intermediate, very rarely life-threatening	Severely impaired, life-threatening
	Diagnostic consequence	Observation, blood count, US and, if necessary, CT	Observation, blood count, US, CT, angiography, endoscopy	CT, angiography, endoscopy
	Therapeutic consequence	No	Transfusion of blood, intermediate care unit, therapeutic endoscopy, embolization, relaparotomy for early PPH	Localization of bleeding, angiography and embolization, endoscopy or relaparotomy, ICU
	Post-pancreatectomy acute pancreatitis			
	Elevated serum amylase levels	Elevated serum amylase levels for at least 48 hours without clinical impact or changes in management	Clinically relevant changes in patient management	Severe, life-threatening complications, organ failure for at least 48 hours, intensive care, reoperation, or death
ISGPS / ISGLS	**Biliary leakage**			
	Increased bilirubin concentration (>3 times upper than serum bilirubin) in intraabdominal fluid or drain fluid on/after POD 3	No changes in clinical management	Diagnostic or interventional procedures required	Reoperation for biliary peritonitis or failure
ISGLS	**Post-hepatectomy hemorrhage**			
	Postoperative reduction of haemoglobin level > 3 g/dl compared to baseline and/or necessity for PRBCs and/or necessity for invasive re- intervention (e.g. embolization, re-laparotomy)	Hb drop >3g/dl and/or ≤2 PRBCs, no intervention	Require for transfusion > 2 units of PRBCs	Require for radiological interventional treatment or relaparotomy
	Post-hepatectomy liver failure			
	Postoperative deterioration of liver function, e.g. increased INR, hyperbilirubinemia on or after POD 5 and/or neurological symptoms.	Abnormal liver function without changes in clinical management	Abnormal liver function with changes in clinical management but no invasive treatment	Invasive treatment required, incl. ICU or death

This table summarizes the clinical definitions, grading systems, and management strategies for major postoperative complications relevant to pancreatic and liver surgery. Complications are listed in procedural order from pancreatic fistula to liver failure. Definitions are based on consensus statements and relevant guideline criteria from the International Study group of Pancreatic Surgery (ISGPS) and International Study group of Liver Surgery (ISGLS).[131–137] Management approaches are stratified by severity and include interventional, medical, and surgical options. ICU = Intensive care unit, PRBC = Packed red blood cells, POD = Postoperative day.

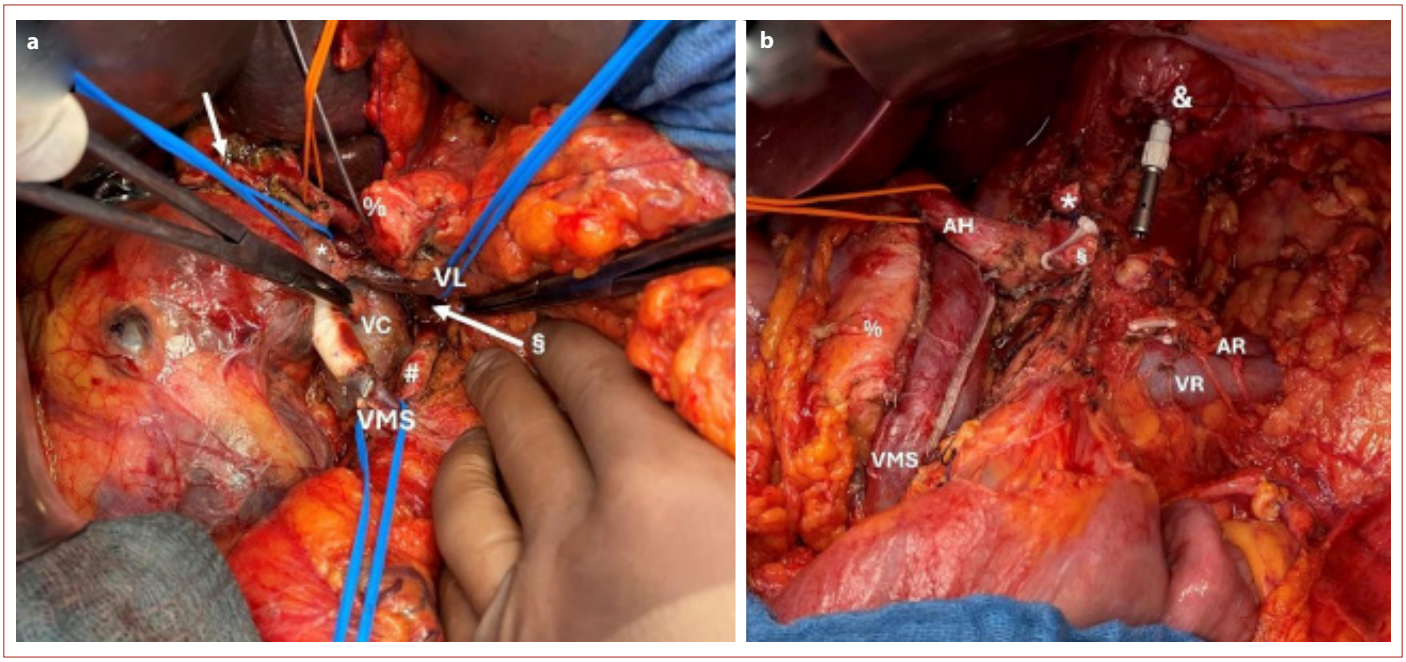

Figure 1. Intraoperative View of Advanced Pancreatic Resections: Triangle Dissection and Posterior RAMPS.

(a) Intraoperative situs following partial pancreatoduodenectomy (Whipple) with completed triangle dissection. The clip (⟶) closes the transected, dilated common bile duct (DHC). The probe (%) identifies a narrow pancreatic duct. The proper hepatic artery (AH) is looped with a red vessel loop. A venous interposition graft connects the superior mesenteric vein (VMS) and portal vein (*). The "triangle" between the superior mesenteric artery (#), celiac trunk (§⟶), and portal vein has been fully dissected. VC = vena cava; blue loops mark the portal vein (*), superior mesenteric vein (VMS), and reimplanted splenic vein (VL). **(b)** Intraoperative situs after extended left-sided pancreatic resection for pancreatic body cancer (posterior RAMPS: radical antegrade modular pancreatosplenectomy). Multivisceral resection including subtotal proximal gastrectomy (anvil of stapler inserted into esophageal stump [&]), left adrenalectomy, and left colonic flexure resection. The staple line (%) indicates the pancreatic transection margin. The splenic vein is stapled at the superior mesenteric vein (VMS). The splenic artery (§) and left gastric artery (*) are transected at the celiac trunk. Dissection includes the left adrenal gland and perirenal fat with identification of left renal vein (VR) and artery (AR). Due to tumor infiltration, the transverse mesocolon and left colonic flexure were resected en-bloc.

cal extend of the tumor, the presence of metastases, and the tumor's involvement in major blood vessels. In patients with resectable tumors, neoadjuvant therapy has not demonstrated a consistent survival benefit and is therefore not routinely recommended by guidelines.[7] A recent meta-analysis confirmed that overall survival of patients with resectable pancreatic cancer who received neoadjuvant therapy are similar to those of patients who underwent upfront surgery.[8,9] Accordingly, neither the "local" German guideline for exocrine pancreatic cancer nor the international NICE guideline recommend chemotherapy, radiotherapy, or chemoradiotherapy for patients with pancreatic cancer assessed as resectable.[7,10]

Criteria for different treatment modalities and resecatbility of PDAC have been clearly defined by multiple international societies, including the National Comprehensive Cancer Network (NCCN), the European Society For Medical Oncology (ESMO), and the International Association of Pancreatology (IAP)[11–13] (Fig. 2). These classifications integrate anatomical, oncological, biological, and functional parameters to guide individualized treatment decisions.

- Anatomical criteria are based on the extent of tumor contact with surrounding vessels – particularly the portomesenteric venous axis and the superior mesenteric artery – and are used to define tumors as resectable, borderline resectable, or locally advanced. Absence of vessel contact defines a resectable tumor, while limited abutment or encasement of venous structures (with reconstructability) or ≤180° contact with the superior mesenteric artery (SMA) may categorize a tumor as borderline resectable.

Unreconstructable venous occlusion or encasement of the SMA >180° indicates locally advanced, non-resectable disease.

- Oncological criteria include the presence or absence of distant metastases (e.g., hepatic, peritoneal, pulmonary), which preclude curative-intent surgery.
- Biological criteria, such as elevated CA 19-9 levels, may indicate occult metastatic disease or biologically aggressive tumor behavior and should be considered in the multidisciplinary assessment.

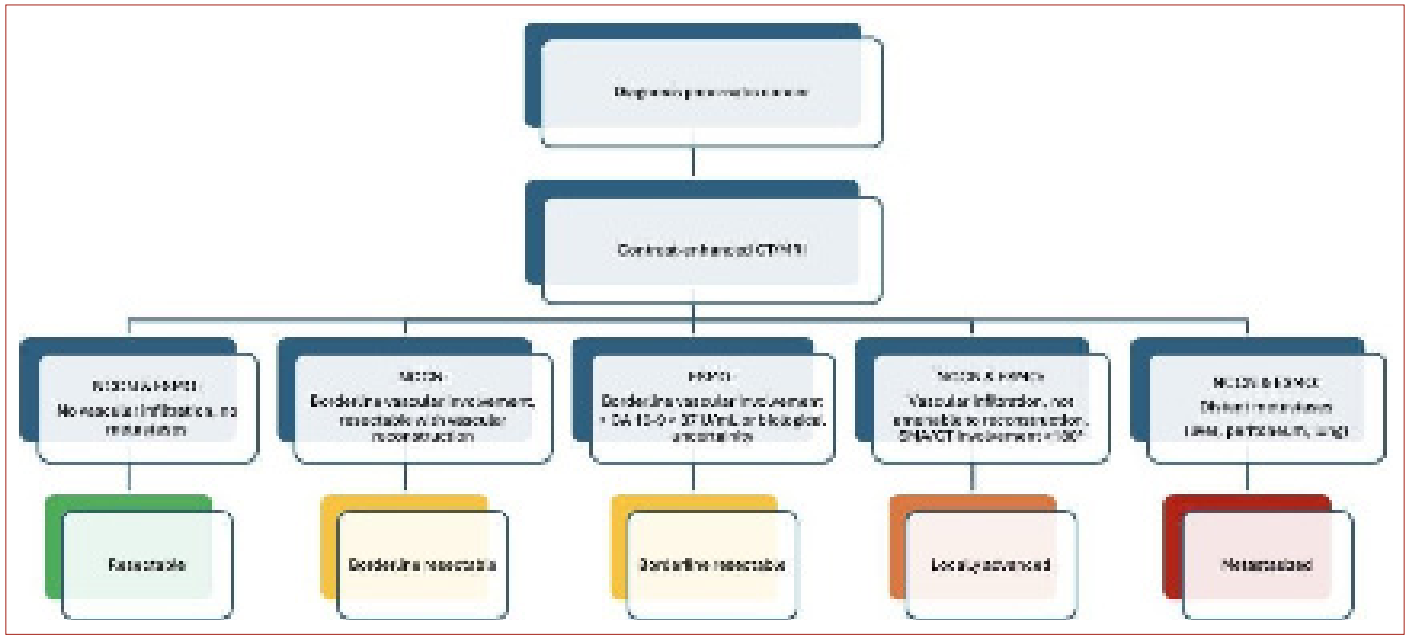

Figure 2. Resectability criteria for pancreatic cancer according to NCCN and ESMO guidelines.

This flowchart illustrates the resectability stratification of pancreatic cancer based on contrast- enhanced CT/MRI and guideline-specific criteria. Resectability is defined by the absence of vascular involvement or metastases. Borderline resectable tumors show limited vascular involvement, potentially resectable after vascular reconstruction (NCCN) or in the presence of biological uncertainty (ESMO). Locally advanced tumors involve major vessels beyond reconstructive options. Distant metastases define non-resectable, systemic disease. CT = Computed tomography, MRI = Magnetic resonance imaging, NCCN = National Comprehensive Cancer Network, ESMO = European Society For Medical Oncology, CA 19-9 = Carbohydrate Antigen 19-9, SMA = Superior mesenteric artery.[11,13]

- Functional or conditional status, commonly assessed via the Eastern Cooperative Oncology Group (ECOG) performance score, is also critical. An ECOG score <2 is generally required for major surgery and is predictive of postoperative recovery and long-term outcome.

In patients without distant metastases, clinical resectability is primarily determined by anatomical criteria, with localized tumors without vascular involvement considered resectable. In contrast, tumors with borderline anatomical involvement – for example, limited contact with the superior mesenteric vein, portal vein, or superior mesenteric artery – are classified as borderline resectable, provided that biological (e.g., CA 19-9) and functional (e.g., ECOG performance status <2) parameters are favourable. For many years, neoadjuvant therapy was offered only to "inoperable" patients, with locally advanced, technically unresectable tumor status.[14] However, its role has significantly expanded. In borderline resectable PDAC, defined by abutment or short-segment encasement of critical vasculature without frank unresectability, neoadjuvant treatment aims to: downstage tumor-vessel involvement, thereby facilitating technically feasible resection, increase the likelihood of R0 resection, and address occult micrometastatic disease early in the treatment course. Emerging evidence from recent trials and meta-analyses suggests that this strategy leads to improved margin-negative resection rates, lower rates of early recurrence, and potentially improved overall survival compared to upfront surgery.[7,15]

One of the earliest randomized trials from Korea in 2018 demonstrated a significant improvement in median overall survival (21 vs. 12 months; p=0.028) and R0 resection rates (51.8% vs. 26.1%) with gemcitabine-based perioperative chemoradiotherapy in 27 borderline resectable PDAC patients versus only adjuvant gemcitabine in 23 patients.[16] Similarly, the large multicentric PREOPANC trial from 2019 confirmed superior outcomes in patients with resectable and borderline resectable pancreatic cancer receiving gemcitabine-based neoadjuvant chemoradiotherapy. The neoadjuvant therapy group demonstrated significantly better outcomes in terms of overall survival (17.1 months vs. 13.5 months; p=0.047), R0 resection rate (65% vs. 31%; p=0.001), disease-free survival (12.1 months vs. 7.9 months; p=0.01), and time to distant metastasis (17.1 months vs. 10.2 months; p=0.012). Furthermore, in the subgroup of patients who ultimately underwent resection after neoadjuvant therapy, overall survival was markedly improved (29.9 months vs. 16.8 months; p=0.001).[17] In more recent studies, the survival benefit is becoming increasingly evident in patients with borderline resectable PDAC. As recently summarized in a meta-analysis, the survival benefits

are most pronounced in this subgroup.[9] Consequently, these data have influenced treatment algorithms in multidisciplinary tumor boards and are reflected in updated NCCN and ESMO guidelines.[11,13]

Preoperative Optimization

Risk Stratification

Although a large meta-analysis involving 49,449 patients found that patients aged <80 years compared to those aged ≥80 years are at higher risk for 30-day postoperative mortality (OR=2,22; 95 % CI 1,48-3,31, p<0,001) and for postoperative complications (OR 1,51 95 % CI 1,25-1,83, p<0,001),[18] but, age alone should not be considered a contraindication for major pancreatic surgery. Nevertheless, the complication profile in elderly patients – including higher incidences of respiratory complications and cardiac events contributing to prolonged hospital stay[18] – highlights the importance of performing a thorough preoperative risk assessment that considers comorbidities and the patient's overall condition. Therefore, the ECOG performance status, which stratifies patients into groups <2 and ≥2, can provide direct prognostic information regarding overall survival.[19]

In a consequence, the IAP recommends in their 2017 International Consensus on Definition and Criteria of Borderline Resectable Pancreatic Ductal Adenocarcinoma that resection should be performed in patients with an ECOG performance status of 0, 1, or 2 – provided the tumor is resectable. Patients with an ECOG performance status of ≥3 should not undergo resection.[20]

Preoperative Optimization, Prehabilitation and ERAS

Multiple measures – avoiding substance abuse, maintaining balanced diet, improving nutritional status, and enhancing physical activity – have shown benefits with regard to postoperative outcomes in patients who are scheduled to undergo major oncologic surgery.[21,22]

Nevertheless, there are no specific recommendations for multimodal prehabilitation in pancreatic surgery. However, prehabilitation during neoadjuvant therapy for PDAC offers a window of opportunity to enhance physical reserve and reduce complication risk.[12–14] The principle of (multimodal) prehabilitation concepts is depicted in Figure 3.

A randomized trial from 2023 has demonstrated that even mild-moderate exercise programs can significantly improve six-minute walk distance.[23] Otherwise, the current status of effective prehabilitation programs in pancreatic surgery remains limited, and robust evidence from randomized trials is scarce. Consequently, clear recommendations regarding comprehensive, resource-intensive, multimodal prehabilitation are currently lacking in existing guidelines.[24]

The ERAS society guidelines for pancreatic surgery from

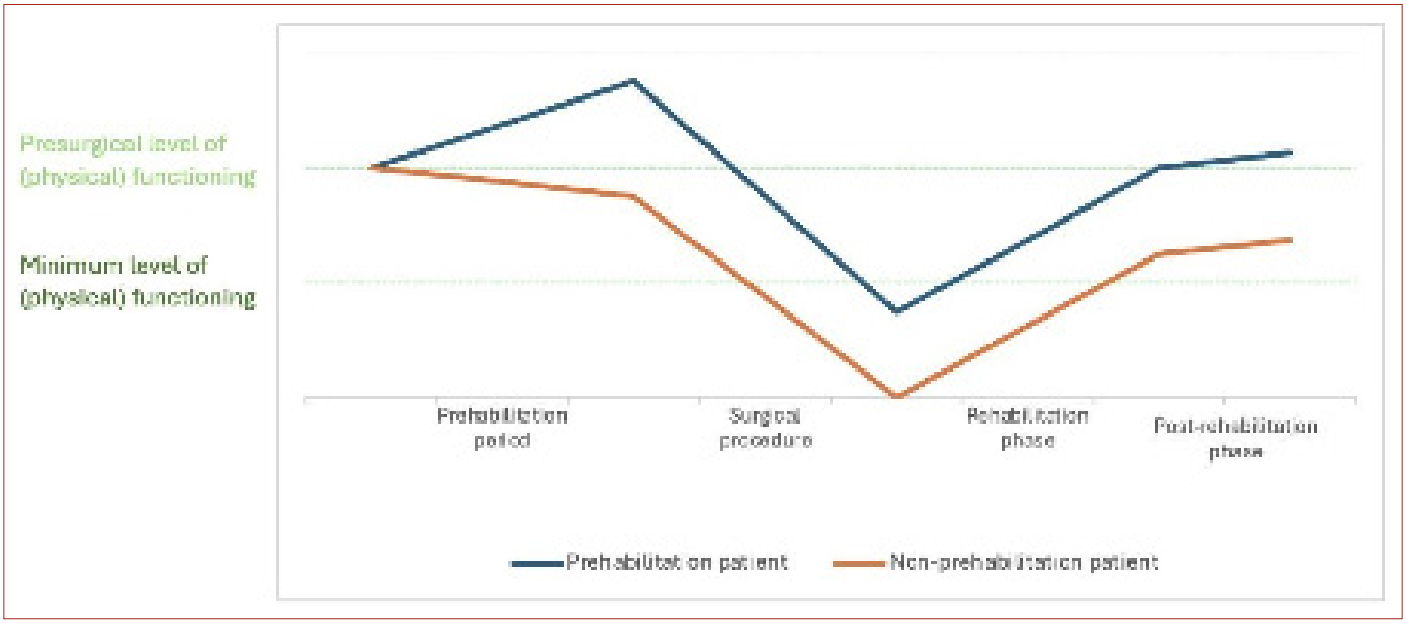

Figure 3. Concept of prehabilitation.

Functional recovery trajectory in prehabilitation vsersus non-prehabilitation patients. The graph illustrates the typical course of functional capacity in patients undergoing major surgery, comparing those who received prehabilitation (blue line) to those who did not (orange line). While both groups experience functional decline following surgery, prehabilitation patients enter the operation with a higher functional reserve and recover more rapidly, surpassing the minimum functional threshold earlier and approaching presurgical levels more consistently in the post-rehabilitation phase. Adapted from Banugo et al.[128]

2019,[25] furthermore, provide a structured framework for perioperative care, emphasizing multiple items that go in line with cornerstones of multimodal prehabilitation (Fig. 4):

- Smoking and alcohol cessation at least 4 weeks preoperatively
- Preoperative nutritional screening and supplementation in malnourished patients
- Encouragement of daily physical activity, including individualized exercise programs
- Patient education and counselling, including expectation management
- Avoidance of prolonged preoperative fasting and implementation of carbohydrate loading
- Standardized anesthesia and pain management protocols
- Early oral intake and early mobilization postoperatively

These ERAS (enhanced recovery after surgery) elements aim to reduce perioperative stress, preserve lean body mass, and improve functional recovery and overall morbidity profiles. Taken together, although robust evidence for pancreas-specific prehabilitation protocols is still emerging, the ERAS recommendations provide a structured, evidence-informed framework for perioperative care in pancreatic surgery. The integration of selected ERAS components offers a pragmatic opportunity to optimize patient condition both before and after pancreatic surgery.

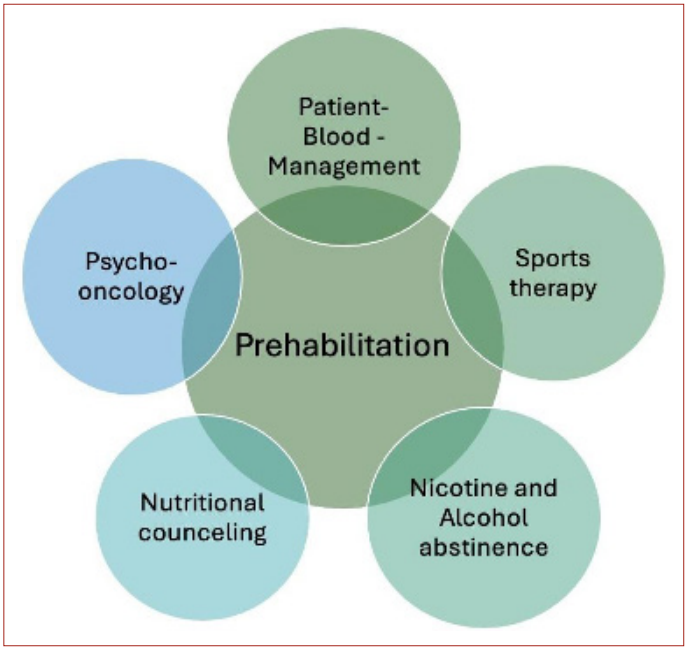

Figure 4. Core components of a multimodal prehabilitation program.

This schematic illustrates the multidimensional nature of modern prehabilitation in surgical oncology. Key components include sports therapy, nutritional counseling, nicotine and alcohol abstinence, psycho-oncologic support, and patient blood management. These interventions aim to optimize the patient's physiological and psychological status prior to major surgery and enhance postoperative recovery. Adapted from Flemming et al.[129]

Preoperative Biliary Drainage

Obstructive jaundice is a common clinical problem in patients with periampullary carcinoma including pancreatic head cancer, and may lead to cholangitis, liver dysfunction, or sepsis. In such scenarios, preoperative biliary drainage (PBD) becomes essential to stabilize the patient and ensure safe subsequent resection. Moreover, PBD is often required when neoadjuvant therapy is planned, as persistent cholestasis has been associated with increased toxicity and poorer treatment tolerance during systemic therapy.

The most commonly used technique for biliary decompression is endoscopic retrograde cholangio[pancreato]graphy (ERCP) with placement of either plastic or self-expanding metal stents. While widely available and effective in most patients, ERCP is associated with a significant risk of post-interventional infection due to retrograde contamination of the biliary tree, especially in the setting of stent occlusion or incomplete drainage.[26] Percutaneous transhepatic cholangiodrainage (PTCD) provides an alternative access route, particularly in patients with surgically altered anatomy, duodenal obstruction, or failed ERCP. Although more invasive, PTCD is associated with lower incidence of post-procedural infections and offers the advantage of external control and monitoring of bile.

Additional drainage strategies – such as endoscopic ultrasound-guided biliary drainage (EUS- BD), including choledochogastrostomy or choledochoduodenostomy, as well as surgical drainage via T-tube[27] – are increasingly applied in tertiary centers, particularly in anatomically challenging or complex cases.

The routine use of biliary drainage prior to surgery in asymptomatic patients remains controversial. The randomized multicenter DRAINAGE trial by van der Gaag et al.[26] demonstrated that routine ERCP with plastic stenting in jaundiced but otherwise stable patients undergoing pancreaticoduodenectomy led to a significantly higher rate of postoperative complications, particularly infectious and septic events, compared to primary surgery without drainage. These results strongly support upfront resection in patients without cholangitis or organ dysfunction.

Nonetheless, in defined clinical scenarios – particularly in patients with manifest cholangitis, liver dysfunction, planned neoadjuvant chemotherapy, or expected delay to surgery – preoperative drainage is clinically justified and often unavoidable. In this context, the optimal drainage strategy remains debated. A recent meta-analysis by Wang

et al.[28] comparing ERCP and PTCD in periampullary cancer patients found both methods to be overall comparable regarding drainage success, technical failure, and general complication rates. Importantly, evidence from retrospective cohort studies suggests that external drainage (e.g., PTCD or surgical drainage) may be associated with lower rates of postoperative cholangitis and pancreatic fistula compared to internal drainage (ERCP), possibly due to the higher bacterial load and bile contamination associated with endoscopic approaches (Reichert et al. unpublished, submitted).

Taken together, these findings underline the importance of individualized treatment planning based on clinical presentation, tumor resectability, timing of surgery, planned neoadjuvant therapy, and local expertise. The choice of an appropriate drainage modality with respect to postoperative morbidity remains the subject of ongoing clinical research.

Perioperative Antibiotic Prophylaxis

It is well established that single-dose perioperative antibiotic prophylaxis (PAP) effectively reduces the risk of surgical site infections in gastrointestinal surgery.[29,30] However, the specific PAP regimens applied in pancreatic surgery remain heterogeneous across institutions and countries.

A recent randomized controlled trial by D'Angelica et al.[31] challenged the use of narrow- spectrum antibiotics by demonstrating that broader-spectrum PAP with piperacillin/tazobactam not only reduced postoperative wound infections but also decreased the incidence of clinically relevant postoperative pancreatic fistula. These findings question the adequacy of smaller- spectrum regimens such as second-generation cephalosporins in high-risk pancreatic procedures.

Retrospective studies support this trend toward broader prophylaxis in selected patient populations, particularly in those with preoperative biliary drainage. Krüger et al. demonstrated significantly higher rates of bacterobilia in PBD patients, highlighting the altered microbial landscape and the increased risk of contamination with bile-resident pathogens.[32] Similarly, Dimitriou et al. emphasized the importance of adapting PAP regimens based on local resistance patterns and individual patient factors, especially in those with biliary drainage.[33] Droogh et al.[34], in a recent meta-analysis, went a step further by identifying a potential benefit of prolonged perioperative antibiotic prophylaxis specifically in patients with biliary drainage. Their findings suggest that this subgroup might profit from an extended PAP strategy beyond the traditional single-shot approach.

Nevertheless, the optimal duration and spectrum of PAP in patients with biliary contamination remain subjects of ongoing investigation.[35,36] Prospective data are required to determine whether prolonged or escalated PAP regimens reduce surgical site infections as well as postpancreatectomy complications such as in high-risk subgroups – without contributing to antimicrobial resistance.

Taken together, while broad-spectrum PAP appears beneficial in selected patient populations, especially those with biliary interventions, a universal escalation of antibiotic prophylaxis is not currently supported by guideline-level evidence. Instead, an individualized, risk-adapted approach – considering prior drainage, microbiological colonization, and institutional resistance data – should be pursued pending further prospective trials.

Minimally Invasive Versus Open Surgery

Distal Pancreatectomy

Minimally invasive distal pancreatectomy has evolved into a preferred approach for selected patients with lesions of the pancreatic body and tail, offering perioperative advantages without compromising oncologic outcomes. Originally met with scepticism due to technical complexity and limited early experience, minimally invasive distal pancreatectomy – either laparoscopic or robotic – has now reached the threshold of becoming standard of care in specialized centers.

The randomized LEOPARD trial, conducted across 14 Dutch high-volume centers, evaluated the clinical effectiveness of minimally invasive distal pancreatectomy versus open distal pancreatectomy in patients with resectable tumors of the pancreatic tail without vascular involvement. Time to functional recovery was significantly shorter in the minimally invasive group, and while rates of major complications (Clavien-Dindo ≥ III) were similar, patients undergoing minimally invasive distal pancreatectomy experienced less delayed gastric emptying and reported better postoperative quality of life.[37]

These findings were corroborated by large retrospective cohort studies: in an analysis of over 8,500 open procedures compared with 382 minimally invasive distal pancreatectomies, minimally invasive surgery was associated with lower rates of postoperative complications (30.1% vs. 39.0%, $p<0.001$), including a significant reduction in postpancreatectomy hemorrhage (13.6% vs. 20.6%, $p<0.001$), as well as shortened hospital stay.[38] Moreover, oncological equivalence was demonstrated in matched cohort studies: operative time, lymph node yield and margin status were comparable between laparoscopic (n=33) and open approaches (n=46). Even survival outcomes, rates of local recurrence and distant metastases showed no differences

between both groups.[39]

Importantly, the international DIPLOMA trial, a non-inferiority randomized controlled trial published in 2023, confirmed that minimally invasive resection (including robotic approaches) in PDAC achieves comparable oncologic results (R0 resection rates, lymph node harvest) while offering perioperative benefits such as reduced blood loss, faster recovery, and shorter length of stay.[40]

The clinical relevance of these findings is underscored in recent reflections by Diaz, Hays, and Hogg,[41] who emphasize that minimally invasive distal pancreatectomy for left-sided pancreatic cancer has moved beyond acceptance and should now be considered the preferred approach in suitable patients. However, they also highlight key prerequisites for safe implementation: structured training, high-volume centers, standardized perioperative care, and appropriate patient selection remain essential. Moreover, the broader adoption of robotic techniques is currently constrained by cost, platform availability, and training infrastructure.[41]

In summary, minimally invasive distal pancreatectomy is now firmly established as a safe, effective, and increasingly preferred approach for tumors of the pancreatic body and tail without vascular involvement. While technical expertise and access barriers remain, the convergence of evidence, training, and innovation will continue to drive the paradigm shift toward minimally invasive pancreatic surgery – offering improved recovery trajectories without compromising oncologic standards.

Pancreaticoduodenectomy

In contrast to minimally invasive distal pancreatectomy, the adoption of minimally invasive pancreaticoduodenectomy has been slower, mainly due to the complexity of the procedure and concerns regarding safety, complications, and oncologic adequacy. Nevertheless, accumulating data suggest that minimally invasive pancreaticoduodenectomy – particularly robotic-assisted approaches – may offer perioperative advantages in selected patients when performed by highly experienced surgeons in high-volume centers.[42]

A meta-analysis published in 2023 analysed data from a total of 40,230 patients across multiple, primarily non-randomized studies. The analysis revealed no significant differences in complication rates, mortality, lymph node yield, blood loss, reinterventions, or hospital readmissions, provided the procedures were performed by experienced surgeons.[42]

However, recent prospective trials present conflicting results. The EUROPA trial, a prospective randomized controlled study published in 2024, compared robotic assisted (RPD) with open pancreaticoduodenectomy (OPD) in 81 patients with resectable periampullary tumors. The 90- day Comprehensive Complication Index (CCI) was comparable between the groups (RPD: 34.0±23.5 vs. OPD: 36.5±27.7; p=0.713). However, the RPD group showed a higher rate of clinically relevant – grade B/C – pancreas-specific complications (58.6% vs. 33.3%; p=0.046).[43] These results suggest that while minimally invasive pancreaticoduodenectomy may be safe overall, certain complications may be more frequent due to the altered tissue handling or learning curve associated with minimally invasive techniques.

Earlier data from the LEOPARD-2 trial, a multicenter randomized study from the Netherlands, raised concerns about safety when the study was prematurely terminated due to an imbalance in 90-day mortality favoring the open group. This trial highlighted the importance of institutional experience, case volume, and structured training when implementing minimally invasive pancreaticoduodenectomy (van Hilst et al., 2019 → PMID: 30685489).

In their recent author reflections, Diaz, Hays, and Hogg (2025) emphasize that minimally invasive pancreaticoduodenectomy cannot yet be considered the new standard, unlike minimally invasive distal pancreatectomy. They stress that safe implementation requires significant institutional resources, highly specialized training, and adherence to standardized perioperative pathways. Moreover, the adoption of robotic platforms is still limited by cost, access, and the need for surgeon-specific credentialing. Ongoing and future randomized trials are expected to provide essential data on long-term oncologic outcomes, functional recovery, and complication rates.[41]

In summary, while minimally invasive pancreaticoduodenectomy is technically feasible and may offer specific perioperative benefits, it currently remains a procedure for selected patients in expert hands. Open pancreaticoduodenectomy continues to represent the gold standard in most settings. Further high-quality evidence is required to establish the role of minimally invasive pancreaticoduodenectomy in clinical practice and to define optimal indications, learning curves, and institutional prerequisites.

Perioperative Drainage Management

In pancreatic surgery, intraoperative drain placement remains a widely used strategy to detect and manage postoperative complications at an early stage. Drains enable monitoring of pancreatic enzyme concentrations in the peritoneal fluid, thereby facilitating the diagnosis as well as management of postoperative pancreatic fistula (POPF). They may also serve as an early indicator of other life-threatening complications such as intra-abdominal bleed-

ing or bile leakage.

However, the clinical benefit of intraoperatively placed routine drainage is subject to ongoing debate. A Cochrane review published in 2021 analyzed four randomized controlled trials comprising 1,110 patients undergoing pancreatic resection, with (n=560) or without (n=550) intraoperative drainage. The analysis found no significant differences between groups in terms of 30-day mortality, surgical site infections, surgical reintervention rates, length of hospital stay or quality of life. These findings suggest that routine drainage placement may not be universally beneficial in all patients undergoing pancreatic surgery.[44] A key limitation of these trials is the lack of stratification by risk factors such as pancreatic texture, duct size, or the type of resection. These anatomical and procedural factors are crucial, as they strongly influence the likelihood of POPF and other complications. The German POMGAT guideline acknowledges this heterogeneity and recommends an individualized drain strategy, rather than a general recommendation for or against intraoperative drainage.[24]

This routine drainage concept was recently corroborated by the PANDORINA trial, a multicenter, randomized non-inferiority trial investigating the safety of a no-drain policy in distal pancreatectomy.[45] In this large multicenter setting the rate of major morbidity was non- inferior in the no-drain group compared to the drain group in both the intention-to-treat as well as per-protocol analysis. Importantly, in the incidence of clinically relevant POPF (ISGPS grade B/C) was significantly lower in the no-drain group (12%) than in the drain group (27%). These results support the interpretation that a no-drain policy is not only safe but may reduce the incidence of clinically relevant fistula in selected patients undergoing distal pancreatectomy. Consequently, selective omission of prophylactic drains should be considered the new standard in eligible patients with low risk for POPF after distal pancreatectomy. However, this interpretation warrants careful consideration. As highlighted in the accompanying editorial by Constant and Doussot,[46] intraoperative randomization in PANDORINA was stratified using the Distal Pancreatectomy Fistula Risk Score, yet precise measurement of pancreatic duct diameter and parenchymal thickness may be more accurate when performed intraoperatively via ultrasound. Moreover, a subset of patients initially randomized to the no-drain group received intraoperative drains at the discretion of the surgeon, introducing an element of crossover and potential selection bias. This underscores the ongoing role of individualized intraoperative judgment, particularly in the presence of intraoperative bleeding, thick gland texture, or difficult anatomy. Furthermore, while superiority in terms of POPF was shown, this difference was driven predominantly by a reduction in grade B fistulas, for which the clinical impact is often moderate. Subclassification could provide more granularity in future studies. The PANDORINA study did not report this subclassification, limiting the interpretability of the clinical impact of drain omission.[45,46]

This evidence suggests that the use of intraoperative drains in pancreatic surgery should be carefully tailored to individual risk profiles and intraoperative findings. While routine drainage placement has not shown consistent benefit across unselected patient populations, its selective use remains critical in high-risk scenarios, such as soft pancreatic texture and small duct diameter. One of the most feared complications following pancreaticoduodenectomy is secondary hemorrhage due to arterial erosion in the context of a clinically relevant postoperative pancreatic fistula. In these cases, prophylactic drainage can be lifesaving by enabling early recognition of hemorrhagic or infected collections and facilitating prompt intervention. Conversely, current evidence supports the interpretation that in low-risk patients, prophylactic drain avoidance – or, alternatively, early drain removal – is beneficial and associated with a reduced incidence of major morbidity and clinically relevant postoperative pancreatic fistula.

Once a POPF is diagnosed, percutaneous image-guided drainage is the preferred first-line therapy. In selected anatomies, endoscopic ultrasound-guided approaches may be viable. If bleeding occurs, angiographic evaluation is essential to detect and manage pseudoaneurysms or arterial bleeding via transarterial embolization – an approach shown to be safer than surgical re-intervention in recent retrospective analyses.[47]

Taken together, these findings highlight a dynamic and individualized drainage strategy to reduce major morbidity, particularly in preventing progression from POPF to life-threatening complications:

- Avoid routine drainage in low-risk distal pancreatectomy
- Use prophylactic drains selectively in high-risk settings
- Implement early removal protocols in favorable postoperative courses
- Apply interventional techniques promptly for complication control

Evidence in Perioperative Medicine of Hepato-Biliary Surgery

Neoadjuvant Concepts Against Liver Cancer

Perioperative therapy for primary hepato-biliary tumors – particularly hepatocellular carcinoma (HCC) and cholan-

giocarcinoma (CCC) – has gained increasing attention in recent years. While adjuvant therapy remains the standard approach in many cases, selected patients may benefit from neoadjuvant or perioperative strategies aimed at improving resectability, downstaging advanced disease, and controlling micrometastatic spread.

Neoadjuvant and Bridging Concepts in Hepatocellular Carcinoma

Curative-intent therapy for hepatocellular carcinoma (HCC) primarily includes either liver resection or transplantation.[48,49] However, at initial diagnosis, up to 70% of patients are deemed unsuitable for surgery due to advanced tumor burden or impaired liver function.[49,50] For patients eligible for resection, long-term oncological outcomes remain unsatisfactory, with recurrence rates exceeding 50% in many series, primarily driven by intrahepatic relapse due to occult micrometastatic disease.[51]

Against this background, neoadjuvant strategies in HCC aim to achieve one of three objectives:

(i) bridging to transplantation in patients already within criteria but at risk of tumor progression;

(ii) downstaging of initially beyond-Milan tumors to transplant eligibility; and (iii) conversion therapy to enable resection of primarily unresectable tumors.[51–54] These multimodal strategies may include locoregional therapy (transarterial chemoembolization [TACE], hepatic arterial infusion chemotherapy [HAIC], stereotactic body radiation therapy [SBRT]), tyrosine kinase inhibitors (TKIs), and immune checkpoint inhibitors (ICIs).

While no neoadjuvant approach has yet been established as standard of care,[48,49] several promising developments have emerged. A recent meta-analysis identified the combination of a TKI, PD-1 inhibitor, and locoregional therapy as the most effective strategy for achieving secondary resectability, with improved overall survival and progression-free survival compared to non-converted-to-resection cases.[55]

Particularly noteworthy is a prospective early phase trial evaluating cabozantinib plus nivolumab in patients with locally advanced or borderline resectable HCC.[52] In this cohort of 15 patients, 12 (80%) underwent successful margin-negative resection, and 5 (42%) demonstrated a major pathological response. Importantly, this approach proved safe and feasible without delaying surgery. Immune profiling revealed enhanced infiltration of effector T cells and tertiary lymphoid structures in responders, suggesting that neoadjuvant immunotherapy may reshape the tumor immune microenvironment and reduce early recurrence risk.

Similarly, immune-oncology combinations such as atezolizumab/bevacizumab or durvalumab/tremelimumab – efficacy currently approved in the palliative setting for advanced HCC in the IMbrave050 study and in the HIMALAYA trial, respectively – have raised interest for potential use in the perioperative context.[56,57] However, there is currently no prospective clinical evidence supporting their routine application in the neoadjuvant setting. It remains to be seen whether these agents can be safely and effectively integrated into multimodal perioperative treatment strategies aimed at reducing micrometastatic disease and improving long-term outcomes.

In summary, emerging data suggest that selected patients with technically unresectable or borderline resectable HCC may benefit from multimodal neoadjuvant strategies. While preliminary results from early-phase trials are promising, the routine implementation of neoadjuvant systemic or combination therapy prior to liver resection awaits validation in large prospective studies.

Neoadjuvant and Perioperative Concepts in Cholangiocarcinoma

Due to different origin – intrahepatic, perihilar and distal – cholangiocarcinomas are anatomically and biologically heterogeneous malignancies with poor prognosis, even after curative-intent resection.[58,59] Surgical resection remains the cornerstone of treatment for resectable disease; however, only a minority of patients are eligible at diagnosis due to advanced tumor stage or unfavorable location.

Currently, there is no established recommendation for neoadjuvant therapy in patients with primarily resectable cholangiocarcinomas. However, the concept of preoperative systemic therapy is increasingly investigated in retrospective cohorts and prospective studies especially for patients with hilar or locally advanced intrahepatic disease. Its goals include tumor downstaging, increasing the R0 resection rate, and controlling occult micrometastatic disease, particularly in patients with borderline resectable or initially unresectable status. Recent retrospective series and early-phase studies suggest that neoadjuvant chemotherapy is feasible and can achieve secondary resectability in selected patients.[60–62] However, uniform criteria for anatomical resectability are lacking, and definitions vary across institutions and studies. In analogy to pancreatic cancer, proposed resectability criteria include the biliary, vascular and future liver remnant factor with tumor contact to the portal vein, hepatic arteries, and bile duct involvement (Fig. 5), although prospective validation is still pending.[63–65] Neoadjuvant systemic treatment strategies are often extrapolated from the advanced-stage setting. The combination of gemcitabine and cisplatin (Gem/Cis) is currently the standard backbone, based on the ABC-02 trial.[66] The addition of checkpoint inhibition with durvalumab or pem-

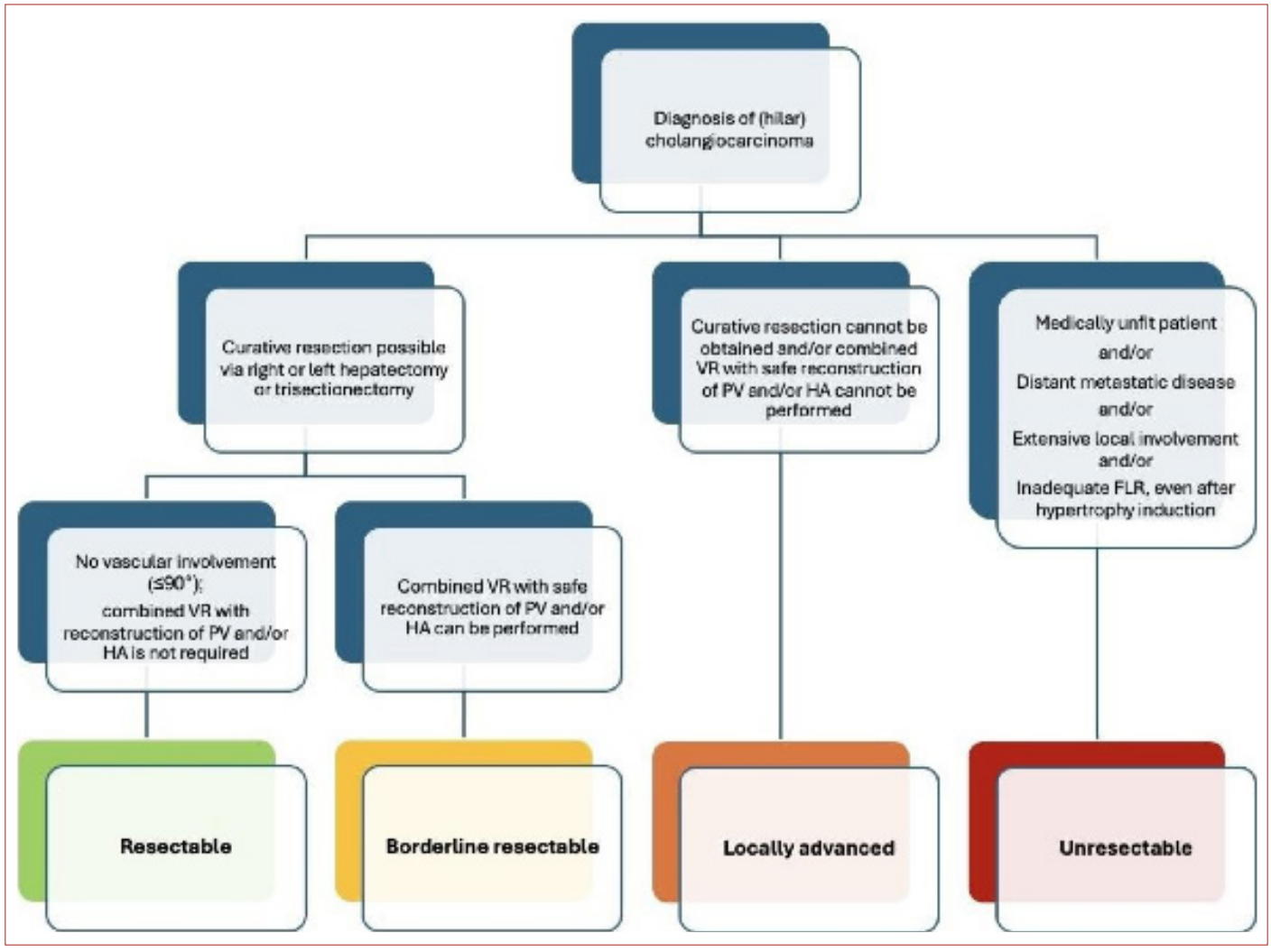

Figure 5. Resectability criteria of (perihilar) cholangiocarcinoma.

This flowchart illustrates a clinical decision algorithm for resectability in patients with (perihilar) cholangiocarcinoma. Tumors without vascular involvement (≤90° contact to portal vein [PV] or hepatic artery [HA]) are considered resectable. Borderline resectable cases allow for safe vascular reconstruction. Locally advanced tumors lack options for curative resection or safe reconstruction of PV/HA. Unresectability is defined by distant metastases, inadequate future liver remnant (FLR) despite hypertrophy induction, or extensive local disease. Medical fitness also factors into the resectability assessment. TSN = Trisectionectomy, VR = vascular resection.[64,65,130]

brolizumab has shown a significant improvement in progression-free and overall survival in the phase III TOPAZ-1 or KEYNOTE-966 trials, leading to its approval for first-line treatment in advanced biliary tract cancer.[67,68]

As demonstrated in the retrospective cohort study by ten Haaft et al., conversion chemotherapy with gemcitabine and cisplatin enabled secondary resectability in approximately 26% of patients with initially unresectable perihilar cholangiocarcinoma.[61] These findings support the feasibility of systemic therapy as a means to downstage tumors in anatomically complex or locally advanced disease. Prospective evidence further underlines the potential value of neoadjuvant chemotherapy: the recently presented GAIN trial, a multicenter randomized phase III study, investigated gemcitabine and cisplatin as neoadjuvant treatment for patients with biliary tract cancer. The trial demonstrated a significant improvement in overall survival (27.8 vs. 14.6 months) and a higher R0 resection rate (62.5% vs. 33.3%) compared to upfront surgery followed by adjuvant therapy.[60]

Building on these findings, the triplet regimen gemcitabine/cisplatin/PD (-L) 1 inhibition – already established in the palliative setting – is currently under investigation in several neoadjuvant trials for patients with high-risk resectable or borderline resectable CCC. However, robust comparative data for this immunochemotherapeutic combination in the perioperative setting are still lacking. Thus, while early clinical evidence supports the feasibility and potential efficacy of neoadjuvant chemotherapy in selected pa-

tients with cholangiocarcinoma, its routine implementation remains investigational. Future prospective studies are required to define precise selection criteria, determine the optimal regimen and duration, and assess long-term oncological outcomes. Until then, integration of neoadjuvant strategies should be guided by multidisciplinary evaluation in experienced centers.

Preoperative Optimization

Risk Stratification

Major liver resections carry significant morbidity and mortality, particularly in patients with impaired hepatic function or reduced cardiopulmonary capacity. A study of liver resections by Dunne et al. demonstrated that a low anaerobic threshold (<11 ml/kg/min) during preoperative cardiopulmonary exercise testing defined high risk patients.[69,70] This was associated with increased postoperative complications and prolonged hospital stay.[71] Other relevant predictors include advanced age, comorbidities, low skeletal muscle mass or sarcopenia, and poor performance status, e.g., ECOG ≥2. Particularly in patients with chronic liver disease, portal hypertension, and impaired synthetic liver function (e.g., elevated bilirubin and international normalized ratio and reduced platelet count), careful functional assessment is essential[72] and liver function assessment can guide surgical decision-making.

Taken together, structured risk stratification – including assessment of liver function, nutritional and physical reserve, and cardiopulmonary fitness – is crucial for selecting suitable candidates for (extended) liver resection and tailoring perioperative management accordingly.

Preoperative Optimization, Prehabilitation and ERAS

Poor preoperative functional status is a key predictor of adverse outcomes in hepato-biliary surgery. Multiple studies have demonstrated that low skeletal muscle mass with sarcopenia, reduced cardiopulmonary fitness, and malnutrition are associated with increased postoperative morbidity, delayed recovery, and prolonged length of stay following liver resection.[69–71]

Multimodal prehabilitation aims to improve patients' physical reserve and nutritional status before major oncologic surgery. A systematic review by Lambert et al. showed that prehabilitation interventions can reduce postoperative length of stay undergoing abdominal procedures including liver surgery as a global indicator of patient recovery.[73] While robust, liver-specific evidence for structured prehabilitation remains limited, high-risk patients – particularly those with impaired cardiopulmonary function, sarcopenia, or malnutrition – may benefit from individualized prehabilitation programs prior to major hepatic resections.[70] Increasingly applied neoadjuvant treatment intervals, e.g., before surgery for colorectal liver metastases or locally advanced primary hepato-biliary cancers, offer a practical window of opportunity to implement such strategies.

The 2022 ERAS guidelines for liver surgery[74] outline key elements of perioperative care, many of which align with the principles of prehabilitation (Fig. 4):

- Encouragement of daily physical activity, and implementation of supervised prehabilitation programs in high-risk patients
- Smoking and alcohol cessation for at least 4 weeks preoperatively
- Preoperative nutritional screening and tailored supplementation in malnourished or sarcopenic patients
- Preoperative biliary drainage in selected patients with obstructive jaundice
- Patient education and shared decision-making, including expectation management
- Minimization of preoperative fasting and use of carbohydrate loading
- Standardized anesthesia and intraoperative fluid management protocols
- Early enteral nutrition and early mobilization after surgery

In summary, although data from randomized trials on liver-specific prehabilitation remain sparse, current ERAS recommendations provide a structured, evidence-informed framework for perioperative care in hepato-biliary surgery. The integration of selected ERAS components and individualized prehabilitation – especially in high-risk patients – may optimize functional status, reduce complication rates, and improve overall postoperative recovery.

Management of Malignant Biliary Obstruction and Preoperative Biliary Drainage

Malignant biliary obstruction is a frequent problem in patients with biliary tract cancer, i.e. cholangiocarcinoma. Jaundice caused by biliary obstruction usually develop at an advanced tumor stage.[75] Obstruction of biliary tracts and occlusion of biliary drainages with consecutive obstructive cholestasis frequently lead to retrograde bile infection, sepsis and probably liver failure. Some studies found that preoperative cholangitis due to biliary obstruction is a negative independent prognostic factor for long-term survival in patients undergoing surgery for extrahepatic bile duct tumors.[76] Acute cholangitis can cause a rapid decline in the patients' condition due to persistent infection. Therefore, the Tokyo Guidelines 2018 recommend a prompt and adequate therapy which consists of antibiotics and interventions for biliary drainage, depending on the severity of cholangitis

and patients' clinical condition.[77] However, there is no clear recommendation for the necessity of biliary drainage in resectable and clinically stable patients with biliary obstruction. According to The European Society of Gastrointestinal Endoscopy (ESGE), biliary drainage should be performed in patients with cholangitis, severe jaundice, before neoadjuvant therapy or in cases of delayed surgery.[78]

Therefore, endoscopic drainage or percutaneous transhepatic biliary drainage (PTBD) are established options for temporary treatment in patients with biliary obstruction due to malignancy with severe jaundice and acute cholangitis prior to surgery or before implementation of a neoadjuvant therapy.[79,80] However currently, a potential superiority of either interventional procedure remains unclear.

Coelen et al. investigated complication-rates associated with preoperative biliary drainage via endoscopic stenting or PTBD in a multicenter randomized controlled trial.[81] Their study was terminated prematurely due to a higher mortality rate in patients that were treated with PTBD.[81] However, severe preoperative complications associated with biliary drainage were similar between both groups (63 % in patients with PTBD vs 67 % in patients with endoscopic biliary drainage).[81] But, these results are based on a relatively small sample size (n=54).[81] Moll et al. investigated the superiority of the respective procedures in a meta-analysis and found that PTBD is superior to EBD in the context of crossover rate, overall post-drainage complications, post-drainage pancreatitis and palliation.[82] However, Kishi et al. found an association of a higher morbidity-rate post major hepatectomy in patients with preoperative PTBD.[83] Thus, there is no clear consensus regarding the preference of either method for biliary drainage and authors recommend an individualized approach for the choice of the favored procedure.[82]

Perioperative Antibiotic Prophylaxis

In patients with malignant obstructive jaundice and preoperative bile drainage, bile duct infection is crucial. The Tokyo Guidelines 2018 recommend a duration of antibiotic therapy for 4 to 7 days after interventional biliary drainage.[77] A recent study by Srinu et al. demonstrated non-inferior outcomes for a shorter duration of antibiotic therapy.[84] Clinical cure as a primary endpoint in patients with a 4-days duration of antibiotic administration for acute cholangitis was seen in 77.79 % and in 79.66 % of patients with an 8-days duration. Additionally, they found no difference in recurrence of cholangitis, length of stay and overall mortality in both groups.[84] The microbial spectrum of ascending cholangitis mainly consists of E. coli, Klebsiella spp. and Enterococcus spp.[85] The antimicrobial treatment of choice is in consideration of the most common pathogens and thus empirical. The current Tokyo guidelines recommend third generation cephalosporines, piperacillin/tazobactam or carbapenems for empirical treatment, depending on standard protocols in the respective institution.[85]

Minimally Invasive Major Hepatectomy

Minimally invasive hepato-biliary surgery has evolved to a dynamic and rapidly expanding field within hepato-biliary oncology. Recent technological and technical advancements – including enhanced imaging, energy devices, and refined surgical techniques – have enabled laparoscopic and robotic approaches even for complex (anatomical) hepato-biliary resections.

Today, minimally invasive liver surgery is increasingly used for both benign and malignant liver lesions, including hepatocellular carcinoma, colorectal liver metastases, and selected cases of cholangiocarcinoma. In expert centers, even complex procedures such as anatomical segmentectomies, extended hepatectomies, repeat hepatectomies and laparoscopic ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) have become feasible with acceptable morbidity and oncological outcomes.[86–89]

Recent literature have confirmed that laparoscopic liver resections – when performed by experienced teams - are associated with reduced blood loss, lower complication rates, shorter hospital stay, and earlier recovery, while maintaining oncological equivalence to open approaches in terms of R0 resection rates and long-term survival[90–92] Robotic liver surgery, although less widespread, offers ergonomic and visual advantages and has shown benefits particularly in complex resections.[86,93–95]

Minimally invasive liver surgery remains technically demanding and should be performed in specialized centers with appropriate expertise, especially in patients with underlying liver disease, portal hypertension, or prior abdominal surgery. In summary, minimally invasive liver surgery represents a significant advance in hepato-biliary oncology and continues to expand its role across the spectrum of benign and malignant indications. With growing experience and increasing standardization, minimally invasive hepato-biliary surgery is poised to become a cornerstone of modern surgery – even for complex resections – in appropriately selected patients.

Management and Classification of Post-Hepatectomy Specific Complications

Despite advances in perioperative management and surgical techniques, the rate of postoperative complications after hepatectomy remains between 38 % to 47 % with lower rates reported by high-volume centers[90–92] Various studies suggest an association of postoperative complica-

tions with preoperative Child-Pugh-class, time of portal occlusion during surgery, duration of operation, volume of blood loss and extent of hepatectomy.[96–98]

Perioperative Drainage Management and Biliary Leakage

Bile leakage is a frequent and potentially serious complication following hepatic resection. Its incidence ranges from 4–12 % after liver resection without biliary reconstruction[99–102] and from 0.4–8 % in procedures involving biliary-enteric anastomosis, such as hepaticojejunostomy.[103]

The International Study Group of Liver Surgery (ISGLS) defines bile leakage as either:

- a bilirubin concentration in the intra-abdominal drain fluid at least three times higher than the corresponding serum level beyond postoperative day 3, or
- the need for interventional or surgical management due to biliary collections or bile peritonitis.[104]

To standardize clinical severity, the ISGLS proposes a three-tier grading system (A–C) based on the clinical consequences and need for intervention (Table 1).[104] Management of bile leakage is guided by clinical presentation and ISGLS grade. While Grade A leaks typically resolve without additional measures, Grade B and C leaks may require step-up strategies involving imaging, interventional radiology, or surgery. Early identification and appropriate classification are critical to initiate timely treatment, avoid secondary complications such as sepsis, and reduce failure-to-rescue.

The use of prophylactic intra-abdominal drains in liver surgery has been critically reassessed in recent years. A comprehensive meta-analysis including over 5,000 patients and summarized in the 2023 German guideline for perioperative medicine evaluated the outcomes of prophylactic drainage in hepatic surgery.[24,105] The analysis revealed that in uncomplicated liver resections, prophylactic drains were associated with higher rates of bile leakage, increased overall morbidity, and longer hospital stays. Notably, patients with drains were more likely to require subsequent percutaneous drainage interventions, without clear benefit regarding wound infections or postoperative bleeding. These findings were supported by a recent randomized controlled trial from Japan and by a Cochrane review, both of which concluded that omitting drains in uncomplicated resections is safe and may reduce complications.[106,107] In contrast, for complex liver resections involving biliary and/or vascular reconstruction, the data remain insufficient to make definitive recommendations. In such high-risk cases, prophylactic drainage may still be considered on an individual basis, particularly when the anticipated risk of intra-abdominal collections or bile leakage is elevated.[24]

The 2023 ERAS Guidelines for Liver Surgery[74] support these findings by advising against routine prophylactic drainage in standard hepatic resections. Instead, the ERAS recommendation emphasizes a selective and individualized approach to drain placement, reserving it for cases where the surgical complexity or intraoperative findings suggest an increased risk of postoperative complications. This strategy aligns with the broader ERAS philosophy of reducing unnecessary interventions and optimizing recovery.

In summary, routine prophylactic drainage should be avoided in uncomplicated liver resections, whereas selective use remains appropriate in complex procedures with biliary reconstruction. Adhering to evidence-based drainage strategies may help minimize complications, reduce hospital stays, and ultimately improve perioperative outcomes.

Post-Hepatectomy Portal Vein Thrombosis

Portal vein thrombosis is a potentially severe complication following liver resection, particularly in patients with pre-existing portal hypertension. It impairs liver regeneration by reducing portal venous inflow and increasing intrahepatic vascular resistance, thereby contributing to post- hepatectomy liver failure and acute portal hypertension.[108–111] Retrospective studies report an incidence of up to 9.1 % after hepatectomy, with higher rates observed following extended right hepatectomies and prolonged (repetitive) Pringle maneuvers exceeding 75 minutes.[111,112] In this context, portal vein flow interruption, technical alterations of inflow hemodynamics, and postoperative hypercoagulability act synergistically to increase thrombotic risk. Management of portal vein thrombosis includes early anticoagulation, endovascular recanalization, or surgical thrombectomy, the latter being indicated particularly in cases of complete occlusion of the main portal vein trunk.[113] Timing is critical: patients undergoing thrombectomy within five postoperative days have significantly better outcomes compared to those with delayed intervention.[114]

The ERAS Society Guidelines for liver surgery recommend routine thromboprophylaxis in patients undergoing hepatectomy due to the high incidence of thromboembolic complications.[74] While the evidence is largely extrapolated from colorectal and general abdominal surgery, this recommendation gains relevance in patients with underlying cirrhosis or splenomegaly, where portal venous flow may be precariously balanced. Perioperative risk stratification should therefore consider the extent of resection, duration of vascular occlusion, baseline portal pressure, and hypercoagulable states. In patients with cirrhosis or small-for-size remnants, intraoperative Doppler assessment and early postoperative duplex sonography are valuable tools for early detection of impaired portal flow.

Small-for-Size and Posthepatectomy Liver Failure

Small-for-size-syndrome (SFSS) is defined as insufficient residual liver-tissue post resection or liver transplantation and thus impaired recovery of a normal liver function.[115] After extended liver resection SFSS occurs in disproportioned relation of remaining liver-mass to body surface, weight and organ-condition prior to surgery.

The increased portal blood-flow leads to hyperperfusion through the relatively small liver mass and subsequent portal hypertension and concurrent reduction in arterial perfusion.[115] These mechanisms induce biliary injury and dysfunction which are aggravated by inflammatory and immunologic responses triggered by ischemia-reperfusion injury.[116] SFSS is associated with prolonged cholestasis, coagulopathy i.e., a persistent INR > 1.5, ascites, portal hypertension and gastrointestinal bleeding with manifestation during the first 1 to 2 weeks post- surgery as well as death from recurrent sepsis after 4-6 weeks.[117,118]

Generally, patients with chronic liver disease or fibrosis are at risk for SFSS with a future liver remnant of less than 30 %, while cirrhotic patients are at risk with a future liver remnant less than < 40 %.[119] In patients with chronic liver disease and fibrosis, indications for extensive hepatectomy should be reviewed critically, as complication rates are increased.[120,121]

To adequately indicate the future liver remnant, baseline liver volume and function need to be assessed in biochemical tests and high-quality imaging, i.e. computed tomography-based volumetry.[119]

Procedures to increase future liver remnant consider the risk of SFSS and postoperative liver failure. The decision for either extensive liver resection or palliative treatment for malignant liver diseases remains challenging. In recent years, multiple strategies to induce liver hypertrophy and increase of future liver remnant have been established.[122] The optimal procedure requires a fast and sufficient hypertrophy induction outracing simultaneous tumor progression, increased R0-resection rates and relatively low morbidity and mortality. Conventional procedures of liver hypertrophy-induction are surgical portal vein ligation (PVL) and interventional portal vein embolization (PVE).

A novel strategy to induce rapid liver hypertrophy in primarily non-resectable liver tumors is a two-stage hepatectomy, associating liver partition and portal-vein-ligation for staged hepatectomy (ALPPS).[122] This procedure is more favorable in comparison to PVL and PVE that fail to induce sufficient hypertrophy in about 14 % of patients mainly due to intraparenchymal portovenous collaterals bridging segmental borders.[122] Generally, ALPPS is indicated in marginally resectable or locally advanced unresectable liver tumors of patients with a FLR of less than 30 % in healthy livers or less than 40 % in diseased livers.[122] Li et al. investigated the potential superiority of ALPPS compared to PVE and TACE in patients with initially unresectable HBV-related HCC in a cohort of 76 patients. They found a significantly shorter interval between stage 1 and stage 2 operations and a significantly higher rate of R0- resections in patients treated with ALPPS.[123] However, they reported a significantly higher rate of major complications in the ALPPS group.[123] As other studies confirm the high morbidity and mortality rate in patients undergoing ALPPS, the procedure is considered as a high-risk alternative to conventional methods of hypertrophy-induction.[124,125]

Recently, the retrospective observational DRAGON0 study demonstrated that combined PVE combined with hepatic vein embolization offers a resection-rate comparable to ALPPS with a safety profile similar to PVE alone.[126] Further, they subsequently reported a significantly higher overall-survival in patients treated with this combined procedure than in patients treated with PVE alone.[127]

In patients with insufficient hypertrophy despite PVE and hepatic vein embolization, a parenchymal split may be used to disrupt intraparenchymal collaterals between liver segments and thereby induce ALPPS-like hypertrophy. While this approach may increase future liver remnant and enhance resectability, its application in borderline cases – especially in patients with compromised or cirrhotic liver parenchyma – remains highly individualized and must be carefully weighed in a multidisciplinary context. These complex cases often require patient- tailored strategies based on detailed risk–benefit assessment.

Conclusion and Outlook

Perioperative medicine in oncologic HPB surgery has undergone a paradigm shift from standardized protocols to personalized, risk-adapted strategies. Future research should focus on validating tailored neoadjuvant approaches, refining ERAS-based interventions, and establishing standardized protocols for multimodal prehabilitation. The integration of advanced imaging, and minimally invasive techniques – including robotic liver surgery – offers exciting perspectives but requires ongoing clinical validation. Ultimately, multidisciplinary collaboration remains the cornerstone of safe and effective perioperative management in this high-risk patient population.

Disclosures

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Review

Liver Transplantation in Autoimmune Liver Disease

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Abstract

Autoimmune liver diseases, including autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis, are the fourth most common cause of transplantation worldwide. Although immunosuppressive therapies can induce remission or slow disease progression, transplantation remains the definitive treatment for patients with end-stage liver disease, intractable symptoms, or acute liver failure. This chapter provides a comprehensive overview of pre- and post-transplant evaluation processes in patients with autoimmune liver diseases.

Keywords: Autoimmune liver disease, chronic rejection, liver transplantation, immunosupression

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Autoimmune liver diseases (AILDs), including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC), are chronic conditions that can culminate in cirrhosis, hepatic decompensation, and ultimately necessitate liver transplantation (LT).[1] Although LT is frequently performed in the context of end-stage liver disease or hepatocellular carcinoma (HCC), AILDs also present unique, disease-specific indications. For instance, AIH may lead to fulminant hepatic failure requiring urgent transplantation, whereas patients with PBC or PSC may suffer from debilitating pruritus or repeated episodes of cholangitis that are refractory to medical therapy.[2] In the case of PSC, additional concerns such as biliary epithelial dysplasia or early cholangiocarcinoma (CCC) may warrant consideration for LT.[3] These diverse clinical scenarios underscore the complex decision-making involved in managing AILDs and determining transplant candidacy In this chapter a comprehensive review of pretransplant evaluation and posttransplant management will be given.

Waitlist Mortality and Transplant Evaluation

Several studies have demonstrated that patients with AILDs face higher waitlist mortality than those with other liver disease etiologies, largely due to a lower likelihood of receiving a transplant.[4, 5] Zhou et al. reported a waitlist mortality rate of 20% for individuals with PBC, which was notably higher than the rates observed for alcoholic liver disease (ALD) at 13% and metabolic dysfunction-associated fatty liver disease (MAFLD) at 18% under the MELD allocation system.[6] Similarly, Singal et al. found that the cumulative 90-day waitlist mortality for patients with PBC reached 20.1%, the highest among all etiologies examined.[7] A significant contributing factor is that most patients with AILD are women who have historically been disadvantaged by the MELD-Na scoring system. Because serum creatinine is used to estimate kidney function and tends to overestimate renal function in women, their mortality risk may be underestimated, resulting in a lower prioriti-

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zation for transplantation. Newer allocation models, such as MELD 3.0, aim to address these limitations.[8] However, further studies are needed to determine whether MELD 3.0 offers superior mortality prediction compared with MELD-Na or the original MELD system in patients with AILD.

Patients with AIH may present with a spectrum of acute liver injury, including acute severe autoimmune hepatitis (ASAIH), acute liver failure (ALF), or acute-on-chronic liver failure (ACLF).[9] ASAIH is typically characterized by jaundice, an international normalized ratio (INR) between 1.5 and 2, the absence of hepatic encephalopathy, and no evidence of chronic liver disease on biopsy. In contrast, ALF is defined by the presence of hepatic encephalopathy and an INR greater than 2. ACLF occurs in individuals with underlying chronic liver disease who develop an acute deterioration.[10]

While corticosteroid therapy is often effective in ASAIH, the outcomes in patients with ALF or ACLF are significantly worse, and these patients should be promptly referred for LT. Although most individuals with ASAIH respond well to steroids, with transplant-free survival rates ranging from 52% to 95.2%, a subset of patients fails to respond to treatment.[9]

To help identify high-risk patients, the Survival and Prognostic Factors for Acute Severe AIH (SURFASA) score was developed from a retrospective multicenter French cohort. This score, calculated as [6.80 + 1.92 × (Day 0 INR) + 1.94 × (% change in INR by Day 3) + 1.64 × (% change in bilirubin by Day 3)], can predict poor outcomes. A score above 1.75 is associated with an 85–100% risk of death or need for transplantation.[11]

Given that corticosteroid therapy increases the risk of infection, particularly if transplantation becomes necessary, the optimal steroid dosing strategy remains controversial. In the absence of definitive studies comparing 0.5 mg/kg/day versus 1 mg/kg/day, a lower dose of 0.5 mg/kg/day may be more appropriate, as it could provide therapeutic benefit while minimizing the risk of infection.[12]

Historically, requests for exception points, frequently due to severe pruritus, were assessed by regional review boards, resulting in inconsistencies across different geographic regions. The implementation of the National Liver Review Board (NLRB) in 2019 aimed to centralize and standardize these evaluations nationwide. However, current NLRB guidelines do not consider pruritus alone to be a sufficient justification for granting a MELD exception, stating that evidence is lacking to support such a policy.[13] Therefore, although severe pruritus can significantly impair quality of life and may warrant liver transplantation, it is not recognized as a formal criterion for MELD exception and must be submitted as an individual appeal.[14]

MELD exception points for liver transplantation may be awarded to PSC patients who have had two or more hospital admissions within a year for acute cholangitis, provided that there is documented bloodstream infection or sepsis requiring vasopressor support for hemodynamic instability. Patients with a confirmed diagnosis of CCA are also eligible for MELD exceptions, according to current guidelines.[15]

Risk of Rejection in Autoimmune Liver Diseases

Patients with AILD have a higher risk of rejection after liver transplantation, particularly those with AIH, who show increased rates of early and late TCMR and chronic rejection compared to non-immune liver diseases. Chronic rejection occurs in approximately 15% of AIH recipients, with a higher risk observed in younger patients. PBC and PSC are also associated with increased early and late TCMR, although chronic rejection rates are closer to those of non-immune diseases. Antibody-mediated rejection is not linked to AILD, but plasma cell-rich rejection (previously called de novo AIH) occurs in 3–5% of non-AIH transplant recipients.[16]

Post-Transplant Outcomes by Disease Subtype

Autoimmune Hepatitis

In North America, AIH has consistently accounted for approximately 4-6% of liver transplants (LT).[1] Data from the European Liver Transplant Registry (ELTR) spanning 1988 to 2016 indicate that AIH was responsible for 2% of liver transplants and 5% of transplants due to cirrhosis.[17] While liver transplantation for AIH is associated with favorable outcomes, as evidenced by the 5- and 10-year survival rates of 86% and 72%, respectively,[18] some studies have indicated a higher risk of mortality and reduced graft survival in AIH patients than in those with other chronic liver diseases.[19, 20]

Recurrent autoimmune hepatitis (rAIH) develops in approximately 20–30% of liver transplant recipients within 5 years, with rates varying depending on whether biopsies are performed only for clinical indications or routinely as part of protocol surveillance.[18, 21, 22] The diagnostic criteria for rAIH are the same as those for the primary disease and include positive autoantibodies, elevated immunoglobulin G (IgG) levels, and characteristic histological findings, such as lymphoplasmacytic portal inflammation with interface hepatitis and lobular collapse with necrosis.[23]

A key clinical challenge is to distinguish rAIH from T-cell–mediated rejection (TCMR). TCMR is characterized by a mixed inflammatory infiltrate, bile duct injury, and endothelialitis, in contrast to the more plasma cell–rich infiltrates

typical of rAIH. Protocol biopsies are particularly valuable because rAIH may be present even in patients with normal liver function tests at 1-, 5 and 10 years interval.[24]

It is also important to differentiate rAIH from de novo AIH, which occurs more than six months after transplantation in patients without a prior diagnosis of AIH. De novo AIH typically demonstrates plasma cell–rich portal inflammation on histology.[25]

Reported risk factors for rAIH include younger recipient age, higher disease activity prior to transplantation (elevated IgG, markedly raised transaminases, and moderate-to-severe inflammation in the explant), donor–recipient sex mismatch, use of mycophenolate mofetil (MMF), and withdrawal of corticosteroid therapy (Table 1).[18, 22, 26-28] A large multicenter study identified a link between MMF use and rAIH; however, some researchers suggest that this association may reflect differences in practice patterns or inter-center variables rather than a direct effect of MMF itself.[18]

Primary Biliary Cholangitis

The use of LT for PBC has declined in recent decades, largely because of the widespread adoption of ursodeoxycholic acid (UDCA) and the introduction of effective second-line agents.[29] Graft survival in PBC remains excellent, with rates of 85–94% at 5 years and 81–90% at 10 years.[30, 31]

Approximately 20–30% of recipients develop recurrent primary biliary cholangitis (rPBC) within 10 years after transplantation.[32] The persistence of antimitochondrial antibodies and elevated immunoglobulin M (IgM) levels post-transplant limits their diagnostic utility for rPBC however ascendance of IgM could predict disease recurrence. Therefore, a liver biopsy is essential for confirmation.[21] The histopathological features mirror those of native PBC, including mononuclear cell infiltrates in the portal tracts, portal granulomas, bile duct injury and loss, and bile ductular proliferation. These findings must be carefully differentiated from immune-mediated injury to small bile ducts caused by rejection.[33]

Risk factors for rPBC include younger recipient age, onset of early post-transplant cholestasis, and use of certain immunosuppressive agents (Table 1).[30, 34, 35] Tacrolimus is associated with a higher risk of rPBC, whereas cyclosporine appears to confer a lower risk. However, the selection of calcineurin inhibitors does not seem to affect long-term graft or patient survival, supporting the ongoing use of tacrolimus after LT in patients with PBC.[36, 37] A multicenter study assessed the long-term effects of preventive UDCA therapy after LT in 941 patients transplanted for PBC, of whom 211 began UDCA (10–15 mg/kg/day) within the first two weeks post-transplant. Preventive UDCA use was associated with a reduced risk of rPBC and improved graft and patient survival.[38]

Primary Sclerosing Cholangitis

Patients who undergo transplantation due to PSC have survival rates of 90% at 1 year and 80% at 5 years after LT.[39, 40] However, PSC recurs in 20% to 25% of transplanted patients within 5 years.[41, 42] In a cohort of 306 PSC liver transplant recipients, the 5- and 10-year recurrence rates were 8.7% and 22.4%, respectively, with no significant difference between living and deceased donor transplants. In a European registry analysis of 29,902 liver transplants, long-term survival after living liver donor transplantation (LDLT) for AILD was generally favorable, but adult and pediatric PSC patients had higher mortality compared to donation after brain death (DBD) transplants. In adults diagnosed with PSC, LDLT has been correlated with an elevated risk of mortality due to disease recurrence and biliary complications. Additionally, the sex of the donor, specifically male, has been identified as a contributing factor to mortality.[43] Recurrent primary sclerosing cholangitis (rPSC) typically manifests 90 days post-transplant, characterized by ischemia and non-anastomotic biliary strictures. It is crucial to distinguish rPSC from ischemia, ABO incompatibility, cytomegalovirus infection, and chronic rejection. Notably, differentiation from chronic rejection is particularly important, as both conditions can present with ductopenia.

Table 1. Risk Factors for Recurrence of Autoimmune Liver Diseases After Liver Transplantation

Disease	Risk Factors for Recurrence
Autoimmune Hepatitis	Younger recipient age; high disease activity prior to LT (elevated IgG, high transaminases, severe inflammation in explant); donor–recipient sex mismatch; use of MMF; corticosteroid withdrawal
Primary Sclerosing Cholangitis	Younger or older recipient age; male sex; recurrent cholangitis before LT; high MELD score; cholangiocarcinoma; HLA DRB1*08 haplotype; IBD; older donor age; T-cell–mediated rejection; certain immunosuppressive regimens (anti-thymocyte globulin, tacrolimus, prolonged corticosteroid use)
Primary Biliary Cholangitis	Younger recipient age; early post-LT cholestasis; tacrolimus use (higher risk); absence of preventive UDCA therapy

LT: Liver transplantation; IgG: Immunoglobulin G; MMF: Mycophenate Mofetil; MELD: Model for end stage liver disease; IBD: Inflammatory bowel disease.

The histological characteristics of recurrent rPSC closely resemble those observed in primary sclerosing cholangitis (PSC) prior to transplantation. These characteristics include fibrous cholangitis, fibro-obliterative cholangitis with or without ductopenia, as well as portal, peri-portal, or bridging fibrosis, and cirrhosis.[44]

Multiple recipient, donor, and disease-related factors have been associated with increased risk of rPSC after liver transplantation. Recipient factors include younger or older age at LT, male sex, recurrent cholangitis before LT, high MELD score, cholangiocarcinoma, HLA DRB1*08 haplotype and the presence of inflammatory bowel disease (IBD).[45-48] While the literature presents inconsistent data regarding the efficacy of colectomy in preventing recurrent primary sclerosing cholangitis (rPSC), a recent meta-analysis has indicated a protective effect of colectomy against rPSC.[49] The evidence concerning the role of immunosuppressive regimens in rPSC is similarly contradictory. On one hand, the administration of anti-thymocyte globulin, tacrolimus, and extended corticosteroid therapy has been linked to rPSC, whereas the data on cyclosporine remain inconclusive.[16, 50-53] Conversely, reduced immunosuppression through single-agent therapy has also been associated with rPSC. Importantly, TCMR appears to be a significant precipitant of rPSC, contrasting with other liver transplant indications where it may facilitate long-term tolerance.[48] Nonetheless, tacrolimus monotherapy continues to be the cornerstone of maintenance immunosuppression in patients who have undergone transplantation for PSC.[54]

Immunosuppressive Strategies in Autoimmune Liver Diseases

Post-transplant immunosuppressive regimens for AILDs are designed to prevent both allograft rejection and disease recurrence while minimizing long-term toxicity (Fig. 1). Induction therapy in the early postoperative period typically consists of either basiliximab or high-dose corticosteroids, followed by tacrolimus-based maintenance. The choice and duration of adjunctive therapy depend on the underlying disease.

In AIH, triple-drug therapy is advised during the first year, then reduced to dual therapy for long-term maintenance,

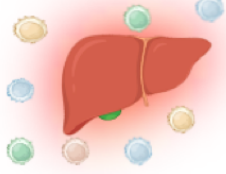
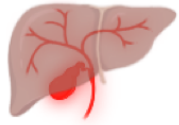
	Autoimmune Hepatitis	Primary biliary cholangitis	Primary sclerosing cholangitis
			
Induction Agent (First Week Post-LT)	Basiliximab IV: 2 × 20 mg at POD 0 & 4 OR Methylprednisolone IV: 500 mg at POD 0, taper over 4 days (250–125–80–40 mg)	Basiliximab IV: 2 × 20 mg at POD 0 & 4 OR Methylprednisolone IV: 500 mg at POD 0, taper over 4 days (250–125–80–40 mg)	Basiliximab IV: 2 × 20 mg at POD 0 & 4 OR Methylprednisolone IV: 500 mg at POD 0, taper over 4 days (250–125–80–40 mg)
Backbone Treatment	Tacrolimus (BID or OD, prolonged release) Target trough: 7–10 ng/mL (1st mo), 4–8 ng/mL (mo 1–12), 4 ng/mL (after 12 mo) Duration: Unlimited	Tacrolimus (BID or OD, prolonged release) Target trough: 7–10 ng/mL (1st mo), 4–8 ng/mL (mo 1–12), 4 ng/mL (after 12 mo) Duration: Unlimited	Tacrolimus (BID or OD, prolonged release) Target trough: 7–10 ng/mL (1st mo), 4–8 ng/mL (mo 1–12), 4 ng/mL (after 12 mo) Duration: Unlimited
Coadjuvant Therapy	Mycophenolate mofetil: 1000–2000 mg/d (1st year), then 250–500 mg BID long term OR Azathioprine: 1–1.5 mg/kg/d (1st year), then 50–75 mg OD long term OR Predniso(lo)ne: start 30 mg OD, taper over 1st year, maintain 5–10 mg OD long term Recommendation: Triple therapy in year 1, dual therapy long term	Mycophenolate mofetil: 1000–2000 mg/d, stop at 6–12 mo Azathioprine: 1–1.5 mg/kg/d, stop at 6–12 mo Predniso(lo)ne: start 30 mg OD, taper, stop at 3–6 mo Note: Long-term predniso(lo)ne not recommended	If IBD present: Azathioprine 1–1.5 mg/kg/d, stop at 6–12 mo (consider long-term if IBD active) If no IBD: Mycophenolate mofetil 1000–2000 mg/d, stop at 6–12 mo Predniso(lo)ne: start 30 mg OD, taper, stop at 3–6 mo Note: Long-term predniso(lo)ne not recommended

Figure 1. Suggested Immunosuppressive Regimens for Patients with AILD After Liver Transplantation.

AILD: Autoimmune liver disease; IBD: Inflammatory bowel disease; LT: Liver transplantation; POD: Postoperative day.

with monotherapy discouraged due to the high risk of recurrence. In PBC, adjunctive agents are used only short term, corticosteroids are withdrawn early, and tacrolimus monotherapy is permissible; prophylactic UDCA should be continued because of its proven benefits in this population. In PSC, azathioprine may be maintained long term in patients with active inflammatory bowel disease, whereas others receive only short-term adjunctive therapy; corticosteroids are tapered early, and tacrolimus monotherapy is an acceptable maintenance strategy.

Management of recurrent autoimmune liver diseases after transplantation is tailored to the specific condition. rAIH is typically treated by intensifying immunosuppression, most often through reintroduction or escalation of corticosteroids, sometimes in combination with everolimus or mycophenolate mofetil, with prolonged maintenance therapy to minimize further recurrence. Primary management of rPBC involves the long-term administration of UDCA, which has been shown to improve biochemical parameters and may potentially decelerate histologic progression. In cases where additional treatment is necessary, second-line agents such as bezafibrate or obeticholic acid may be incorporated. Baseline immunosuppression is generally unchanged unless concomitant rejection is present. rPSC management is largely supportive, involving endoscopic dilation or stenting of dominant strictures, antibiotic treatment of recurrent cholangitis, and careful optimization of immunosuppression to prevent further injury. No proven medical therapy halts rPSC progression, and severe or progressive cases may necessitate re-transplantation.[54] Treatment of chronic rejection is similar to that for other disease etiologies and involves increasing tacrolimus trough levels, along with the addition of a second-line agent, typically everolimus or MMF.[55]

Conclusion

AILDs are important indications for liver transplantation and carry higher risks of rejection and recurrence than non-immune etiologies. Optimizing outcomes relies on tailored immunosuppression, disease-specific adjunctive therapies, and vigilant long-term follow-up to detect and manage recurrence or chronic rejection early.

Disclosures

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Review

Liver Transplantation for Colorectal Liver Metastases

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Abstract

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer-related mortality worldwide. Over 50% of CRC patients develop liver metastases either at diagnosis or during follow-up. While hepatic resection offers 5-year survival rates of 25–60%, only 20–40% of patients have resectable disease, and recurrence rates remain high. The role of liver transplantation (LT) for non-resectable CRLM has re-emerged over the past two decades with promising results in selected patients.

To evaluate the evolving role of LT in non-resectable CRLM, summarizing key studies, patient selection strategies, and outcomes.

We reviewed pivotal studies including SECA I/II, European Consortium, TRANSMET, and recent LDLT series from Toronto, Pittsburgh, and multicenter U.S. cohorts. Inclusion criteria, patient characteristics, surgical and oncological outcomes, and prognostic factors were analyzed.

Early European experiences in the 1980s–1990s showed poor outcomes (5-year overall survival (OS) 12–21%). However, the SECA studies demonstrated 5-year OS of 60–83% in carefully selected patients. The TRANSMET trial, the first randomized study, showed significantly improved 5-year OS in the LT+chemotherapy arm (73.2%) versus chemotherapy alone (9.3%). Living donor liver transplantation (LDLT) series reported comparable survival benefits without impacting organ-sharing systems. Key prognostic factors influencing outcomes include Fong and Oslo scores, tumor biology (KRAS, BRAF, SMAD4 mutations), metabolic tumor volume on PET, CEA levels, and tumor sidedness.

LT for non-resectable CRLM is no longer experimental but a promising option in selected patients with favorable tumor biology and controlled disease. Advances in systemic therapy, imaging, and genomic profiling are critical for refining patient selection. Multidisciplinary collaboration and expansion of LDLT programs may mitigate ethical concerns related to deceased donor organ allocation.

Keywords: Colorectal cancer, colorectal liver metastases, liver transplantation, living donor liver transplantation

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Colorectal cancer (CRC) is the third most frequent cancer and the second leading cause of cancer-related death for men and women worldwide.[1] More than 50% of patients with CRC are diagnosed with liver metastases either at the time of initial diagnosis or later during the course of the disease. To elaborate, 15–25% of CRC patients present with distant metastases at diagnosis, and an additional 18–30% will develop distant metastases within 5 years after diagnosis and treatment. The median survival of untreated patients with colorectal liver metastases (CRLM) is approximately 6–13 months. Hepatic resections for CRLM can achieve 5-year survival rates of 25–60%; however, only 20–40% of CRLM cases are resectable, and as few as 10–15% are amenable to curative resection. Nevertheless,

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recurrence occurs in 40–75% of patients within 3 years after hepatic resection, with approximately 50% of recurrences localized to the liver.[2,3]

In patients with CRLM, survival outcomes have improved in the early stages with oxaliplatin-based chemotherapy. However, long-term survival remains poor. Patients treated with regimens containing 5-fluorouracil, irinotecan, and oxaliplatin (including antibody therapies such as cetuximab) have a median overall survival of approximately 20 months, with a 5-year survival rate of only 10%.[4] When a response to systemic chemotherapy is achieved, R1 hepatic resections should be pursued, as studies have shown that R1 resections can yield survival outcomes comparable to R0 resections in such cases. Furthermore, in patients undergoing systemic chemotherapy and hepatic resection, better survival has been observed in those with ECOG performance status 0–1, absence of K-RAS and B-RAF mutations, and left-sided primary colorectal tumors.

Is there a role for liver transplantation (LT) in CRLM? Currently, the waiting list mortality is approximately 25%. Adding CRLM as an indication for transplantation would likely further widen the gap between the demand for liver grafts and their availability. Outcomes of deceased donor liver transplantation (DDLT) for CRLM before the 2000s were poor. Prominent studies from that period reported 5-year survival rates of only 12–21%.[5-7] When these poor outcomes are analyzed, several contributing factors emerge: issues with patient selection, underdeveloped surgical techniques, the absence of standardized immunosuppressive protocols, and suboptimal results from systemic chemotherapy regimens of that era. Following the first publication by Müchlbacher and colleagues from the University of Vienna in 1991, their second study provided a more detailed analysis of the Vienna center's results.[8] This group had, at the time, the most extensive single-center experience in this field. Between 1983 and 1994, they performed LT in 25 patients for CRLM, reporting a 30-day mortality rate of 30% and a 5-year survival rate of 12%. In their initial study, the authors included patients with negative lymph nodes on primary CRC surgical specimens. In their second publication, they retrospectively re-examined the histopathologically negative lymph nodes for micrometastases. Among the 21 patients evaluated, 15 had no micrometastases in their lymph nodes and demonstrated a median survival of 118 months. In contrast, 6 patients with lymph node micrometastases had a median survival of only 28 months. Furthermore, molecular analysis for p53 and K-RAS mutations was performed using MASA (mutant allele-spesific amplification) techniques in 9 of the 21 patients without micrometastases. Mutations were detected in 3 patients, all of whom were still alive at 4, 5, and 20 years of follow-up. The authors concluded that long-term survival was favorable in patients without lymph node metastases (even micrometastases) and negative for p53 and K-RAS mutations. However, it is important to note that this conclusion was based on only 3 patients.

Studies shedding new light on LT for CRLM were initiated in 2006. In Norway, organ donation rates are remarkably high at 25 per million population (pmp) and LT is performed at a rate of 17 pmp annually. Oslo and its surrounding area, with a population of 4.8 million, has a particularly efficient system where patients on the LT waiting list can access a deceased donor organ in less than one month. It is evident that organ donation exceeds the needs of patients requiring LT. Building on this favorable context, a study was launched in 2006 at Oslo University Hospital Rikshospitalet, named SECA. The acronym SECA stands for "Secondary Cancer." The inclusion criteria for LT in CRLM patients were: R0 resection of the primary CRC, absence of extrahepatic metastatic disease, unresectable CRLM confined to the liver, completion of at least 6 weeks of one or more chemotherapy regimens, and an ECOG performance status of 0–1. All patients underwent staging laparotomy prior to LT, during which hilar lymph nodes were assessed via frozen section. Patients without tumor involvement proceeded to LT. Staging laparotomy was performed either on the same day as LT or earlier, without strict adherence to one approach.

While the SECA study was still ongoing, the Oslo team and European Liver Transplant Registry (ELTR) published an article in 2010 titled "Revisiting the Concept".[9] The aim of this article was summarized as reviewing past experiences with LT for CRLM and discussing several factors that could potentially improve outcomes. Interestingly, it also mentioned some preliminary data from an ongoing pilot study (SECA) investigating the role of LT in CRLM treatment. The authors suggested that, with appropriate patient selection using modern imaging techniques, effective chemotherapy regimens, and aggressive multimodal treatment of metastases, long-term survival and even curative outcomes could be achieved. The SECA study reported an overall survival (OS) rate of 94% at 25 months. Remarkably, they speculated that if LT for CRLM could achieve long-term survival rates of ~80% after primary LT and ~50–55% after re-transplantation—comparable to other LT indications—it might be challenging to justify allocating deceased donor liver grafts for these patients, and living donors could become a viable option.

Three years later, the results of the SECA study were published.[10] This study initially enrolled 25 patients with

CRLM, but only 21 underwent DDLT because 4 patients developed extrahepatic metastases and were excluded. Post-transplant, sirolimus was used as immunosuppression, targeting blood levels of 5–10 ng/mL during the first month and 10–20 ng/mL thereafter. The median follow-up was 27 months. OS at 1, 3, and 5 years was 95%, 68%, and 60%, respectively. Thus, the 94% survival at 25 months declined to 60% at 5 years. The 1-year disease-free survival (DFS) was 35%. At the end of the study, 90% of patients (19/21) had experienced recurrence, and 6 patients eventually died of disseminated disease after a median of 24 months. Recurrences typically occurred early, with a median time to recurrence of 6 months. The lungs were the most frequent site of recurrence (13/19). Among the 19 patients with recurrence, 7 had isolated lung metastases, while 7 had lung and liver metastases, 5 had lung and bone metastases, 3 had lung and ovarian/adrenal metastases, 1 had peritoneal metastasis, and 2 had lymph node metastases. Additionally, 2 patients experienced recurrence of rectal cancer. Of the 7 patients with isolated lung metastases, 3 underwent resection, and at 27 months, all 7 were still alive (5-year OS of 72%). The authors concluded that lung metastases after LT for CRLM appeared indolent and did not negatively impact survival. Poor prognostic factors identified in this study included a maximum tumor diameter >55 mm, pre-transplant CEA >80 ng/mL, progression of disease while on pre-transplant chemotherapy, and an interval of less than 2 years between CRC resection and LT.

In 2015, the Oslo group published a new study[11] comparing the results of their SECA trial with those of the NORDIC VII study, which included patients with CRLM treated only with first-line chemotherapy regimens.[12] The NORDIC VII trial (2005–2007) had evaluated various chemotherapy strategies. These can be summarized into three groups: (1) bolus administration of 5-fluorouracil/folinic acid and oxaliplatin; (2) the same regimen combined with cetuximab; and (3) an intermittent administration of the first regimen combined with cetuximab. Notably, no patients in NORDIC VII underwent liver resection for CRLM. The study reported no significant differences in survival among the three groups. Median CEA levels differed markedly between the two studies: 42 ng/mL in NORDIC VII versus 15 ng/mL in SECA. The 5-year overall survival (OS) was 56% in SECA compared to only 9% in NORDIC VII. Even when comparing the 19 longest-surviving patients from NORDIC VII to those in SECA, the 5-year OS remained significantly lower in NORDIC VII (19%) than in SECA.

The European Consortium study was published in 2017 by Toso and colleagues.[13] Four centers from Portugal, Switzerland, and France participated in the study, enrolling a total of 12 patients. Following CRC resection, 11 patients received irinotecan and oxaliplatin-based chemotherapy, with 6 of these also receiving bevacizumab. The remaining patient was treated with hepatic arterial infusion. After a median interval of 41 months, all 12 patients underwent LT. The patients were followed for a median of 26 months. The reported OS rates at 1, 3, and 5 years were 83%, 62%, and 50%, respectively. Six patients developed recurrence, five of whom had pulmonary metastases. At 48 months, four patients remained alive and disease-free, leading the authors to emphasize the significance of this study in demonstrating the potential for long-term cancer-free survival. DFS at 1, 3, and 5 years was reported as 56%, 38%, and 38%, respectively.

The Oslo group published the SECA II study in 2020, involving 15 patients enrolled between 2012 and 2016.[14] Patients remained on the transplant waiting list for a median of 29 days, and the interval between CRC diagnosis and LT was 24 months. The immunosuppressive regimen consisted of tacrolimus for the first 4–6 weeks post-LT, followed by a switch to sirolimus. The mean follow-up duration after LT was 3 years. The inclusion criteria for SECA II were notably more stringent compared to SECA I. For instance, CRLM could have previously undergone resection and relapsed as unresectable disease to qualify for the study. Before starting chemotherapy, no single lesion was allowed to exceed 10 cm in diameter. If the number of lesions exceeded 30, none of them could be larger than 5 cm. Furthermore, patients with such tumor burdens had to show at least a 30% response to chemotherapy according to RECIST criteria. Patients with smaller lesions needed to achieve at least a 10% response to chemotherapy. If the response was less than 10% by RECIST, additional locoregional treatments such as TACE or TARE had to elicit a minimum 20% response for eligibility. In summary, SECA II included patients with more favorable tumor biology compared to SECA I. This was reflected in lower median CEA levels (15 ng/mL in SECA I vs. 2 ng/mL in SECA II) and lower SUVmax values of CRLM (9 vs. 5.9). Consequently, SECA II achieved improved survival outcomes: the 1-, 3-, and 5-year OS rates were 100%, 83%, and 83%, respectively. DFS was 53% at 1 year and 35% at 3 years. Median survival was also stratified: patients with fewer than 8 hepatic metastases had a median survival of 23.4 months, while those without lymph node involvement had a median survival of 11.6 months.

At this point, it is also important to discuss the Fong and Oslo clinical scoring systems. Both are based on adverse prognostic factors, with each criterion contributing 1 point.

The **Fong score**[15] includes the following:

- Development of CRLM within 12 months after CRC resection

- Positive lymph node involvement in the primary CRC
- Liver metastases larger than 5 cm
- CEA level >80 ng/mL

The **Oslo score**[14] incorporates:

- Interval between CRC diagnosis and metastasis <2 years
- Disease progression during chemotherapy
- Largest metastasis >5.5 cm
- CEA level >80 ng/mL

Lower scores in both systems were associated with prolonged survival. In the SECA II study, patients with Fong and Oslo scores of 0–2 had longer median DFS compared to those with scores of 3–4. At 3 years, OS was 75% in patients with lower scores, versus 25% in those with higher scores. In summary, SECA II included patients with more favorable tumor biology and achieved superior outcomes compared to SECA I.

Additionally, Dueland and colleagues published another study in 2020.[16] This analysis included patients from both SECA I and SECA II but only examined those with PET-CT scans performed within 90 days of LT. Patients without PET-CT within this timeframe were excluded to avoid missing potential disease progression. Fourteen patients from SECA I and five from SECA II were included. In this study, patients with a metabolic tumor volume (MTV) <70 cm^3 had a 5-year OS of 78%. Those with a Fong score of 0–2 achieved a 5-year OS of 100%, while patients with an Oslo score of 0–2 had a 5-year OS of 67%. Interestingly, CEA levels and KRAS mutation status (mutated or wild-type) did not show a significant impact on survival outcomes.

Living donor liver transplantation (LDLT) may represent a distinct approach in the management of CRLM, as it does not infringe upon the rights of other patients in the organ-sharing system. Elective operations can be planned following appropriate neoadjuvant treatments. Preliminary reports from a study conducted in Toronto outlined the inclusion criteria as follows: the primary CRC must be stage T2a or lower; the CRLM must remain stable or regress for at least 3 months before LT; and pre-transplant CEA levels must demonstrate stability or a downward trend. Additionally, CRC resection must have been performed at least 6 months prior to LT, and patients with BRAF mutations were excluded. During systemic chemotherapy following CRC resection, the disease needed to remain stable for at least 6 months. Furthermore, CEA levels had to be <10 ng/mL. A wash-out period of 4–6 weeks after systemic chemotherapy was required before proceeding to LT. In this study, 7 patients underwent LDLT, with 1- and 3-year OS rates of 100% and 100%, respectively. Recurrence was observed in 2 patients (29%). DFS was 85.7% at 1 year and 68.6% at 3 years. For comparison, 22 patients with similar baseline characteristics underwent resection of CRLM. In this resection group, the 1-year OS was 93.8% and the 3-year OS was 43.3%, while DFS at both 1 and 3 years was only 11.4%. Although overall survival was similar between the two groups, DFS was significantly better in the LT group.[17]

In the United States, one out of every six patients on the LT waiting list dies each year while waiting for an organ. However, this does not mean that the remaining five patients all receive transplants—some eventually do, while others continue to wait. Recent changes in UNOS allocation policies have prioritized patients with higher MELD scores, which has negatively impacted patients with cancer indications for LT. A multicenter study involving three institutions analyzed patients treated between 2017 and 2021.[18] Patients who demonstrated disease progression while receiving systemic therapy were excluded. Twelve patients who had undergone both local and systemic treatments were included; of these, two received DDLT and ten received LDLT. The median interval from metastasis diagnosis to LT was 1.7 years. Local and systemic treatments included liver resection in four patients, hepatic arterial infusion (HAI) chemotherapy in three patients, and tumor ablation in three patients. All patients had received systemic therapy with regimens such as FOLFOX, FOLFIRI, and targeted agents. Genetic analysis revealed KRAS mutations in three patients and one patient each with TP53, SMAD4, and BRAF variations. The median follow-up duration was 1 year. Recurrence was observed in three patients. At 1.5 years, DFS was 62.5% and OS was 100%. By year 3, OS decreased to 75% and DFS to 60%.

In the TRANSMET randomized clinical trial,[19] inclusion criteria were as follows: age 18–65 years, ECOG performance status 0–1, histological confirmation of CRC, confirmed CRLM with curative resection of the primary tumor, no local recurrence on colonoscopy within 1 year prior to enrollment, absence of extrahepatic disease, and stable disease or partial response for more than 3 months according to RECIST criteria on the last chemotherapy protocol. Patients were required to have received no more than three chemotherapy regimens, have no BRAF tumor mutations, serum CEA levels <80 ng/mL or at least a 50% reduction from baseline, and demonstrate adequate compliance. After stopping chemotherapy, patients were planned to undergo LT within 2 months. If progression occurred within those 2 months, LT was deferred, and chemotherapy was resumed. Upon re-establishing disease stability, LT could be reconsidered. In terms of organ allocation, a MELD score of 35 was assigned for prioritization. Immunosuppression

consisted of tacrolimus for the first 2 months, followed by everolimus, with corticosteroids continued for 6 months. The study included 20 centers across France (14), Belgium (4), and Italy (2). A total of 157 patients were enrolled, with 94 randomized (47 to the LT+chemotherapy arm and 47 to the chemotherapy-alone arm). LT was performed in 38 patients, with three re-transplantations required; one patient died. Among patients in the chemotherapy arm excluded due to tumor progression, 1-year OS was 71% and 2-year OS was 26%. Post-LT, 68% of patients initiated adjuvant chemotherapy at a median of 71 days, while 32% could not receive adjuvant treatment due to poor fitness. Eligible participants were selected by the local multidisciplinary tumour board a teach centre. Eligibility was assessed by an independent multidisciplinary committee of international expert oncologists, radiologists, and liver surgeons via monthly video conferences in the presence of local investigators. The interim results represented the first large multicenter randomized trial in CRLM and focused on the feasibility and safety of post-LT chemotherapy rather than survival data.

In September 2024, the more detailed results of the TRANSMET trial were published.[20] Post-LT chemotherapy was initiated in uncomplicated cases but was not mandatory. Patients in the LT+chemotherapy group received a median of 21 chemotherapy cycles, compared to 17 cycles in the chemotherapy-alone group. The 5-year overall survival (OS) was 56.6%, with 73.2% in the LT+chemotherapy group versus 9.3% in the chemotherapy-alone group. Among LT patients who experienced recurrence, secondary progression-free survival (PFS) was 35.4 months, and 5-year secondary PFS was 36.1%. The excellent outcomes of the TRANSMET trial were attributed to three key factors:

1. **Strict patient selection,** limiting prior chemotherapy to no more than three regimens.
2. **Independent validation committee** assessments to avoid emotionally driven decisions regarding LT eligibility.
3. **Timely transplantation**, ensuring patients reached LT within 2 months of enrollment.

In the study from Pittsburgh,[21] the inclusion criteria required that the primary CRC be resected with at least a 2 cm surgical margin, LT be considered at least 6 months after CRC diagnosis, patients receive 6–12 weeks of chemotherapy without disease progression, and serum CEA levels be <100 ng/dL. Between 2019 and 2022, 10 patients underwent LDLT. Among these patients, 50% had T3 stage primary CRC and 50% had lymph node involvement. Histologically, 90% of tumors were moderately differentiated. Molecular analysis revealed KRAS mutations in 2 patients, SMAD4 mutation in 1 patient, and PIK3CA mutation in 1 patient. The median interval between CRLM diagnosis and LT was 2.8 years. Each patient received an average of 10.5 cycles of chemotherapy. The selected LT patients had a mean Fong score of 2 and an Oslo score of 1.5. Four donors were altruistic. The median follow-up period was 1.6 years. The mean DFS was 2.2 years, and the mean OS was 3 years. During the study period, 3 patients developed recurrence. At 1.5 years, recurrence-free survival (RFS) was 62% and OS was 100%.

Currently, there is a growing body of research on LT for CRLM. Expanding international experience will be critical in optimizing recipient and donor selection for LT in patients with non-resectable CRLM. Advanced genomic analyses—including liquid biopsy, tissue profiling, and nuclear medicine approaches—will play a pivotal role in refining patient selection and improving outcomes. The landscape of LT for CRLM is far more promising today than it was two decades ago. Factors such as the Fong score, Oslo score, PET-based metabolic tumor volume and liver uptake values, tumor location (right- vs left-sided), histological differentiation, lymph node status of the primary tumor, and tumor-specific genetic mutations all significantly influence post-transplant outcomes. Thus, meticulous patient selection through a multidisciplinary and collaborative approach remains essential.

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Review

Liver Transplantation for Hemangioendothelioma

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Abstract

Epithelioid hemangioendothelioma is a rare vascular endothelial cell-derived tumor that occurs in one in a million cases, and one of the most common organs affected is the liver. Clinically, it can range from benign to aggressive. Due to its rarity, clinical management has not been standardized. For this reason, diagnosis is difficult, and it is often confused with other liver tumors. The prognosis is better than that of other liver malignancies. Laboratory findings are nonspecific, and tumor markers may also be elevated but are nonspecific. Imaging methods, particularly computed tomography and magnetic resonance imaging, are used. For a definitive diagnosis, a biopsy and immunohistochemical staining must be performed to demonstrate the staining of various endothelial cell antigens. Here, it is important to determine the hemangioma and sarcoma patterns with the help of genetic markers, as this will closely affect the course of the disease. Treatment is divided into two main categories: surgical and non-surgical. If possible, surgical treatment is the first recommended curative option. Surgical treatment includes liver resection and liver transplantation. Liver resection may be preferred in unilobar and unifocal disease. However, liver transplantation may be more appropriate in patients with late diagnosis and multilobar and multifocal disease at the time of diagnosis. Extrahepatic metastasis is not considered a contraindication for curative surgery. Lung metastasis is the most common type of metastasis. The success rates of both surgical methods are similar, but it should be noted that studies have shown that patients who undergo resection are in earlier stages of the disease, while those who undergo transplantation are in later and more advanced stages. Being over 60 years of age, Asian ethnicity, male gender, tumors larger than 10 centimeters, symptomatic disease, and involvement of serosal surfaces in the body are poor prognostic factors. The success rate after transplantation is over 90% in the first year, while the 5-year results are around 80%. The presence of macrovascular invasion reduces the 5-year survival rate by half. The rate of complications after transplantation is also around 20%. Non-surgical treatments include chemotherapy, radiotherapy, immunotherapy, radiofrequency ablation, hormone therapy, chemoembolization, radioembolization, and arterial embolization. These treatments are more commonly used as a bridge to surgical treatment rather than as a curative first step. With chemotherapy alone, the 5-year survival rate is below 30%. Due to the vascular origin of the tumor, commonly used chemotherapeutic agents include anti-VEGF agents and interferon alpha-2B. It has been observed that this rate is much lower when no treatment is administered. New studies will also help to better understand tumor biology and improve neo- and adjuvant treatment protocols.

Keywords: Epithelioid hemangioendothelioma, hepatectomy, liver transplantation, transplant oncology

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Epithelioid hemangioendothelioma (EHE) is a rare vascular endothelial cell tumor composed of epithelioid and histiocyte-like vascular endothelial cells in a mucus or fibrotic matrix.[1] It can occur in multiple parts of the including the liver, lungs, soft tissue, head and neck, pleura, spleen, bones and many other organs.[1] The incidence of hepatic hemangioendothelioma (HEHE) is 0.1 per 100.000 population.[1] The malignancy potential changes between

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hemangioma and hemangiosarcoma.[2] Due to its rarity and protean behavior, the optimal clinical management of HEHE has not been standardized.[3] This study aims to review the clinical characteristics of HEHE and evaluate the outcomes of liver transplantation as a treatment strategy.

Pathology and Genetic basis of HEHE

The disease is more prevalent in women and is most commonly seen in the 30 to 50 age group.[1] The mean age of patients who underwent LT because of HEHE are changing between 32 and 43 years in previous reports (Table 1).[4-11] Females more frequently underwent LT, although two studies reported a higher proportion of males.[6,9] No definitive cause has been identified for the disease, but various risk factors have been suggested. These include oral contraceptive (OC) use, alcoholic hepatitis, viral hepatitis, primary biliary cholangitis, and exposure to toxic substances such as vinyl chloride, asbestos, polyurethane, chloroethylene, and silica.[12] Among patients who underwent LT, the incidence of alcohol abuse, nonalcoholic steatohepatitis (NASH), cirrhosis and Budd-Chiari syndrome is 16%, 4.7%, 2%, and 4%, respectively.[10] Most HEHE patients undergoing LT do not have significant underlying liver disease. Patients generally do not suffer from underlying liver disease or portal hypertension-related symptoms. The Model End-Stage Liver Disease (MELD) scores of patients who underwent LT are between 6 and 10 in most of the studies.[4, 9, 10] The patients with higher MELD scores have suffered from portal hypertension due to portal vein thrombosis or huge tumors that decrease the functional liver parenchyma. In a study by Rodrigue et al. nearly 20% of patients were followed intensive care unit before liver transplantation and the mean MELD score was 27 (Range between 6 and 40).

Like the etiology, the pathological mechanism of the disease has not been fully elucidated. Genetic mapping has revealed changes in two genes, WWTR1-CAMTA1 and YAP1-TFE3, that contribute to in the development of the disease.[13] These gene mutations are oncogenic in nature and activate tumor formation.[13] As the underlying genetic mutation exists throughout the liver, there might be several tumor origins in the liver. As in the early phase of HEHE, there're several nodular lesions among the parenchyma. It has been suggested that hepatotrophic, regenerative cellular signalling after hepatic resection may lead to rapid hyperproliferation of residual malignant disease in some patients.[14] After nodular formation, diffuse pattern is seen in whole liver and invasion of vessels are seen.

In addition to this genetic mapping, the downregulation and upregulation of microRNA (miRNA) have also been shown to play a role in the etiology of the disease.[15] Although our current knowledge suggests that mapping has limited prognostic and therapeutic effects in HEHE, we believe that it has significant impacts in such rare diseases and will become more effective in the future.

Diagnosis

Due to the lack of specific clinical features and rarity of HEHE, it is often misdiagnosed or overlooked at first.[16] It is most commonly misdiagnosed with cholangiocarcinoma, angiosarcoma, hepatocellular carcinoma (HCC), or metastatic carcinomas.[1] More than a quarter of cases are asymptomatic, and approximately 40% are diagnosed incidentally.[16] In the previous studies, the incidence of asymptomatic patients who underwent LT for HEHE was between 19% and 36%.[7,10,17] As the tumor grows slowly and a significant number of patients are asymptomatic, the patients are mostly diagnosed in late phases, such as bilobar involvement. The most common symptom is right upper quadrant pain; however, hepatomegaly, weight loss, jaundice, nausea, and anorexia may also be present. The

Table1. Summary of previous studies about Liver Transplantation for Hemangioendothelioma

Study	n	Male (%)	Mean Age (years)	Mean MELD score	Ratio of LDLT (%)	Re-Transplantation rate (%)	Survival			Recurrence (%)
							1-year survial	3-year survial	5-year survival	
Brahmbhatt et al.[1]	31	29	43	7	5	22	88.6	78.9	77,2	6.8
Rodrigue et al.[6]	10	20	40.5	NA	0	0	NA	87.6	NA	NA
Lerut et al.[2]	59	27	42	NA	5	NA	93	85	83	23.7
Krasnodebski et al.[3]	18	16	39	7	0	0	94		82	0
Nudo et al.[4]	11	27	38.7	NA	0	NA	NA	NA	82	36.4
Na et al.[11]	4	25	41.3	10	100	0	75	75	75	25
Larson et al.[5]	121	56	43	7	11	NA	NA	NA	72	4.9
Lai et al.[6]	149	33	43	9	3.4	NA	NA	NA	80	24.8

LDLT: Living Donor Liver Transplantation; MELD: Model for End Stage Liver Disease; NA: Not Avaliable; n: Number of patients.

incidence of right upper quadrant discomfort or pain is 57%-62% among patients with LT.[7,10,17] The severity of disease symptoms increases as the disease progresses, with an increase in the number and size of lesions. Rarely, an association with Kasabach-Merritt syndrome or Budd-Chiari syndrome has been reported.[10,16,18] Portal vein thrombosis or hepatic vein thrombosis may occur due to compression from liver lesions. These compressions might lead portal hypertension and Budd-Chiari symptoms. In the study of Agrawal et al, one patient waiting for LT died due to liver failure accompanied by jaundice, ascites, and abnormal liver function tests.[19]

Although there are no specific laboratory findings, liver function tests (LFTs) may be abnormal, with approximately 15% of patients show no abnormalities. Among LFT's, the incidence of abnormal Aspartate transaminase (AST) and Alanine transaminase (ALT) were found around %35 of patient who underwent LT for HEHE.[7,10,19] The incidence of abnormal gamma glutamyl transferase (GGT) and alkaline phosphatase (AP) was around %50 that is much higher than the incidence of other abnormal LFTs.[5,7,10] The incidence of abnormal international normalized ratio (INR) and albumin was around 2%, which is lower than the incidence of other abnormal values. Increased cholestatic enzymes are related to tumor compression of the biliary system. Deterioration of INR and albumin is mostly related with portal hypertension and liver insufficiency. Patients who underwent LT for HEHE generally have normal tumor marker levels (AFP, CEA, and CA 19-9) and these levels may only be used to rule out primary or metastatic liver tumors.[16] However, some studies have shown that CEA levels may be elevated. In a study by Lai et al., the incidence of abnormal AFP, CEA and CA 19-9 was 8%, 18% and 2%, respectively.[10] In studies by Larson et al. and Remiszewski et al., the tumor marker levels were normal.[5,9]

On ultrasound imaging, lesions are predominantly hypoechoic in appearance, but may also appear hyperechoic or isoechoic in a smaller proportion of cases. Calcifications within the tumor, as well as splenomegaly and capsular retractions, may be observed.[16,20]

Lesions generally appear hypodense on non-contrast computed tomography (CT).[20] Capsular retraction or coarse calcifications within the tumor may be better visualized on non-contrast CT than on contrast-enhanced imaging. Cholangiocarcinomas and metastatic tumors may also cause capsular retraction.[21] A target sign may be seen on contrast-enhanced CT. This is caused by early peripheral arterial filling accompanied by central filling in the portal and delayed phases.[21] The lollipop sign, which is uncommon in other tumors, may also be indicative of HEHE. Here, the image forms as a result of the flow ceasing and the hypodense lesion becoming visible when the lesion protrudes while the flow continues in the portal or hepatic vein branches. The blood flow in the vessel represents the stick, while the lesion represents the sugar part.[21]

Magnetic resonance imaging (MRI) is superior to CT in showing small and subcapsular lesions.[22] In contrast-free T1-weighted sequences, the lesion appears hypointense centrally and hyperintense peripherally, whereas in T2-weighted sequences, it appears hyperintense centrally and hypointense peripherally. This can be explained by central hyposignal intensity due to thrombosis, necrosis, or calcification.[22] In contrast-enhanced MRI scans, images similar to those seen in contrast-enhanced CT are observed. In the arterial phase, homogeneous contrast uptake, ring-like or heterogeneous uptake may be observed. In diffusion imaging, a target sign with hyperintense appearance at the outer edge and centrally may be observed.[21,22]

The patients who underwent LT were mostly evaluated with MRI. In the study of Agrawald et al., all patients were evaluated with MRI and capsule formation was a common finding.[19] In the study of Lerut et al., %86 of patients had bilobar tumors in their livers and more than 15 lesions. The "cocarde image", capsule formation, and calcifications were seen with percentages of 24%, 25% and 13%, respectively.[7] The incidence of portal and hepatic vein thrombosis was 50% and 54%, respectively in the study of Lerut et al., whereas the incidence is portal vein and hepatic vein thrombosis was 36% and 23%, respectively in the study of Lai et al.,[7,10] The bilobar tumor or existence of major vein thrombosis might be higher in transplantation cases as they're mostly selected as inoperable, but on the other hand it should be kept in mind that, cases are mostly presented late. As in the study of all HEHE cases, unilobar disease was seen in only 13% of cases, and only 9% were suitable for resection.[16] In previous studies, the tumor dimensions of patients who underwent LT for HEHE ranged from 3 to 18 cm.[5,8,19] It was suggested that LT is advised for the patients who had multiple lesions (>10 lesions and involvement of >4 segments). Radiological evaluation is performed not only for liver but also for extrahepatic tumor metastasis. Extrahepatic metastasis is not accepted as a contraindication for LT. In the previous studies, incidence of extrahepatic metastasis to lung, brain, peritoneum, spleen and bones were around %16-%26.[5, 7, 10] The most common organ was the lung. As differentiation of lymph node metastasis may not always be possible with radiological evaluation, lymph node metastasis was found in around 20% of the sampled cases.[5, 17, 23] While most of the studies emphasize the lymph node metastasis as a risk factor for recurrence and survival, the study of Cardinal et al. did not show a relationship.[7,10,17]

This may be because not all cases in LT sampled lymph nodes. For this reason, sampling lymph nodes will be beneficial during LT.

FDG metabolism, uptake, and excretion show considerable variation in HEHE cells. Therefore, PET-CT scans performed at different times may be useful for detecting lesions.[24] A study showed that FDG uptake is associated with tumor cellularity and may shed light on the histopathology of the lesion.[24] Approximately one-third of cases show uptake similar to that of normal liver parenchyma. Central fibrosis and peripheral FDG uptake caused by peripheral neoangiogenesis are present in the images, but this pattern is also present in diseases such as peripheral cholangiocarcinoma. The fact that FDG uptake is lower in HEHE cells than in other hepatic malignancies such as peripheral cholangiocarcinoma, which may be helpful in differential diagnosis.

The most reliable method for diagnosis is biopsy followed by a histopathological examination.[25] However, the false-negative rate after biopsy can reach 10%. Among patients who underwent LT for HEHE, percutaneous liver biopsy has mostly been performed with an incidence of 87%-100%.[10, 17, 19] In one of the studies, biopsies were obtained by diagnostic laparoscopy before LT.[5] Only one case of seeding during the biopsy has been reported.[7] Histopathological examination reveals dendritic and epithelioid cells showing vascular differentiation.[25] Immunohistochemical examination reveals CD31, CD34, cytokeratins, and Factor VIII-related (FVIII-RAg) antigens in endothelial cells.[26] Factor VIII-RAg positivity is 98% in HEHE. Histological features of HEHE might resemble with sclerosing hemangioma, angiosarcoma, or cholangiocarcinoma; an immunohistochemical examination is needed. However, there is no histopathological feature that can predict the prognosis of the tumor. With increasing experience about HEHE, more molecular findings are accepted as prognostic factors and the nature of tumor. WWTR1 and CAMTA1 genetic markers for HEHE can be used for dominancy of hemangioma or sarcoma like patterns of HEHE.[27] Also, new genetic markers will help us for monoclonal nature of the disease. By this way, approach to multiple liver lesions or extrahepatic lesions might be changed.

Treatment

Due to the rarity of the disease and the lack of homogeneity in its clinical course, there is no definitive treatment guideline. The prognosis is better when compared to other liver malignancies. It has been reported that 25% of patients with HEHE did not receive any treatment have 1-year survival rate less than 50%, 5-year survival rate is around 5%-30%.[16,28] Treatment modalities are divided into surgical and non-surgical treatments. Only 19% of patients present with unilobular disease, and of those, only 9% are candidates for liver resection.[16] Grotz et al. suggest liver resection only for patients with solitary lesions.[28] Negative surgical margins are considered sufficient for surgical treatment. Extrahepatic lesions are not contraindication for liver resection. The respectability rate is low and the 5-year survival rate following liver resection is around 75%.[16,28,29] This is probably due to hepatotropic, regenerative cellular signaling after liver resection or an underlying genetically defective liver. Additionally, after radical or palliative resection, aggressive disease recurrence or fulminant hepatic failure have been reported.[30] Although there is no underlying liver disease with HEHE, patients with multiple HEHE lesions have died from hepatic failure while waiting for a LT[19] HEHE lesions probably deteriorate liver function in addition to occupying mass. The presence of extrahepatic metastases, the patient being over 60 years of age, Asian ethnicity, male gender, a tumor larger than 10 cm, symptomatic disease, and serous effusion have been shown to be poor prognostic factors.[31] Also, in liver diseases such as underlying liver cirrhosis, multifocal diseases, and cases where radical resection is not possible. In the study of Lai et al., the incidence of underlying liver diseases (Budd-Chiari, cirrhosis, portal hypertension) is 13.4%.

Non-surgical treatments such as radiotherapy, radiofrequency ablation, hormone therapy, arterial embolization, chemoembolization, and irreversible electroporation have been performed in a limited number of cases and without uniform treatment modalities.[16, 32, 33] It is unclear whether these treatments are performed for a limited number of lesions or for advanced diseases. However, the 5- year survival for chemoradiotherapy is less than 30%.[16, 28] These treatment modalities may be preferable for bridging treatment before LT. In a study of Cardinal et al., 2 patients underwent LT after Transarterial Chemoembolization (TACE) and achieved survival of more than 100 months.[17] In non-surgical treatments, anti-VEGF agents have been emphasized, considering that the tumor is of vascular origin. Thalidomide, sorafenib, bevacizumab, and paclitaxel are among the agents used. In addition to these agents, interferon alpha-2B (IFN-a 2b) has begun to be used to reduce post-transplant recurrence and metastatic lesions.[34] Other studies have shown that IFN-a 2b therapy provides partial response, complete response, and disease stabilization. The proposed mechanism involves hepatic NK cell activation, inhibition of COX-2 and VEGF expression.[35] Sirolimus is an immunogenic agent that exerts its effect by inhibiting endothelial growth factor and can be used in treatment. However, in previous studies, everolimus has

not been mentioned as part of an immunsuppressive protocol. Everolimus may be preferred as an immunosuppressive agent after LT. It has been shown that chemotherapy is more useful for stabilization than radical treatment. In patients awaiting transplantation or those who are not candidates for surgery, the combination of capecitabine and bevacizumab has been shown to significantly reduce tumor size. Chemotherapy treatment has been shown to have a negative impact on survival in localized tumors. If distant metastasis is present, no difference in survival has been observed between the surgical and non-surgical groups. Adjuvant therapies after transplantation are recommended to prevent graft loss and recurrence. In a randomized, multicenter study conducted in China demonstrated that Huaier granule, a substance that inhibits angiogenesis, reduces the risk of recurrence in the postoperative period.[35]

As HEHE is usually multifocal and therefore not suitable for partial resection, LT appears to be an acceptable treatment method. In a recent analysis, the 5-year survival rates for HEHE recipients and non-HEHE recipients were 72% and 77%, respectively.[9] Similarly several recent studies have found the 5-year survival rates to be around 80% in HEHE recipients[4, 7, 8, 10] (Table 1). The 1-year survival rates are also around 90% in previous studies.[4,7] However, in Rodriguez et al.'s study, the one-, three-, and five-year survival rates were 80%, 68%, and 64%, respectively, which are lower than in other reports.[6] This is probably due to the high percentage of pediatric HEHE cases in this study (38%). It should also be kept in mind that patients who underwent LT had more advanced liver lesions than patients who underwent liver resection. For this reason, a comparison of LT and liver resection with similar tumor features has not been performed. Compared to liver resection, LT is thought to have fewer advantages due to the need for immunosuppression and the complexity of the procedure. However, the multifocal nature of HEHE makes LT a better therapeutic option. However, nearly 20% of cases have extrahepatic metastasis, which raises concerns about high-risk recurrence after LT. In the study by Cardinal et al., the existence of extrahepatic disease beyond the regional portal nodes was a negative predictor of the outcome after liver transplantation (LT). However, several other studies have shown that patients with extrahepatic metastases can have long survival rates after LT. In the study by Lerut et al., one patient underwent mediastinal tumor resection before LT. In the study by Lai et al., 4.7% of patients underwent surgery due to extrahepatic metastasis.[7,10] Some studies have also shown that pulmonary resections, splenectomies, peritoneal resections, omentectomies, and diaphragmatic peritonectomies were performed during LT.[7,8,10,34] In the study of Lai et al, %18 patients underwent organ resections during LT and %53 underwent lymphadenectomy during LT.[10] Lymphadenectomy is advised during LT. Among these studies, the localization of extrahepatic disease is reconfirmed not to be a contraindication for LT. As presented in a previous study, patients can die from rapidly progressive disease while on the waiting list, and most cases are unresectable. In countries where deceased donor liver transplantation (DDLT) is performed, patients with HEHE receive exceptional points on the liver transplantation waiting list.[4, 10, 19] In the study by Larson et al., it was shown that the exception point rate is 74% for HEHE patients.[9] This high rate of exceptional points shows how severe the tumors are. However, of the 131 candidates with HEHE who were waitlisted for LT, only 67% underwent LT, and 10% were removed due to death or illness. The study in which exceptional points were given showed that the median waiting time for LT for patients with HEHE was 78.5 days.[4] In Agrawal et al.'s study, the mean waiting time for LT for three out of four patients with HEHE was 80 days; however, one patient with HEHE died while on the waiting list.[19] Previous studies have shown that the LDLT rate is limited (Table 1). Only in the study by Na et al. did all patients undergo LDLT.[11] The rate of domino liver transplantation for HEHE in the study by Lai et al. was 2%. For these reasons, living donor liver transplantation, which has no waiting period, is strongly suggested.[4] Increased post-transplant survival was achieved with LDLT.[9] In countries in which extra points are not given for HEHE should wait longer period for LT. In these countries LDLT is a better option for patients with HEHE.[11] On the other hand, the Lai study found that a waiting period of less than 120 days was associated with an increased risk of post-LT recurrence.[10] Waiting time is a tool for observer tumor behavior and aggressiveness and a means to permit the delivery of neoadjuvant therapy. Lai et al. suggested observing patients under neoadjuvant treatment to select patients based on tumor aggressiveness. They also stated that recurrence after LT for hepatic hemangiosarcoma (HHS), which is difficult to differentiate from HEHE, is mostly seen within the first six months.[10] However, HHS is a completely different and aggressive disease and a comment is not possible regarding difficult differentiation. Additionally, this registry did not provide waiting drop-out rates.[10] For these reasons, longer waiting period might risk the loss of chance for LT for patients with HEHE.

In countries where DDLT mostly performed, the patients with HEHE in waiting list are taken into neoadjuvant treatments. In the study of Lerut et al., 15% of patients underwent systemic or locoregional chemotherapies before the LT.[7] Liver TACE treatment was performed in the 4% of patients in the study of Lai, and two patients in the study of Cardinal et al.[10,17] The rate of neoadjuvant treatment is

42% in previous studies.[10] No study has compared patients with HEHE who underwent LT with or without neoadjuvant treatment; but Lai et al. describe some of the potential mechanisms for neo- and adjuvant treatments.[10] In the study of Lerut et al., survival was not affected by lymph node metastases, prior treatment, or the presence of extrahepatic disease.[7]

The recurrence rate after LT for HEHE is between 4-32% in previous studies.[6,7,9,10] In the study of Lerut et al., the mean recurrence time is 49 months (range 6-98 months).[7] The most common metastatic sites are the liver and lungs. Lung resection, lung transplantation, radiotherapy and chemotherapy have been used for the treatment of metastasis.[7] The 1-, 5- and 10-year disease free survival rates are 90%, 82%, and 64%, respectively.[7] The estimated recurrence related mortality rate is 15.3%.[7] In the study of Rodriguez et al., the rate of mortality due to HEHE metastasis is 16%.[6] In the study of Lai et al., the recurrence rate was 24%, and nearly half of the recurrent cases were treated with surgery, chemotherapy, radiotherapy, or hormonal therapy.[10] The median time for recurrence is 18 months (range, 8-65 months).[10] The 1-, 5- and 10-year disease free survival rates are 88%, 79.4% and 72.8%, respectively.[10] In a study with limited number of cases, the recurrence rate was 36%, with a median recurrence time of 25 months.[23] The reports indicate that recurrences occur soon after LT and are treated with other options. Lymph node invasion, macro- and microvascular invasion were shown as risk factors for recurrence after LT.[7,10] The 5-year DFS rate were 84.7% versus 44% in patients without or with macrovascular invasion.[10] The 5-year DFS rate were 84.2% versus 65.4% in patients without or with LN invasion.[10] On the other hand, in another study with a limited number of cases, the rate microvascular invasion was 11%, and the rate of macrovascular invasion was 0%. However, the recurrence rate was much higher 36%.[23] In the study of Cardinal et al., angiolymphatic invasion or positive LN involvement was not a prognostic factor for recurrence.[17] These conflicting results show that the tumor biology and features should be defined in detail. There is no standard treatment modality for LT patients with HEHE.

The complication rate after LT in patients with HEHE were between 18% and 24%.[7,17] Complication rates after LT for HEHE are not significantly different than the LT for non-HEHE cases.[9] The immunosuppressive protocols are not mentioned in the literature for LT for HEHE.

At the Acibadem Atakent Organ Transplantation Unit, two female patients who initially presented with right upper abdominal pain underwent LT. In their first MRI evaluation, there were bilobar multiple nodular lesions without vascular invasion. The largest lesions measured 5 and 6 cm. The lesions were suspected to be metastases, but the the pathological diagnosis was HEHE. One of the patients underwent domino liver transplantation from a Criggler-Najar child. The second one underwent LDLT from her brother. They are 25 and 53 years old. They have survived for 20 and 86 months without recurrence. The immunosuppressive changed from Tacrolimus to Everolimus 6 months after the LT.

Conclusion

LT remains the most effective treatment for HEHE. The biological behavior of HEHE mostly depends on its molecular markers. Defining the molecular background may affect its hemangioma or hemangiosarcoma like growth or metastasis. New studies on biology and structure of tumors may help us devedlop neo- and adjuvant treatment options for LT. Further research is needed to establish the efficacy of LDLT in patients with HEHE.

Disclosures

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Review

Liver Transplantation for Cholangiocarcinoma: An Update and Review

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Abstract

Cholangiocarcinoma (CCA) is an aggressive malignancy of the biliary epithelium. Its management is significantly challenging, as most cases are diagnosed at an advanced stage and treatment options are limited. Surgical resection is the standard treatment approach. However, approximately 70% of patients are diagnosed with unresectable disease due to distant metastases, extensive local disease, or poor hepatic reserve. Liver transplantation (LT) has gained attention as an alternative for select cases of unresectable perihilar (pCCA) and intrahepatic (iCCA) CCA.

This review aims to evaluate the role of LT in the management of CCA.

Earlier studies assessing the use of LT in treating CCA reported poor outcomes. However, the development of new neoadjuvant chemoradiotherapy protocols has led to remarkable improvements in post-transplant outcomes, with five-year survival rates exceeding 80% in selected pCCA patients. As for early-stage iCCA, limited data suggest that LT combined with neoadjuvant therapy yields more favorable outcomes than surgical resection, suggesting its potential benefit.

LT combined with neoadjuvant chemoradiotherapy appears to be a promising treatment option for unresectable CCA, especially in select cases of pCCA. Yet, there is still a significant gap in the literature, and further studies are needed to address this issue.

Keywords: Cholangiocarcinoma, liver transplantation, living-donor liver transplantation, peri-hilar cholangiocarcinoma

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Cholangiocarcinoma (CCA) is an aggressive malignancy of the biliary epithelium, being adenocarcinoma histologically.[1,2] It is the second most common primary malignancy of the liver after hepatocellular carcinoma, with an estimated prevalence of around 6 persons per 100,000 population.[2,3] CCA occurs more frequently in certain areas around the world, such as Chile, South Korea, and Thailand.[3] CCAs are categorized into three primary subtypes according to their anatomical site of origin: intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA) CCA.[2,4] Primary

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sclerosing cholangitis (PSC) is one of the most common risk factors for the development of CCA. Among patients with PSC, the annual risk of developing CCA ranges from 0.5% to 1.5%.[5] Other risk factors implicated in the development of CCA include liver fluke infection, congenital biliary cystic disorders, intrahepatic gallstones, and cirrhosis.[6] CCA is associated with a generally poor prognosis with a 5-year overall survival rate of less than 10%.[7–9] In addition, CCA has a high rate of recurrence treatment (>75%).[10,11]

The standard treatment for CCA has been radical surgical resection due to its potentially curative nature. However, surgical resection is often not feasible due to either local advancement and metastasis of the tumor at presentation or inadequate hepatic functional reserve secondary to underlying liver disease. It is estimated that up to 70% of cases of CCA are not amenable to resection, which underscores the challenges associated with the treatment of CCA.[12] Patients with unresectable CCA have a survival of only 12-16 months after development of symptoms.[13] The dearth of feasible treatment options is especially clinically relevant given the generally poor prognostic outcomes associated with CCA.[10,11]

In recent years, liver transplant (LT) has increasingly been explored as a potentially curative treatment option for locally advanced iCCA and pCCA without distant metastasis. LT for CCA was first performed in the 1980s with poor treatment outcomes due to a high incidence of recurrence (~50%) and mortality (5-year survival ~15%).14 These early studies showed LT alone was associated with poor overall outcomes in patients with CCA. However, in 1987, the transplant team at the University of Nebraska devised a protocol of high-dose neoadjuvant brachytherapy and 5-fluorouracil (5-FU) preceding LT. Early results reporting survival were encouraging.[15] In 1993, the Mayo Clinic developed its own neoadjuvant chemoradiation protocol for LT along with strict patient selection criteria. Preliminary results reported in 2000 showed promising results, and a 2004 update by the Mayo Clinic reported a 5-year survival rate of 82% for 28 patients.[16,17] Results from the Mayo Clinic and other retrospective studies have led to the acceptance and adoption of LT as a treatment option for pCCA in carefully selected patients. A standard model for end-stage liver disease (MELD) exception was also introduced in 2009 to facilitate patients with pCCA listed for LT.[18] While earlier research indicated that liver transplantation was not recommended for iCCA because of poor outcomes, more recent studies have shown better outcomes, particularly in patients with very early or early-stage iCCA.[19] This may reflect the importance of improved neoadjuvant therapy, stricter patient selection criteria, and increased center experience in patients undergoing LT for CCA.

In this review, we will discuss the existing literature on LT for CCA, focusing on pCCA and iCCA, explore outcomes and complications associated with LT for CCA, and compare LT outcomes with surgical resection for CCA. Additionally, we also aim to highlight any differences in outcomes between LT from living donors versus deceased donors. Given surgical resection is precluded in up to 70% of pCCA cases due to advanced disease at presentation, it is important to assess the feasibility of other treatment options with acceptable survival and recurrence rates.[20,21]

Classification of Cholangiocarcinoma

CCAs are categorized into three primary subtypes according to their anatomical origin: intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA) CCA.[2,4] iCCA arises proximal to the second-order bile ducts; pCCA develops in the region extending from the right and left hepatic ducts to the confluence of the cystic duct and common bile duct; and dCCA occurs distal to this confluence.[2] pCCA is the predominant subtype of CCA, representing approximately 50% of cases. dCCA and iCCA follow with a prevalence of approximately 42% and 8%, respectively.[22]

The reported incidence of iCCA has shown an upward trend across the US (0.44 cases per 100,000 in 1973 to 1.18 cases per 100,000 in 2012), whereas the incidence of extrahepatic CCA has been relatively stable.[23,24] It remains unclear whether the observed rise in iCCA cases reflects a true increase in incidence or is a result of improvements in diagnostic accuracy.

Surgical Resection

Surgical resection remains the primary treatment option for CCA with curative intent. The affected lobe or segments containing the tumor are typically removed in cases of iCCA. dCCA is usually treated with a pancreatoduodenectomy, while for pCCA, the surgical approach often involves resecting the affected intrahepatic and extrahepatic bile ducts, along with the ipsilateral liver, gallbladder, and regional lymph nodes, depending on tumor extent.[12]

Recommendations for surgical resection must take into account the patient's suitability for surgery, the size of the tumor, any metastatic spread, biochemical characteristics, and vascular and/or lymphatic involvement.[25] Survival after surgical resection varies by CCA subtype; 5-year survival rates following surgical resection vary depending on the CCA subtype, ranging from 22% to 44% for iCCA, 11% to 41% for pCCA, and 27% to 37% for dCCA.[12] R0 resection is key for long-term survival.[22] Positive tumor margins, cirrhosis, portal hypertension, and lymph node metastases are all associated with worse outcomes in patients who undergo surgical resection for CCA.[22,26,27] Neither neoadjuvant nor adjuvant therapy seems to favorably impact survival in patients who undergo resection for CCA.[28]

Notably, most patients are diagnosed with tumors that are not amenable to surgical resection — up to 70% of CCA tumors are classified as inoperable due to locally advanced tumors, distant metastases, lack of functional hepatic reserve secondary to underlying liver disease, etc.[12,29] This has contributed to the growing use LT as a treatment option for unresectable CCA.

Liver Transplantation

History of LT for CCA

The success of LT as a curative treatment for hepatocellular carcinoma encouraged the consideration of LT as a treatment option for CCA. Since LT achieves radical resection and often results in clean/R0 resection margins, it was thought that LT could be an ideal operation for CCA, especially in cases of underlying PSC. However, early studies reported poor survival outcomes and high recurrence rates. The Cincinnati Transplant Tumor Registry, which included data until 1997, reported a 5-year survival rate of 23% and a recurrence rate of 51%.[14] In those with recurrence, the median time from LT until recurrence was only 10 months. Another study, which included data from 1984 up to 1992, reported results from a center after the development of a protocol involving adjuvant chemotherapy and radiotherapy following LT for CCA.[30] Although the adjuvant therapy was well-tolerated, they found that their adjuvant therapy protocol failed to demonstrate a significant benefit. They reported 1-year survival to be 53% and the disease-free survival after 1-year to be 40%.[30] A study from Japan reported an overall survival rate of 35% at 3 years.[31] A multicenter Canadian study examined data from 1996 to 2003 of patients undergoing LT with incidental CCA found in the explant and reported a 3-year survival rate of 30% and a median recurrence time of 26 months.[32] A Spanish retrospective study of 36 patients with pCCA reported similar results with a 30% 5-year survival rate and a 53% tumor recurrence rate.[33]

The poor outcomes reported in the early studies may be due to poor patient selection criteria, lack of neoadjuvant therapy use, and lack of differentiation between tumor subtypes.

Neoadjuvant chemoradiotherapy

In 1987, the University of Nebraska introduced a neoadjuvant treatment protocol prior to LT involving the use of 5-fluorouracil (5-FU) combined with high-dose biliary brachytherapy. The rationale behind this approach was to curb and potentially downstage the tumor.[15] Although complications developed in some patients, survival outcomes were encouraging — long-term, tumor-free survival was 45% in transplanted patients. In 1993, the Mayo Clinic developed its own neoadjuvant protocol that included three weeks of continuous infusion of 5-FU and a subsequent two weeks of brachytherapy.[16] Capecitabine was then given until LT. For staging purposes, patients underwent abdominal exploration a few days before deceased donor transplantation and one day before living donor transplantation. Details of this protocol are outlined in Table 1, including strict patient selection criteria (Table 2 and Table 3).[16]

Table 1. Criteria for neoadjuvant therapy and liver transplantation for pCCA

Transcatheter biopsy or brush cytology
CA19-9 >100 mg/ml and/or mass on cross-sectional imaging with a malignant-appearing stricture on cholangiography
Biliary ploidy by FSH with a malignant-appearing stricture on cholangiography
Unresectable tumor above cystic duct
Pancreatoduodenectomy for microscopic involvement of CBD
Resectable CCA arising in PSC
Radial tumour diameter <-3 cm
Absense of intra- and extrahepatic metastases
Candidate for liver transplantation.

Table 2. Mayo Clinic protocol for neoadjuvant therapy and liver transplantation

External beam radiation therapy (45 Gy in 30 fractions, 1.5 Gy twice daily) and continuous infusion 5-FU - administered over 3 weeks
→ Brachytherapy (20 Gy at 1 cm in approximately 20-25 hours) – administered 2 weeks following completion of external beam radiation therapy
→ Capecitabine – administered until time of transplantation, held during perioperative period for staging
→ Abdominal exploration for staging – as time nears for deceased donor transplantation or day prior to living donor transplantation
→ liver transplantation

Table 3. Exclusion criteria

Intrahepatic cholangiocarcinoma
Uncontrolled infection
Prior radiation or chemotherapy
Prior biliary resection or attempted resection
Intrahepatic metastases
Evidence of extrahepatic disease
History of other malignancy in the past 5 years
Transperitoneal biopsy (including percutaneous and EUS-guided FNA)

Although most of the existing literature reports experience with a neoadjuvant protocol consisting of external beam radiotherapy combined with brachytherapy, continuous intravenous 5-FU, and subsequent oral capecitabine administration prior to LT, as described previously, there are some publications that have reported the use of different neoadjuvant protocols. A 2018 study by Loveday et al. reported the use of concurrent administration of conformal radiotherapy and capecitabine followed by maintenance cisplatin and gemcitabine after surgical staging.[34] Another study reported use of gemcitabine alone or combined with cisplatin.[35] No comparative studies have been carried out to evaluate any difference in outcomes between different neoadjuvant regimens.

Neoadjuvant therapy increases the risk of radiation-related injury, which can pose challenges to surgery. Portal vein and hepatic artery stenosis, with or without thrombosis, occurs in up to 20% of transplanted patients after undergoing neoadjuvant therapy.[29] However, these vascular complications are amenable to treatment with stents and vascular grafts with an excellent success rate.[36]

Current Evidence and Outcomes

LT in Perihilar Cholangiocarcinoma

The success of the Mayo Clinic protocol led to a shift among centers in terms of patient selection criteria and neoadjuvant therapy preceding LT. A 2014 study detailed the experience of the Irish National Liver Transplant Programme.[37] 20 patients underwent LT, provided they were progression-free after receiving brachytherapy, external beam radiotherapy, and 5-FU. Although they found short-term mortality to be high (20% hospital mortality), they reported a 61% survival rate at 4 years for patients who successfully underwent the LT. In addition, they reported tumor residue in explant and high CA 19-9 levels to be predictors of disease recurrence, similar to a study by the Mayo Clinic.[37,38] A 2012 study included outcomes from 12 high-volume liver transplant centers across the US and aimed to assess the survival rates in patients with pCCA who underwent neoadjuvant therapy followed by LT. They found a 65% recurrence-free 5-year survival rate, indicating neoadjuvant therapy followed by LT to be a highly effective treatment option for suitable patients with pCCA.40 Additionally, they found that despite the majority of patients originating from a single center, the remaining 11 centers reported similar outcomes following treatment, suggesting that good survival outcomes can be universally achieved and reproduced provided adherence to the Mayo Clinic or Mayo-like protocol of neoadjuvant therapy followed by LT.[39] A 2005 Mayo Clinic study compared neoadjuvant therapy and LT with surgical resection in patients with pCCA.[40] They reported a 5-year survival of 82% in patients who underwent LT compared to 21% after resection. Moreover, they noted fewer recurrences in the LT patients (13% versus 27%).[40] In a multicenter study, outcomes of pCCA were compared between 41 patients who underwent LT and 191 patients who underwent surgical resection.[41] They found a significant improvement in 5-year overall survival rates in the LT group (64%) versus the resection group (18%). These findings persisted even when comparing those who underwent resection for pCCA while also meeting the criteria for LT (eg. tumor size < 3 cm, lymph node-negative disease); 5-year overall survival of 54% versus 29% (p=0.03).[41] Based on these results, it was recommended that further prospective studies continue to be conducted to compare LT with resection, particularly in those patients with resectable disease. In a 2022 multicenter benchmark study, Breuer et al. reported data from 134 patients with pCCA who underwent LT after completion of Mayo-like neoadjuvant therapy.[42] They found LT was associated with a superior 5-year disease-free survival (62%) versus a matched group of patients who underwent curative liver resection (32%). They recommended updated treatment algorithms for pCCA based on their findings. A meta-analysis comparing LT and resection outcomes for pCCA. They found a significantly increased 3-year overall survival in patients who underwent LT as opposed to resection (p=0.02).[43] In addition, patients undergoing LT had a shorter hospital stay than those who had resection, and no statistically significant difference was found between LT and resection regarding postoperative mortality. They postulated that neoadjuvant therapy and/or strict selection criteria for the patients that underwent LT may have contributed to the improved survival outcomes as compared to resection and believed no certain conclusions could be drawn from their results to support the use of LT for technically resectable early-stage pCCA due to the absence of high-quality data from randomized controlled trials (RCTs).[43]

The only RCT (NCT02232932) to directly compare radio-

chemotherapy and LT against liver resection in resectable pCCA was highly anticipated for the results due to its potential to guide future direction and management of resectable pCCA by directly comparing the two treatment modalities in this patient population.[44] However, the study was ended prematurely due to insufficient patient enrollment and a high dropout rate of 55% among the first 20 patients assigned to the LT group.[42,44] The experience of this clinical trial may underscore the difficulty and limited feasibility of conducting an RCT directly comparing LT with resection.

Since the development and success of the Mayo Clinic and Mayo-like protocols, some have questioned whether improved outcomes should be attributed to neoadjuvant therapy or strict selection criteria.[43] One retrospective study aimed to assess the role of patient selection alone on LT outcomes for pCCA. They used the European Liver Transplant Registry (ELTR), from 1990 and 2010, to identify 28 patients who fulfilled the strict eligibility requirements of the Mayo Clinic protocol and did not receive neoadjuvant chemoradiation therapy. They reported a 59% 5-year survival rate, which is similar to results published by the Mayo Clinic concerning patients who underwent LT following neoadjuvant chemoradiation therapy.[45] They suggested that strict selection alone leads to improved survival outcomes in patients with pCCA; however, they did stress caution in the interpretation of their results. It is likely that both neoadjuvant therapy and strict selection criteria have an important role in the management of patients who are suitable candidates for LT.[17]

Center experience also appears to play a role in treatment outcomes in patients with pCCA who undergo LT. Kitajima et al. aimed to assess the effect of center experience on outcomes with LT and classified included transplant centers into two groups: well-experienced (defined as ≥6 LTs; n = 7 centers) and less-experienced (defined as < 6 LTs; n = 23 centers).[45] They found post-LT outcomes were significantly better at well-experienced centers, with 1-, 3-, and 5-year survival rates of 91.8%, 56.9%, and 45.8%, respectively, compared to 65.6%, 48.8%, and 26.0% at less-experienced centers. They also found a statistically significant increased risk of tumor recurrence and all-cause mortality in the less-experienced group.[46] Based on their results, Kitajima et al. suggested the potential introduction of center approval for LT to ensure consistent and comparable treatment outcomes between centers.

Predictors of Disease Recurrence Post-transplant

A 2006 Mayo Clinic study studied data from 65 patients with pCCA who underwent deceased-donor LT with the aim of assessing predictors of disease recurrence after neoadjuvant chemoradiotherapy and LT.[38] They identified several predictors, including advanced age; a pretransplant CA 19-9 level exceeding 100 U/ml; presence of > 2 cm residual tumor in the explant on cross-sectional imaging; prior cholecystectomy; and tumor grade and perineural invasion in the explant.[38] Updates to this study reported that age and prior cholecystectomy are not predictors of disease recurrence, but perineural and lymphovascular invasion, elevated CA 19-9, portal vein encasement, and size of residual tumor on explant are predictors.[47,48]

As previously mentioned, high CA19-9 levels and residual explant tumors were also found to be predictors of tumor recurrence according to a study of the Irish National Liver Transplant Program, in line with results from the Mayo Clinic.[37]

These predictive factors assist in identifying patients at elevated risk for disease recurrence and, hence, can guide post-transplant management of such patients (i.e. additional therapy in the form of adjuvant therapy etc.).[49]

PSC-associated pCCA versus De Novo pCCA

Outcomes also differ between pCCA occurring de novo and pCCA developing in the context of PSC. An intention-to-treat analysis from the Mayo Clinic reported survival rates for patients with PSC-associated pCCA at 1, 5, and 10 years to be 78%, 60%, and 52% versus 83%, 39%, and 32% in patients with de novo pCCA.50 A statistically significant difference in survival after LT at 1, 5, and 10 years was also noted (92%, 76%, and 70% versus 90%, 58%, and 49%).[49]

LT in Intrahepatic Cholangiocarcinoma

LT for iCCA historically produced poor outcomes and, as a result, has largely been a contraindication in this patient population.[50,51] A large 2016 multicenter cohort study aimed to further evaluate whether LT could result in acceptable outcomes in patients with "very-early" iCCA.[19] The study included patients who underwent LT for HCC or decompensated cirrhosis and were diagnosed with iCCA based on the explant pathology. Two study groups were then established: one with "very-early" iCCA (defined as single tumor ≤2 cm; n = 15) and the other with "advanced" iCCA (defined as single tumor >2 cm or multifocal disease; n = 33). In the very-early iCCA group, the actuarial survival rates at 1, 3, and 5 years were 93%, 84%, and 65%, respectively, while in the advanced iCCA group, these rates were 79%, 50%, and 45%. The very early iCCA group also demonstrated a statistically significant lower risk of recurrence.[19] However, it remains unclear how clinically significant these results

could be given that iCCA is frequently asymptomatic until advanced disease and the challenges associated with diagnosing iCCA at such an early stage (i.e, single tumor <2 cm, etc). A 2023 propensity score-matched study compared LT for iCCA with resection and noted better prognosis in patients who underwent LT versus those who underwent resection in both unmatched (HR 0.65, p=0.002) and matched cohorts (HR 0.62, p=0.009).[53] Their results also indicated an improved 5-year overall survival rate (61.7%) in patients who received neoadjuvant chemotherapy with LT. This suggests that neoadjuvant chemotherapy before LT may improve outcomes in patients with iCCA, much like in pCCA.

Standard MELD Exception and Living-Donor LT

In 2009, a standard MELD score exception was introduced for pCCA in patients listed for LT.[18] Currently, the standard MELD exception score for pCCA patients aged 18 and older is calculated as the Median MELD at Transplant (MMaT) minus 3 points.[18] There is an extensive set of criteria to qualify for the MELD exception for pCCA. A detailed patient care protocol must be submitted to the Liver and Intestinal Organ Transplantation Committee for review and approval. This protocol should include patient selection criteria, administration of neoadjuvant therapy prior to LT, and operative staging aimed at excluding patients with regional hepatic lymph node metastases, intrahepatic metastases, or extrahepatic disease, along with any additional information requested by the committee. The patient must meet the diagnostic criteria for pCCA, which includes a malignant-appearing stricture on cholangiography along with at least one of the following: (i) biopsy or cytology confirming malignancy, (ii) CA19-9 level >100 U/ml without evidence of cholangitis, (iii) presence of aneuploidy, or (iv) a hilar mass <3 cm in radial diameter. Moreover, the tumor must be considered unresectable either due to technical considerations or poor hepatic reserve secondary to underlying liver pathology. Cross-sectional imaging must demonstrate a single tumor <3 cm in radial (perpendicular to duct) diameter, with no consideration for the longitudinal extension of the stricture along the bile duct in terms of measurement. Cross-sectional imaging of the chest and abdomen must also exclude intrahepatic or extrahepatic metastases. Operative staging must also be performed after completing neoadjuvant therapy to evaluate regional hepatic lymph node involvement and detect peritoneal metastases. Importantly, transperitoneal biopsy or aspiration of the primary tumor is contraindicated due to the high risk of tumor seeding regardless of the percutaneous, endoscopic, or surgical approaches.[18,53]

Despite a MELD score exception for pCCA, the waiting time for patients is still considerably long secondary to critical organ shortage. This could lead to increased morbidity and mortality for those awaiting transplantation.[54] In addition, patients experiencing prolonged wait times before transplantation are at higher risk of developing radiation-induced fibrosis, which complicates staging and presents technical challenges during transplantation.[49] Living-donor LT allows for more timely access to LT, which may reduce waitlist-associated morbidity and mortality.[29,54] Outcomes with living-donor LT and deceased-donor LT for pCCA developing in the setting of PSC are comparable.[49] However, living-donor LT for de novo pCCA may be related to increased tumor recurrence and slightly inferior survival rates compared to deceased-donor LT.[49] Hence, it may be useful to monitor select patients for disease progression post-neoadjuvant therapy to potentially exclude at-risk patients from undergoing LT to avoid eventual recurrence after transplantation.

Living-donor LT may also increase the risk of late vascular complications (i.e., of hepatic artery and portal vein), but these complications have not been shown to affect long-term survival.[55]

Directions for Future Research

There remains a need for larger, high-quality studies to provide more information to guide the use of LT in patients with pCCA, particularly regarding the use of living-donor organs. A similar need for robust studies is required for iCCA, as current data is limited, although promising, for LT use in early-stage, small iCCA. If new studies provide results similar to early data, a shift in management towards LT for early-stage iCCA may be warranted.[19] Challenges persist for RCTs and other prospective trials, as demonstrated by the premature termination of trials secondary to issues like low accrual and recruitment.[44,56]

Avances in neoadjuvant and adjuvant therapy also present potential to further improve outcomes in patients who undergo LT for CCA. Newer neoadjuvant techniques like stereotactic radiation have demonstrated efficacy with reduced toxicity compared to conventional external beam radiotherapy and might offer advantages for patients undergoing LT.[57] Further research is needed to evaluate the role of newer advanced neoadjuvant therapies for LT.

Furthermore, continued refinement of patient selection criteria will be helpful to improve outcomes in patients who undergo LT and exclude those who are at high risk of falling out prior to LT. Analysis of future large studies will be helpful to aid further refinement of patient selection criteria.

Conclusion

In summary, LT following neoadjuvant chemoradiation is a viable and effective treatment alternative for patients with pCCA who meet strict selection criteria, with outcomes comparable or superior to surgical resection. LT for pCCA has also achieved outcome results comparable to other indications for LT, justifying MELD score exception and the potential use of living-donor organs. The evidence for LT use in iCCA remains limited, but some studies have shown promise in patients with early-stage iCCA, comparable or superior to resection. Advances in neoadjuvant therapy also represent potential to further improve outcomes in patients undergoing LT. Larger, multicenter studies are needed for each CCA subtype, particularly to provide further elucidation on whether LT is an acceptable treatment for early-stage iCCA.

Disclosures

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Review

CARES: Improving Quality of Life for Patients with Chronic Illnesses and their Family Caregivers

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Abstract

CARES, is a novel integrated screening and stepped collaborative care intervention developed for those with chronic illnesses and their family caregivers. This paper provides a history of collaborative care and the findings of Phase I-III trials in oncology and nephrology as well as transplantation. CARES is currently being testing in Hybrid Type I and II effectiveness-implementation cluster randomized controlled trials in oncology and nephrology, respectively.

Keywords: Stepped collaborative care, chronic illness, caregiving, oncology, nephrology, transplant

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History of Collaborative Care

Collaborative care may be defined as integrated care designed to treat mental health conditions in medical settings.[1] From 1990 to 1996 several collaborative care trials were funded by the National Institute of Mental Health (NIMH) and the Agency for Healthcare Research and quality (AHRQ) were being conducted to improve the management of depression in the primary care setting.[1,2] As a result of these trials, Wagner's Chronic Care Model was developed and the primary goal was to transform the care of patients with chronic illnesses to be proactive rather than reactive (Fig. 1).

The Chronic Care Model includes five key elements critical to improving outcomes.[1] These elements included (1) the delivery system was designed where each patient had proactive follow-up visits or phone contacts, (2) monitoring of adherence and treatment response, (3) a registry was development to track care according to the individual's treatment plan, and (4) self-management training and support was provided to the patient and/or family, and (5) decision support was provided to the physicians to access guidelines, expert systems, and consultation.[1]

A seminal trial, the IMPACT trial, demonstrated the effectiveness of collaborative care in over 1800 patients.[3] Similar to many of the earlier trials, the collaborative care approach included pharmacological treatment of depression with brief psychotherapy, most often problem solving therapy, to manage depression.[3] After this trial, Unutzer and colleagues have further refined the principles of collaborative care to include (1) a patient centered care team, (2) population-based care, (3) measurement-based treatment to target, (4) evidence-based care, and (5) accountable care. Over 90 randomized controlled trials and several meta-analyses have been conducted to demonstrate that

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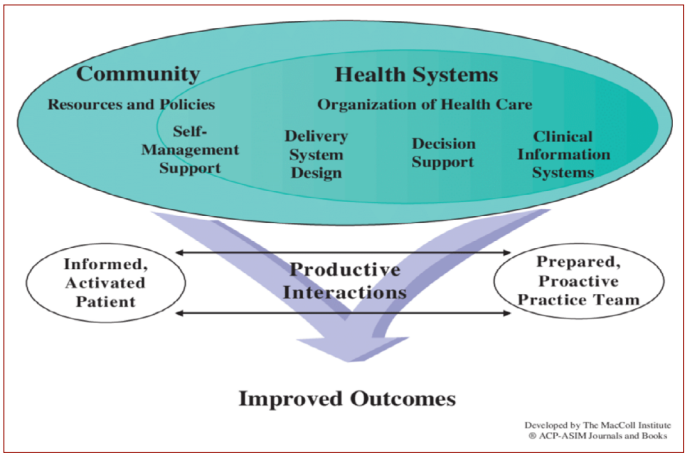

Figure 1. The chronic care model.

the collaborative care model is more effective than usual care for patients with comorbid depression, anxiety, and other mental health conditions. This approach has been shown to be effective across chronic conditions including cancer, diabetes, cardiovascular disease, and HIV.[4] Collaborative care has been also shown to be effective in those from different racial and ethnic groups and under resourced communities.[5] The collaborative care approach has also been demonstrated to be cost-effective in several meta-analyses.[6-9]

CARES: A Novel Stepped Collaborative Care Intervention

For decades the American Society for Clinical Oncology (ASCO), American College of Surgeons' Commission on Cancer (CoC), the National Comprehensive Cancer Network, and the Center for Medicaid and Medicare Services (CMS) have recommended that cancer centers screen and treat symptoms such as distress (depression and anxiety) and pain.[10-13] Despite the recommendations, and incentives (e.g., CMS Oncology Care Model, ASCO accreditation) to screen and treat these symptoms, the current standard of care (e.g., screening and referring patients for treatment) is ineffective at reducing symptom severity, improving patient HRQoL, and/or reducing unplanned health care utilization and costs as was originally intended with the guidelines.[14,15] Many cancer centers still do not routinely screen patients due to the time and resources required.[16]

Further, if patients are screened and have symptoms in the clinical range and are referred to treatment, multi-level barriers (e.g., patient, provider, health care system) exist that prevent the initiation and/or completion of treatment.[14,16] Consequently, the goal to improve patient HRQoL, by screening and referring patients for treatment, has not been relaized.[14] Steel and colleagues developed a solution to solve this problem, an integrated screening and stepped collaborative care intervention, CARES. The screening is integrated with treatment and the treatment is based on the principles of collaborative care.

In the first Phase I randomized controlled pilot trial, Steel and colleagues enrolled 28 patients comparing the intervention (later names, CARES) to an attention-standard of care arm.[17] While the intervention followed the principles of collaborative care, rather than pharmacological treatment being primary, psychotherapy was the primary modality of treatment with adjustments in medications for depression or anxiety if recommended.[17] The intervention initially included a combination of psychoeducation, cognitive-behavioral therapy, supportive-expressive therapy, and collaboration with the patients' psychiatrist, primary care physician, and/or oncologist to adjust or initiate pharmacological treatment.[17] Patients diagnosed with hepatobiliary cancer would receive 3-4 face-to-face sessions when the patient visited their oncologist or surgeon and 5-6 telephone contacts.[17] Patients who were randomly assigned to the intervention arm of the study reported clinically, but not statistically, significant improvements on symptoms of depression and anxiety, disease-related symptoms and treatment side effects, health-related quality of life (HRQL), and modest improvements in peripheral blood leukocytes were observed when compared with the standard of care group.[17]

At the same time as the first trial was conducted, a consensus statement by the National Institute of Health on cancer-related symptoms concluded that the three most common and distressing symptoms for those diagnosed with cancer were depression, pain, and fatigue.[18] It is estimated that approximately 50% of patients report one or more of these symptoms in the clinical range.[19,20] These symptoms are associated with increased morbidity and mortality.[18,21-25]

Steel and colleagues then performed a Phase II trial of CARES funded by the National Cancer Institute. The aim of this study was to examine the efficacy of a collaborative care intervention in reducing depression, pain, and fatigue and improve quality of life.[20] A total of 261 patients with advanced cancer and 179 family caregivers were randomized to a web-based collaborative care intervention or enhanced usual care.[20] The NCI reviewers recommended that family caregivers be included in the study as proxy raters as the patients with hepatobiliary cancers often presented at advanced stages and they were uncertain if patients would be able to complete outcome measures as the disease progressed.[20] We decided to also assess caregiver outcomes not only proxy ratings of patient outcomes. This proved to be an important decision as we have since observed reductions in these caregiver symptoms such as depression and

stress with improvements in patient quality of life.

During this trial, we integrated the screening of patients with the treatment. Once a patient was screened the treatment team reached out to the patient to initiate treatment. In this iteration of CARES the intervention included (1) a website with written and audiovisual self-management strategies, a bulletin board, and other resources; 2) visits with a care coordinator during a physician's appointment every 2 months; and 3) telephone follow-up every 2 weeks.20 Primary patient outcomes included measures of depression, pain, fatigue, and health-related quality of life. Secondary outcomes included Interleukin (IL)-1α, IL-1β, IL-6, and IL-8 levels, Natural Killer (NK) cell numbers, and caregiver stress and depression.[20]

At the baseline, 51% of the patients reported 1 or more symptoms in the clinical range.[20] For patients who presented with clinical levels of symptoms and were randomized to the intervention, reductions in depression, pain, and fatigue and improvements in quality of life were observed when compared to those in the enhanced usual car arm at 6 months which included patients receiving educational information and referral to treatment in their community.[20] We also observed in the CARES arm reductions in IL-6, IL-1β, IL-1α, and IL-8 and increases in NK cell numbers when compared to the enhanced usual care arm at 6 months.20 We also observed reductions in caregiver stress and depression were observed at 6 months for caregivers whose loved ones were randomized to the intervention arm.[20]

At the same time, the Symptom Management Research Trials (SMART) trial in the United Kingdom which was a pharmacotherapy-based collaborative care intervention for depression which was found to be effective for those with cancer.[25] Walker and colleagues also recommended the need for integrated screening and evidence-based treatment for those with depression.[20,26]

CARES includes a "stepped" care approach which includes measuring the patients response every 4 weeks and providing individualized treatment (e.g., additional sessions, pharmacotherapy) until symptoms have been effectively reduced.[27] Our novel stepped collaborative care intervention delivers CBT via telemedicine as the primary treatment modality, unlike other collaborative care approaches in which pharmacotherapy is often the primary modality.[28] Moreover, CARES targets not only depression but also pain and fatigue, the three most common and distressing symptoms in those with cancer.28 The duration of treatment is 6-24 weeks depending on the number and type of symptoms the patient reports at the time of screening.[20,26,28] CARES can also include pharmacotherapy to reduce symptoms, if preferred by the patient and the symptoms are not effectively reduced with CBT alone.[20,26,28] The care coordinator collaborate with the oncologist as well as the patients' primary care physician (PCP) and/or psychiatrist in the patients' community to initiate or change medication (Fig. 2).[20,26,28]

In our Phase III trial of CARES we observed that patients randomly assigned to CARES were more likely to initiate treatment (75%) than patients who were referred to a provider (standard of care arm, 4%).[26] Statistically, and clinically meaningful, improvements in HRQoL through reductions in symptom burden as well as lower unplanned health care utilization (e.g., ER visits, 90-day readmissions) and cost savings of $17,085 per patient per year were observed with CARES when compared to SC.[26] A large body of research has found that family caregivers of those caring for loved ones with dementia and more recently cancer, are at increased risk of cardiovascular disease.[29,30] In the general population, treating stress and depression have been shown to reduce risk of cardiovascular related mortality.[31] As a result of our findings from our Phase II trial, we assessed cardiovascular risk in family caregivers as an outcome. We observed that when the patients' quality of life improved with CARES that the family caregivers, of patients randomized to CARES, also had reductions in lifetime risk of

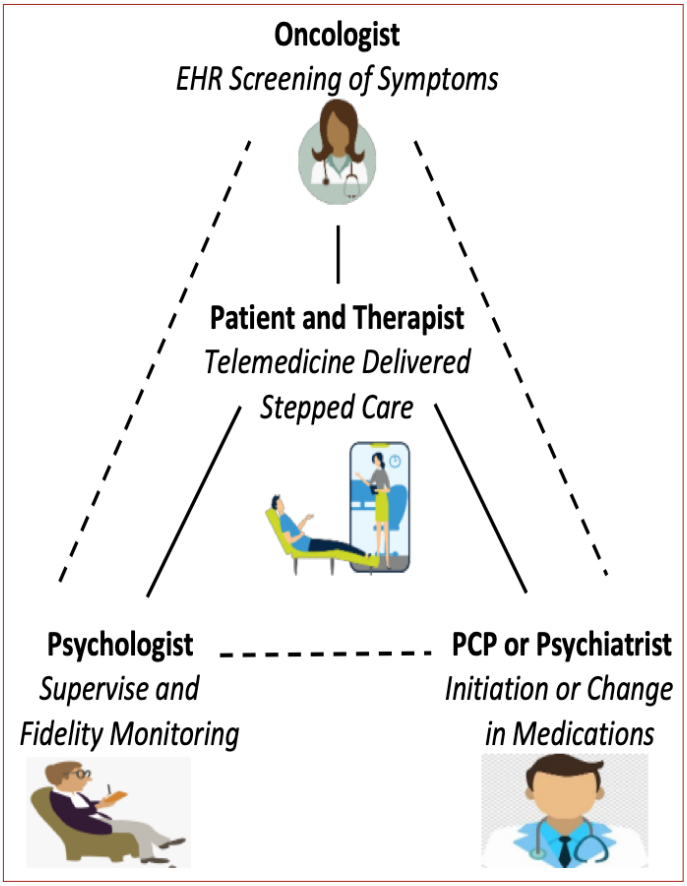

Figure 2. Novel collaborative care approach.

cardiovascular disease as measured by the American College of Surgeons ASCVD risk calculator.[26]

While we believed integration, of screening and treatment, is critical for patient initiation of treatment, and ultimately better patient HRQoL, we found through a pilot of implementing the electronic health record (EHR) screening, the importance of an evidence-based treatment in addition to integrated screening and treatment. Consecutive patients were screened December 12, 2022 and January 15, 2025 using the EHR using a 3-step process to reduce health disparities (e.g., patient portal, tablet at the front desk, and/or verbal administration by the medical assistant).[32] Patients who screened positive were automatically referred to the treatment team who had therapeutic orientations including humanistic and psychoanalytic approaches. Patients' symptoms were assessed every 6 months.[32]

Of 169 patients were contacted by the treatment team, 21 (12.4%) reported thoughts of death or wanting to harm themselves on the PHQ-9, however only 1 (<0.05%) had active suicidal ideation.[32] A total of 56 (36.1%) initiated treatment. A significant reduction over time was observed with depressive symptoms at baseline 14.5 (SD=6.7) to 13.8 (SD=8.3) at 6 months to 11.3 (SD=7.1) at 12 months.[32] Similarly, reductions in anxiety from 14.9 (SD=4.3) on the GAD-7 to 11.8 (SD=7.6) at 6 months to 9.7 (SD=7.1) at 12 months were observed.[32] A trend was observed over time in which patients reported a decrease in pain intensity and interference from 6.2 (SD=1.1) on the PEG to 2.1 (SD=2.6) at 6 months to 0 (SD=0). Of those who initiated treatment, no significant differences were observed on depressive symptoms or anxiety.[32] Due to the lack of expertise in pain management by the treatment team, patients with cancer-related or chronic pain were referred to specialized treatment for pain based on reported etiology. While the sample size was small and so the conclusions should be interpreted cautiously, robust evidence-based interventions are warranted to observe clinically meaningful changes in symptoms.[32]

Traditionally, new psychosocial and/or health interventions have been tested in a staged approach which has focused on ensuring that interventions perform well in ideal conditions before considering translation to real-world practice.[33,34] As a result, translation from the research to practice setting is associated with significant delays.[33,34] Experts argue that the process of moving evidence-based interventions from the research to clinical or real-world practice setting can be expedited by using "hybrid" type trials that blend elements of effectiveness (Phase IV) and implementation research (Fig. 3).[33,34] Based on the findings of our Phase III trial and clinical pilot testing integration without

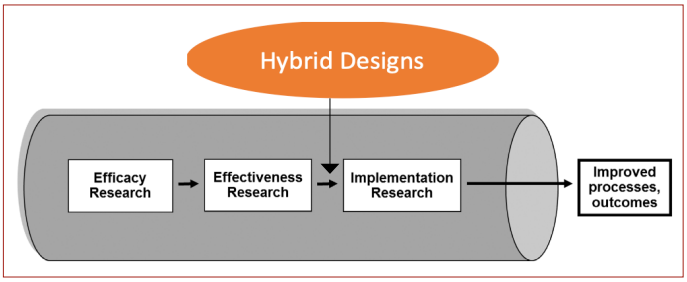

Figure 3. Traditional Research Pipeline and Hybrid Design.

evidence-based treatment, we proposed a Hybrid Type I effectiveness-implementation cluster randomized trial which is currently underway. We will employ the EHR and non-EHR screening (for community cancer centers who may not have Epic) which takes patients approximately 2 minutes to complete, in the patient's health portal prior to their appointment. Studies that use patient portals to screen patients have been shown to result in health disparities.[35-37] As a result, we have added two additional steps (e.g., tablet at the front desk and verbal administration while rooming patients). If a patient reports symptoms in the clinical range are then automatically sent to the CARES treatment team. The medical team does not need to perform any action or place an order to connect the patient with the treatment team.

The proposed study will employ a Hybrid Type I effectiveness-implementation cluster randomized design which will not only examine effectiveness but will also begin to examine the "implementability" of CARES including cost- saving and effectiveness. We will evaluate, using the recently updated RE-AIM framework, the uptake of CARES by patients and health care providers and anticipated barriers to and facilitators of its successful integration into practice.38-41 The findings of this study will provide the necessary information for cancer centers, or other stakeholders (e.g., CMS), to better understand the effectiveness, and cost- savings and effectiveness, of CARES under real world conditions. We anticipate that we will uncover several important barriers to adoption, implementation, and maintenance (e.g., sustainment), necessitating additional implementation strategies to be operationalized/tested in future hybrid type II/III trial.[33,34] This proposed pragmatic trial meets the Readiness Assessment for Pragmatic Trials (RAPT) criteria and is the next logical step in moving CARES from research into clinical practice.[42]

While the focus on improving patient HRQoL is imperative, demonstrating cost- and effectiveness is beneficial for the potential adoption and sustainability of CARES in clinical practice. The Hospital Readmissions Program (HRP) was introduced in 2012 in the U.S. as unplanned readmissions were resulting in higher rates of morbidity, mortality, and

healthcare costs. Since that time, several strategies have been tested to reduce unplanned readmissions secondary to the negative effect of these unplanned readmissions on patient morbidity, hospital revenue (e.g., lower reimbursement, penalties), operations, and CMS Quality Star Rating. In 2015, episode-based payment models were introduced and readmissions within 90-days also resulted in lower reimbursement rates. Two of the symptoms, depression, and pain, have been long associated with higher rates of emergency room visits, unplanned readmissions, and longer length of stay in the hospital.[7-8,36] Therefore, in our Phase III trial we focused on 30- and 90-day readmissions as well as associated events (e.g., emergency room visits, length of stay in the hospital) and activity based costs linked to these unplanned health care events.[9] For the proposed effectiveness-implementation trial, we plan to further evaluate the cost savings with a larger and more "real world" sample as we have added additional program costs including fidelity monitoring, leveraged by artificial intelligence, and case tracking software to be able scale up CARES efficiently. Further, we will also evaluate overall cost-effectiveness using cost per quality-adjusted life year based on established benchmarks that we did not include in the Phase III trial.[9,83] We will also assess financial toxicity and cost coping and while it is unlikely that we will observe a reduction in a short period of a year, it will provide important information across cancer types and stages.

The findings from this study have the potential to shift the paradigm of screening and treatment nationwide resulting in improved patient centered outcomes for those diagnosed with cancer. The evaluation of the facilitators and barriers of CARES in a real-world clinical setting will critically inform future implementation and allow for the development of best practices for cancer centers across the nation who want to implement CARES. The goals of the study reflect the mission of the NCI which includes testing strategies to overcome barriers to the adoption, effectiveness, scaling-up, and sustainability of evidence-based interventions focused on improving HRQoL of patients with cancer.

The CARES intervention has been demonstrated to be efficacious not only in the setting of oncology but also nephrology and renal transplant. We have tested CARES in Phase II and III trials in patients with end stage kidney disease on in center hemodialysis. The Phase II trial demonstrated the feasibility of CARES and preliminary efficacy in reducing depression, pain, and/or fatigue. Patients met weekly with a therapist for eight sessions, each 45-60 min, during HD sessions via a video-conferencing platform. Of 10 patients screened, 100% screened positive for at least one symptom, 100% of eligible patients consented, and eight (of 10) completed the intervention (mean age 59 years, 50% male, 50% African American).43 Satisfaction with the intervention was high, and seven of the eight patients completed all eight prescribed sessions. Preliminary results indicate improvement in SF-36 Physical Component, and four of the six patients (67%) with clinically elevated pain at baseline reported improvement at follow-up.[43]

As a result of the findings from our Phase II trial, a parallel-group, single-blinded, Phase III randomized clinical trial was conducted to test the stepped collaborative care intervention to reduce fatigue, pain, and/or depression.[44] The stepped collaborative care intervention group received 12 weekly sessions of cognitive behavioral therapy delivered via telehealth in the hemodialysis unit or patient home, and/or pharmacotherapy using a stepped approach in collaboration with dialysis and primary care teams.[44] The attention control group received 6 telehealth sessions of health education. In the intention-to-treat analyses, when compared with controls, patients in the intervention group experienced statistically and clinically significant reductions in fatigue and pain severity at 3 months.[44] These effects were sustained at 6 months.[44] Improvement in depression at 3 months was statistically significant but small.[44]

Patients awaiting kidney transplant also carry a high symptom burden which has been associated with waitlist inactivation, mortality, and poorer post-transplant outcomes. However, few studies have tested the effects of symptom management interventions in this population. The Phase II randomized controlled trial designed to test the efficacy of CARES-Transplant versus standard of care (SC).[45] Nineteen patients (mean age = 65±6 years, 74% male, 90% White) and 8 caregivers were randomized to CARES or standard of care (screening and referral to treatment).[45] Reductions in pain intensity and interference were observed for CARES while patients in the SC arm had increases in pain intensity and interference.[45] Similar trends were observed for fatigue and depressive symptoms.[45] Lower rates of transplant-related complications, fewer emergency room visits and 90-day readmissions were also observed.[45] A moderate to large effect size was observed for changes on caregiver reported depressive symptoms and sleep quality.[45] The findings of this pilot study warrant a Phase III trial to test the efficacy of CARES-Transplant.[45]

The novel integrated screening and stepped collaborative care intervention (CARES) has been demonstrated to be efficacious across chronic illnesses including cancer and end stage kidney disease, including those awaiting transplant. The teams are currently moving the intervention from research into clinical practice with two implementation studies spanning over 70 cancer center clinics as well as in dialysis clinics across six states. The findings from this trial

will contribute to understanding the effectiveness of the CARES intervention but also to the barriers and facilitators to implementing CARES into clinical practice across medical settings.

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Review

Current Clinical Importance of Fecal Microbiota Transplantation Treatment (FMT) in Liver Diseases and Liver Transplant (LT) Recipients

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Abstract

The gut microbiota (GM) constitutes a complex, metabolically active "organ" weighing 1–2 kg and comprising more than 100 trillion microorganisms whose collective genome far exceeds that of the human host. Culture-independent sequencing techniques have clarified its taxonomic structure and functional roles in host metabolism, immunity, and inflammation, and have established the bidirectional "gut–liver axis" as a key pathway in liver homeostasis and disease. Dysbiosis, increased intestinal permeability, and altered bile acid and microbial metabolite profiles contribute to the pathogenesis and progression of a broad spectrum of liver diseases, including viral hepatitis (HBV, HCV, HEV, HAV, HDV), alcoholic liver disease, metabolic dysfunction-associated steatotic liver disease, autoimmune hepatitis, primary sclerosing cholangitis, cirrhosis, drug-induced liver injury, and hepatocellular carcinoma. Characteristic disease-specific shifts in bacterial composition and diversity have been described and may serve as potential diagnostic or prognostic biomarkers. Fecal microbiota transplantation (FMT) has emerged as an effective strategy to restore intestinal microecological balance, with robust evidence for antibiotic-refractory *Clostridioides difficile* infection and encouraging early data in chronic hepatitis B, severe alcoholic hepatitis, and PSC. In liver transplantation (LT) recipients, who are highly susceptible to infections and profound post-transplant changes in GM, FMT appears to be a safe and potentially valuable adjunct, particularly for recurrent *C. difficile* infection. Overall, modulation of the gut microbiota through FMT, probiotics, prebiotics, bacteriophages, and targeted antibiotics represents a promising avenue for prevention and treatment of liver diseases and for improving outcomes after LT, although large, well-designed prospective studies are still needed to define indications, protocols, and long-term safety.

Keywords: Gut microbiota; gut–liver axis; fecal microbiota transplantation; liver transplantation

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As a novel approach to reconstruct the intestinal microecological balance, fecal microbiota transplantation (FMT) has been gradually and widely practiced in the treatment of a variety of diseases in recent decade. This method transfers processed fecal materials from healthy donors to patients to rebuild the balance of their gut microbiota. Under normal conditions, the human gastrointestinal (GI) tract, which is colonized with numerous bacterial species, individually differs and is relatively stable over time , while several genetic backgrounds and environmental factors, such as diet, viruses, and use of drugs can alter the balance and further cause a variety of diseases.[1] The gut microbi-

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ota (GM) is a diverse ecosystem that consists of bacteria, protozoa, archaea, fungi, and viruses, which exist in a specific symbiosis between each other and the human body as well.

Currently, it is well known that GM plays relevant roles in physiological and pathological conditions of human health, taking part in digestion, vitamin B synthesis, immunomodulation, and promotion of angiogenesis and nerve function. In addition, it is unavoidable that the GM has an impact on pathogenesis of gastrointestinal, hepatic, respiratory, cardiovascular, endocrine, and many other disorders, arising as "a new virtual metabolic organ". The GM colonizes human intestinal tract, which accounts for more than 100 trillion bacteria, and has a complex genome of 150-fold more genes than the human genome. The majority of gut microorganisms cannot be cultured using standard techniques, so the development of culture independent molecular methods based on sequencing of the phylogenetic marker—16S/18S ribosomal RNA offer better insight in the GM structure. The GM is essentially ecomposed of the five phyla-Firmicutes (79.4%) (Ruminococcus, Clostridium, and Eubacteria), Bacteroidetes (16.9%) (Porphyromonas, Prevotella), Actinobacteria (2.5%) (Bifidobacterium), Proteobacteria (1%), and Verrumicrobia (0.1%). Lactobacilli, Streptococci, and Escherichia coli are found in small numbers in the gut. Different genetic and environmental factors influence the GM composition. For example, children born by natural childbirth inherit about 40% of the mother's intestinal flora, while GM composition is very different after the caesarean section. During the first two years of life, the diet is the most prominent factor that determines GM. Later in life, GM composition depends on age, diet, medications, and the environment.

Studies published in the last decade confirmed that the GM is implicated in the pathogenesis of various diseases, such as cancer and autism, depression, Clostridium difficile infection, inflammatory bowel disease, irritably bowel syndrome, colorectal carcinoma, infectious and non-infectious chronic liver diseases, obesity, diabetes mellitus type 2, atherosclerosis, and chronic kidney diseases.

On the other hand, some diseases (such as chronic liver diseases) can also break the balance of gut microbiota. In 2013, Els et al. performed the first randomized controlled trial and demonstrated that duodenal.

infusion of donor feces into patients with Clostridium difficile infection (CDI) had a significant efficacy in resolving symptoms than use of antibiotics alone.[2]

To date, FMT has earned endorsement of professional societies in the treatment of antibiotic-refractory CDI. In addition, FMT has been applied to treat other diseases, such as autoimmune diseases, behavioral diseases, metabolic disorders, and organic diseases.[3]

In fact, a great number of studies demonstrated that gut microbiota is associated with liver diseases. In 1987, it was first found that the relationship between the gut and liver was bidirectional and a cyclic process, and this physiological process was described as the gut–liver axis.[1]

İn recent two decades, the gut microbiota plays a pivotal role in the pathogenesis and progression of various liver diseases, including viral hepatitis, alcoholic fatty liver disease, metabolic dysfunction-associated steatotic liver disease, drug-induced hepatitis, liver cirrhosis, hepatocellular carcinoma, and other hepatic disorders. Research indicates that dysbiosis of the gut microbiota can disrupt the integrity of the intestinal barrier and interfere with the immune functions of the gut-liver axis, thereby mediating the progression of liver diseases. Analysis of microbial composition and metabolites in fecal samples can assess the diversity of gut microbiota and the abundance of specific microbial populations, providing auxiliary diagnostic information for liver diseases. Furthermore, interventions such as fecal microbiota transplantation, probiotics, prebiotics, bacteriophages, and necessary antibiotic treatments offer multiple approaches to modulate the gut microbiota, presenting promising new strategies for the prevention and treatment of liver diseases.[4-6]

The gut-liver axis has an impact on pathogenesis of numerous chronic liver diseases such as chronic hepatitis B (CHB), chronic hepatitis C (CHC), alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), development of liver cirrhosis, and hepatocellular carcinoma (HCC). In recent years, the clinical value and place of FMT in liver transplant (LT) recipients has begun to be discussed. To fully understand the subject, it is necessary to briefly mention the Gut Microbiota, the Gut–Liver Axis and FMT.

The Gut Microbiota and the Gut – Liver Axis

The gut microbiota consists of millions of species, with weight of approximately 1–2 kg.[6] The gut microbiota has been considered as an indispensable "organ". In recent twenty years, the advent of genetic tools and the metagenomics assisted scholars to realize the composition and function of gut microbiota and their association with several potential diseases. The gut microbiota has important functions in hormonal responses, inflammatory pathways, immune reactions, and metabolites.[7]

Generally, the gut–liver axis refers to the bidirectional communication between GI tract and liver by biliary tract, portal vein, and systemic circulation. Through portal vein,

liver mainly receives almost two-thirds of its blood and nutritional supply from the gut, as well as gut-derived toxic factors, such as metabolites, damage/pathogen-associated molecular patterns, and detrimental microbiota.[8] On the one hand, probiotics and beneficial compositions from the gut can protect liver through the gut–liver axis. On the other hand, liver regulates the intestinal function and balance of gut microbiota through circulation of bile acid. Therefore, the close interaction between gut and liver may be a very important factor in the pathogenesis of liver diseases.

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Fecal Microbiota Transplantation

FMT is also known as stool transplantation. FMT is the process of placing the stool obtained from an individual who is determined to be healthy by all laboratory tests, through various processes, and then placing this material into the patient's gastrointestinal system by endoscopic means. The components of the fecal transplants contain about 55% of microbiota and 24% of soluble components, including mucus, fat, proteins, small molecules, short chain fatty acids, etc.[10]

To date, FMT has been widely used in the treatment of recurrent CDI. In addition, with the fast development of high-throughput sequencing technologies, a variety of diseases, such as diabetes, various types of cancer, and organ diseases were found to be associated with the gut microbiota.[11]

Fecal Microbiota Transplantation (FMT) in the Treatment of Liver Diseases

As mentioned earlier, it was confirmed that the gut–liver axis plays an important and critical role in progression of liver diseases. Disturbances in the intestinal barrier may increase the portal influx of bacteria and their products into the liver, and further worsen a range of hepatic diseases. Recently, a growing body of evidence demonstrated that dysfunction of gut microbiota plays a key role in the pathogenesis of ALD and NAFLD. Furthermore, other liver-associated infections, autoimmune hepatitis (AIH), and HCC have been demonstrated to be caused by dysfunction of gut microbiota.[12]

Alteration of gut microbiota in Chronic Hepatitis B Virus (CHB) Infection

HBV infection is one of the most common public health challenges in the world, and about 15–40% of HBV-infected patients may finally develop chronic liver diseases, including cirrhosis, liver failure, and even HCC. The ideal endpoint of HBV-infected patients is hepatitis B surface antigen (HBsAg) loss. For HBV e-antigen (HBeAg)- positive chronic hepatitis B (CHB) patients, HBeAg seroconversion is mainly the first step for treatment. With the significant advances in the treatment of HBV infection, several approved therapies, including oral nucleos(t)ide analogue(s)—entecavir (ETV), tenofovir disoproxil fumarate (TDF)/tenofovir, alafenamide (TAF), and peg-interferon can be used. Despite using these methods, only few patients could obtain HBeAg clearance or seroconversion, even after multiple years of antiviral therapy. The specific reason has not been clearly expounded.[13] İn recent years, some studies demonstrated that recent therapies neglected the role of gut microbiota and it may play a key role in immune clearance of HBV. Several pilot trials with the small sample size have been conducted to explore the therapeutic effects of FMTonCHB patients.[14]

In 2017, Ren et al. first carried out a case-controlled, open-label pilot study on the application of FMT in 18 CHB patients who remained HBeAg-positive, following >3 years of ongoing ETV- or TDF-based antiviral therapy. Among them, 5 patients were included in the FMT arm who received 1–7 cycles of FMT, and 40% (2/5) of patients achieved HBeAg clearance after 1–2 cycles of FMT.[15]

In 2021, Chauhan et al. performed another similar pilot study, and their results showed that in the FMT arm, 16.7% (2/12) of patients had HBeAg clearance. While in the AVT arm, no patient achieved HBeAg clearance. These clinical studies confirmed the significant effects of FMT on stubborn CHB patients. However, more evidence from large-scale prospective studies is required.[14] Several studies attempted to explain the mechanism underlying whether the gut microbiota composition could affect the HBV infection.

The CHB infection has been found to be associated with the dysfunction of HBV-specific immune responses, causing failure in the treatment of infected hepatocytes. Furthermore, it has been reported that HBV infection could alter the intestinal microbiota. For instance, compared with healthy controls, the levels of Bifidobacteria and Lactobacillus were higher, and the levels of Enterococcus and Enterobacteriaceae were lower in CHB patients. Moreover, compared with healthy controls, Enterobacteriaceae, Faecalibacterium prausnitzii, and Enterococcus faecalis showed a noticeable increase

in asymptomatic HBV carriers, and the increased range was significantly greater in HBV patients. These changes caused an increase in bacterial translocation and endotoxin load, in which activation of Toll-like receptor (TLR) facilitated immune-mediated liver injury. Most concerningly, HBV-related liver disease patients exhibit a pro-inflammatory microbiome signature characterized by opportunistic pathogens (Proteus, Klebsiella e.g) enrichment and butyrate-producing bacteria (Ruminococcus e.g) depletion.[16]

Recent studies on HBV have shown that there are significant changes in the intestinal microbiota of those with HBV infection. In the study conducted by Lin et al. in patients with CHB, changes in the intestinal microbiota were seen. İncreased; Firmicutes, Verrucomicrobia, Fusobacteria, Streptococcus, Blautia, Veillonella, Fusobacteria, Akkermansia. Decreased; Bacteroidetes, Bacteroides, Megamonas, Bacteroides, Sutterella, Lachnoclostridium.[17] Another study found that the dominant strains of Bacteroides affected the treatment.[18]

How Does Intestinal Microbiota Affect Viral Hepatitis?

The gut microbiota plays a crucial role in metabolic processes, not only facilitating the digestion and absorption of food but also producing various metabolites that influence host metabolic functions. During HBV infection, bacteria from the Leptospiraceae family may exert a positive role in managing HBV infection by reducing bacterial translocation and lowering lipopolysaccharide (LPS) levels. Multi-omics analysis has demonstrated that electroacupuncture combined with tenofovir disoproxil fumarate can increase the abundance of gut microbiota such as Bacteroides and Blautia by modulating the PPAR signaling pathway, while enhancing the expression of tight junction proteins (ZO-1, Occludin, Claudin-4), thereby improving intestinal barrier integrity. Additionally, Enterocloster bolteae isolated from chronic HBV patients can produce ethanol, potentially promoting the progression of liver disease. Ruminococcus gnavus promotes cholic acid production by secreting bile salt hydrolase, which activates the farnesoid X receptor alpha (FXRα) signaling pathway. This process enhances the transcription of HBV core antigen (HBcAg), thereby prolonging the HBV immune tolerance phase. Conversely, Akkermansia muciniphila suppresses Ruminococcus gnavus growth and its bile acid-converting function through metabolite secretion, reduces CA levels, blocks the FXRα-HBcAg axis, and facilitates HBV clearance. The reduction of BA in viral hepatitis is associated with increased intestinal permeability, leading to elevated levels of LPS and other endotoxins, which promote the progression of liver disease.[19]

HCV infection drives disease progression by inducing alterations in the intestinal bile acid profile and gut microbiota dysbiosis, which downregulate CYP8B1 expression (a key enzyme in cholic acid biosynthesis), thereby perpetuating pathogenesis through the gut-microbiome-liver axis . Increased circulating LPS levels in CHC patients indicate that microbial translocation is closely linked to hepatic inflammation and injury, thereby driving disease progression. Additionally, impaired intestinal barrier function in HCV patients is evidenced by elevated levels of zonulin-1, LPS, and calprotectin, suggesting that intestinal inflammation, microbial imbalance, and increased barrier permeability play significant roles in the pathophysiology of HCV infection. These studies demonstrate that the pathogenesis of viral hepatitis is closely related to intestinal barrier function, microbiota-derived metabolites, and BA metabolism. Viral infections can alter the diversity and composition of gut microbiota, leading to gut-liver axis dysregulation and exacerbating hepatic inflammation and injury. Therefore, modulating gut microbiota may emerge as a novel strategy to improve intestinal barrier function and mitigate liver disease progression. Metabolites and microbiota signatures may serve as potential biomarkers for disease diagnosis, though their clinical application requires further validation. Future research should focus on elucidating the specific mechanisms of gut microbiota in liver diseases to enhance clinical diagnosis and treatment efficacy.[20]

Alteration of Gut microbiota in Chronic Hepatitis C Virus (CHC) Infection

In 86 patients with HCV infection, the abundance of 10 taxa, including Desulfovibrio, Eubacterium eligens, and Prevotella, was significantly higher than that in the HC group, while the abundance of 11 genera, such as Barnesiella, Colidextribacter, and Dorea, was significantly reduced. Additionally, treatment-naïve HCV patients exhibited increased gut microbiota diversity, with elevated abundances of Prevotella, Megasphaera, and Ruminococcaceae and decreased abundances of Bacteroides, Streptococcus, and Enterobacteriaceae. 16S RNA sequencing analysis also revealed lower bacterial diversity in 166 Japanese patients with chronic hepatitis C (CHC), characterized by a reduction in the order Clostridiales and an increase in Streptococcus and Lactobacillus. Compared to the HC group, the total abundance of Lactobacillus and Lactobacillus acidophilus was significantly lower in patients with chronic HCV infection.[21, 22]

Alteration of Gut microbiota in HEV, HAV and HDV

In 33 patients with acute hepatitis E (AHE), the abundance of Proteobacteria, Gammaproteobacteria, and Enterobacteriaceae was significantly higher in the gut compared to the HC group. Furthermore, compared to the AHE group, the HEV-associated acute liver failure (ALF) group showed increased abundances of Gammaproteobacteria, Proteobacteria, Xanthomonadaceae, and Stenotrophomonas, and decreased abundances of Firmicutes, Streptococcus, Subdoligranulum, and Lactobacillus. HAV, an acute and self-limiting disease, has limited research on gut microbiota changes during infection. 16S rRNA analysis revealed gut microbiota dysbiosis in HIV patients co-infected with HAV, characterized by reduced Proteobacteria abundance and enrichment of Bifidobacterium and Bacteroides, with this dysbiosis persisting long after clinical recovery.. As for HDV infection, no relevant studies on gut microbiota have been identified, likely because HDV is an incomplete virus requiring HBV for replication, making it challenging to obtain relevant data. These findings suggest that regional, dietary, and ethnic differences may contribute to the variability in gut microbiota expression in viral hepatitis-related liver diseases. Therefore, long-term, multicenter studies are still needed to further explore the relationship between gut microbiota and viral hepatitis.[21, 23]

How can Intestinal Microbiota be Treated in Viral Hepatitis?

Currently, targeting the gut microbiota has emerged as a novel therapeutic approach for viral hepatitis infections and their complications. FMT as a method to restore and reconstruct the balance and diversity of gut microecology, has demonstrated promising outcomes. In a study involving 20 patients with liver disease related to CHB progression, FMT treatment significantly improved the Shannon and Simpson indices of gut microbiota, repaired the impaired abundance of gut microbiota, and subsequently promoted the improvement of amino acid metabolism. In a preliminary study in China, FMT induced HBeAg clearance in 18 HBeAg-positive patients who had undergone long-term antiviral therapy. Similarly, in a non-randomized pilot clinical trial involving 14 CHB patients in India, the potential safety and efficacy of FMT in achieving viral suppression and HBeAg clearance in HBeAg-positive CHB patients were observed.[24]

Alteration of Gut microbiota in Alcoholic Liver Disease (ALD)

ALD, driven by chronic excessive alcohol intake, progresses from hepatic steatosis to fibrosis and cirrhosis via gut microbiota dysbiosis. ALD is a spectrum of diseases, ranging from asymptomatic liver steatosis to the development of fibrosis, cirrhosis, and alcoholic hepatitis. Over the past few years, studies demonstrated that gut microbiota played a key role in the progression of ALD.[25]

In 2017, Philips et al. first reported a patient with severe alcohol hepatitis who was a steroid non-responder and underwent FMT. In this case, the patient's clinical, biochemical, and liver disease severity scores were significantly improved after FMT, which demonstrated that a distinct bacterial population changed before and after FMT.[26] Subsequently, another open-label study was performed with follow-up of 3 months to compare the outcomes in patients with severe alcoholic hepatitis using different methods, including nutritional therapy (n=17), corticosteroid therapy (n=8), pentoxifylline therapy (n=10), and FMT (n=16) from healthy donors. This clinical trial finally indicated that FMT for severe alcoholic hepatitis could improve survival beyond what is suggested by other therapies. After 1–2 years, the relative abundance of Porphyromonas was significantly lower and that of Bifidobacterium was higher in patients who underwent FMT than in patients who underwent corticosteroid therapy. Furthermore, FMT could function as a cost-effective bridge to LT or to improve survival without transplantation. FMT was also demonstrated as a safe therapeutic approach to reduce the incidence of ALD. Based on the clinical evidence, FMT is suggested as a safe and efficient therapy for ALD, especially for noncorticosteroid- responsive patients and without history of undergoing LT.[27]

Alteration of Gut Microbiota in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

MASLD, formerly known as non-alcoholic fatty liver disease, is a chronic liver condition affecting approximately 30% of the global population. Characterized by abnormal lipid accumulation in hepatocytes, MASLD can progress from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), and ultimately lead to hepatic fibrosis, cirrhosis, and even hepatocellular carcinoma.[28]

Studies have shown that the diversity and abundance of gut microbiota are significantly reduced in MASLD patients compared to HC.[29]

However, findings vary across regions and ethnicities. For example, a study in Indonesia involving 37 MASLD patients reported a predominance of Firmicutes and an elevated F/B ratio.[30]

In contrast, a study in Taiwan involving 50 biopsy-confirmed MASLD patients demonstrated a higher abundance

of Bacteroidetes, a lower abundance ofFirmicutes, a reduced F/B ratio, and decreased levels of Ruminococcaceae, Clostridiales, and Clostridium compared to healthy individuals.[31] A study in Korea involving 23 MASLD patients with elevated liver enzymes found an enrichment of Firmicutes, an increased F/B ratio and a significant rise in the abundance of Veillonella, Dialister, Collinsella, Latilactobacillus, and Bifidobacterium. In MASLD patients, the abundance of beneficial bacteria such as Akkermansia muciniphila, Faecalibacterium prausnitzii and Bifidobacterium is significantly reduced. A study involving 100 adolescent MASLD patients found a notable decrease in the abundance of Lactobacillus and Escherichia coli and a significant increase in Prevotella.[32,33]

These findings indicate that the gut microbiota of MASLD patients exhibits significant diversity, which may be closely related to factors such as ethnicity, dietary habits and geographic environment.

Alteration of Gut Microbiota in Autoimmune Hepatitis (AIH)

AIH is an entity of chronic and immune-mediated hepatitis characterized by hepatocyte injury, with the presence of circulating autoantibodies and elevated level of serum immunoglobulin G (IgG). At present, the main pathogenetic mechanism of AIH is considered as a loss of tolerance against the patient's own liver antigens, which is potentially triggered by both genetic and environmental risk factors, such as xenobiotics and pathogens. AIH may develop to liver cirrhosis and HCC, and it may even lead to fulminant hepatic failure.[34]

In fact, triggers of AIH are very complex and have not yet been identified. For treatment, AIH patients favorably respond to corticosteroids, while some patients who are irresponsive to standard treatment may quickly develop to fibrosis and cirrhosis. Therefore, development of effective therapies for patients who are irresponsive to corticosteroids is essential. In recent years, evidence from murine models exhibited that the gut microbiota is an important environmental risk factor, participating in the pathogenesis of AIH. Wei et al. performed a cross-sectional study on 91 patients with AIH and 98 healthy controls by 16S rRNA gene sequencing, and the results showed that compared with healthy controls, the gut microbiome of patients with AIH before steroid treatment was accompanied by a lower alpha-diversity and a distinct microbial composition.[35, 36] However, to our knowledge, no clinical study has yet assessed the therapeutic value of FMT for AIH.

Alteration of Gut Microbiota in Primary Sclerosing Cholangitis (PSC)

PSC is a chronic immune-related cholestatic liver disease, which can lead to cholestasis, bile duct stenosis, and hepatic fibrosis. A previous study demonstrated that PSC is closely associated with inflammatory bowel disease (IBD) suggesting that gut microbiota plays a key role in the PSC. Compared with healthy controls, PSC and PSC-IBD patients have significantly distinct gut microbial profiles with decreasing expression of Prevotella copri (P. copri). Several studies demonstrated that P. copri could improve glucose homeostasis with GI resection by enhancing the bile acid metabolism and signaling and promote immune tolerance.

For the treatment of PSC, there is no effective therapy. LT seems to be the only therapeutic option. However, there is still a risk of recurrent PSC after LT. According to the protective role of gut microbiota in PSC. Over the past few years, additional studies have concentrated on the therapeutic effects of gut microbiota on PSC. In 2019, Allegretti et al. performed an open-label pilot study on 10 patients with PSC-IBD. These patients underwent FMT and 30% of them experienced a more than 50% decrease in alkaline phosphatase (ALP) levels. Moreover, no relevant adverse event occurred. Following FMT, the patient's liver biochemistry, bile acid, and bacterial community were significantly improved, suggesting the applicability of FMT in the treatment of PSC. However, further evidence is required to verify the above-mentioned findings.[37] Following FMT, the patient's liver biochemistry, bile acid, and bacterial community were significantly improved, suggesting the applicability of FMT in the treatment of PSC. However, further evidence is required to verify the above-mentioned findings.

Gut microbiota dysbiosis plays a crucial role in the development and progression of autoimmune and genetic liver diseases (such as Wilson's disease). These diseases are closely associated with gut microbiota dysbiosis. Modulating the gut microbiota may provide new insights for the diagnosis and treatment of these diseases. Future research should further explore the specific mechanisms of gut microbiota in these liver diseases and develop gut microbiota-based early diagnostic and therapeutic approaches, thereby offering more precise and personalized treatment strategies for patients.

Alteration of gut microbiota in Liver Cirrhosis (LC)

LC represents a severe stage of chronic liver disease characterized by extensive hepatocyte degeneration, fibrosis, and nodular regeneration, leading to significant morbidity and mortality.

In hepatitis B-related cirrhosis, a common subtype of LC, progressive liver damage is further aggravated by gut microbiota dysbiosis and associated metabolic dysfunction. Studies consistently demonstrate that LC patients exhibit markedly reduced gut microbial diversity compared to healthy individuals, with notable depletion of beneficial bacteria such as Agathobacter and Prevotella, with Chinese LC patients showing elevated Bacteroidota/Firmicutes ratios and Proteobacteria abundance correlated with inflammatory responses, while North American cohorts demonstrate distinct associations between Enterobacteriaceae / Streptococcaceae dominance and clinical outcomes including extrahepatic organ failure.

The clinical relevance of these microbial alterations is underscored by their correlations with disease complications, including the association between Akkermansia muciniphila depletion and sarcopenia development, as well as the close relationship between pathogenic bacterial overgrowth and systemic inflammatory markers like TNF-α and IL-6. These findings collectively establish gut microbiota dysbiosis as a key contributor to LC progression through multiple interconnected pathways.

The gut microbiota plays a critical role in the pathogenesis of LC. In LC patients, gut microbiota dysbiosis, bacterial overgrowth and increased intestinal permeability disrupt the protective mechanisms of the gut, leading to pathological bacterial translocation and increased endotoxin uptake. These endotoxins subsequently reach the liver and mesenteric lymph nodes, activating immune cells and triggering the release of pro-inflammatory cytokines such as TNF-α and IL-8.

Meta-analysis results indicate that endotoxin-producing Enterobacteriaceae and Enterococcus are significantly increased in LC patients, which may be related to the impaired intestinal mucosal barrier function caused by LC.

The impaired intestinal barrier and gut microbiota dysbiosis not only lead to bacterial translocation and endotoxemia but also exacerbate liver injury and fibrosis through abnormal related metabolites. In LC patients, dysbiosis of the ascending colon mucosa-associated microbiota, particularly the reduction of SCFA-producing bacteria, compromises intestinal barrier integrity and BA metabolism, thereby exacerbating liver fibrosis progression via the gut-liver axis.[38, 39, 40]

The gut microbiota plays a pivotal role in the development of cirrhosis, with its dysbiosis not only directly affecting liver inflammation and fibrosis but also influencing systemic metabolism and immune responses through the gut-liver axis.

Alteration of Gut Microbiota in Drug-İnduced Liver Injury (DILI)

Drug-induced liver injury (DILI), a leading cause of ALF and acute hepatitis globally,[1] is a severe adverse drug reaction associated with medications such as anti-infectives, herbal products, and non-steroidal anti-inflammatory drugs. Emerging evidence highlights the critical role of gut microbiota in DILI pathogenesis. Patients with DILI exhibit significant gut microbial dysbiosis, characterized by reduced richness and diversity (99), with distinct patterns across drug types. In acetaminophen (APAP)-induced models, APAP exposure increases Cyanobacteria and Deferribacteres while decreasing Firmicutes at the phylum level, and elevates Bacteroides/Enterococcus but depletes Bifidobacterium/Lactobacillus at the genus level. These findings collectively underscore gut microbiota as a pivotal mediator in DILI progression.[41]

Alteration of Gut Microbiota in Hepatocellular Carcinoma (HCC)

HCC is the fourth leading cause of cancer-related deaths globally, with its incidence primarily associated with hepatitis B (40%), hepatitis C (40%), alcohol (11%) and MASH. Recent studies have shown that alterations in the gut microbiota are closely related to the occurrence and progression of HCC.[42] By 2025, over one million cases will be globally affected by HCC. LT has become a standard treatment for patients with early stage HCC in several countries. However, for those patients with advanced HCC whose number and size of tumor beyond Milan criteria, the 5-year survival rate after LT remains poor. Over 80% of HCC cases are associated with liver cirrhosis, representing inflammation and hepatocellular proliferation. A study demonstrated that bacteria derived from gut might play a role in the recurrence of cirrhosis and HCC.

In early-stage HCC patients, the species richness of fecal microbiota is increased compared to the LC group. Analysis of published fecal datasets from four different regions in China revealed that the relative abundance of Firmicutes was significantly lower in HCC patients compared to HC and further decreased with disease progression, while the relative abundance of Bacteroidetes and Proteobacteria significantly increased.

However, Yan et al. reported inconsistent findings in a study conducted in Beijing, showing that the abundance of both Bacteroidetes and Firmicutes gradually decreased in HCC patients. Additionally, the abundance of Proteobacteria, Streptococcus, and Ruminococcus was significantly higher in the HCC group compared to controls,

while the abundance of Subdoligranulum was significantly reduced.[43]

In early-stage HCC patients, the abundance of Actinobacteria increased, and 13 genera, including Gemmiger and Parabacteroides, were enriched in early HCC. The relative abundance of potentially beneficial bacteria, such as Lactobacillus, Bifidobacterium, and Bacteroides, was significantly reduced in HCC patients, while the relative abundance of potentially pathogenic bacteria, such as Escherichia-Shigella and Enterococcus, was significantly increased. Furthermore, Akkermansia was most enriched in LC patients, while its abundance was relatively lower in the HC group, CHB patients and HCC patients.[44]

When the literature is examined, Some clinical trials related to gut microbiota in HCC have been performed or are ongoing. However, to our knowledge, no clinical study has assessed the applicability of FMT for HCC. Only Baruch et al. Reported the first human clinical trial where they found how treatment with FMT was associated with favorable changes in gene expression profiles and immune cell infiltrates in the tumor microenvironment. These data indicated the benefits of FMT for the treatment of HCC.[45]

Clinical Value of Fecal Microbiota Transplantation for Liver Transplantation (LT) Recipients

It is widely accepted that LT is still the only therapeutic option for patients with end-stage liver disease, acute liver failure, and HCC. Over the recent decades, LT has been used as a mature and conventional surgical method for liver diseases. However, patients receiving LT are at a particularly higher risk of infection, such as CDI, cytomegalovirus (CMV) infection, fungi infection, recurrent HBV infection, etc. A previous cohort study demonstrated that about 19% of deaths occurred at five years after LT were related to various sources of infection.[46]

That is mainly due to administration of immunosuppressive agents after LT attenuates immune surveillance, enabling pathogens to evade natural immunity and facilitate infection. Furthermore, pre- transplant infection and some other risk factors are also associated with post-LT infection. In addition, several studies demonstrated that the types of gut microbiota may significantly change after LT.[47]

Hence, restoring the gut microbiota balance by FMT may be particularly critical for LT recipients. For instance, Schneider et al. reported a case of successful FMT in a LT recipient with severe CDI that was complicated with acute kidney injury.[48] Furthermore, the safety of FMT in immunocompromised patients has been demonstrated in a meta-analysis of 44 studies.[49] Therefore, FMT may be a potential therapeutic method for CDI after LT. However, to our knowledge, no clinical study has yet assessed the applicability of FMT for infectious diseases.

The gut–liver axis has shown a mutual association between the intestine and liver. Hence, the close interaction between gut and liver may be a very important factor in the pathogenesis of liver diseases. In addition, a growing body of evidence demonstrated that FMT is a novel approach to reconstruct the intestinal microecological balance, therefore, FMT has been gradually and widely utilized in the treatment of several liver diseases. Moreover, restoring the gut microbiota balance by FMT may be particularly critical for LT recipients.[50]

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