The Role of Nuclear Medicine in Liver Transplantation

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INTRODUCTION

The Ancient Perspective on Liver Regeneration

According to *Greek* mythology, **Prometheus** was punished by having his *liver eaten daily by an eagle* — and each day, the liver regenerated.

This highlights an early understanding of the liver's unique regenerative ability, a concept central to modern liver transplantation.

Liver transplant procedures in word

- Orthotopic liver transplantation (OLT) has been performed since 1967
- **2021**: >9,000 liver transplants performed in the USA alone.
- 1-year survival rate: ~80%;
- 5-year survival rate: ~70%.
- The longest surviving recipient has lived >25 years post-transplant.

Organ Procurement and Transplantation Network [OPTN] 2022)

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Liver Transplantation in Iran

- **First liver transplant** in Iran performed at Shiraz Organ Transplant Center (SOTC) in **1993**.
- Between **1993–2015**:
  - 3,191 liver transplants performed from 3,110 donors.
- ***Survival Rates:***
  - 1-year: 84%
  - 5-year: 80%
  - 10-year: 73%
- **Improved outcomes over time:**
  - Era I (1993–2005) vs Era II (2006–2015)
  - 10-year survival increased from **60%** to **78%.**

Ghods et al., 2014

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Role of Nuclear Medicine in Preoperative Evaluation

Preoperative Work-up for Liver Transplantation

- **Cardiac Evaluation:**
  - MUGA scan for left ventricular ejection fraction.
  - Stress Thallium or Adenosine testing for coronary artery disease.

- **Cancer Screening:**
  - Whole-body bone scan for metastases (especially in hepatocellular carcinoma).
  - PET/CT scan : metastasis evaluatin

- **Pulmonary Evaluation:**
  - Ventilation-Perfusion (V/Q) scan for hepatopulmonary syndrome diagnosis.

- **Liver Assessment:**
  - Tc-99m-GSA and HBS

Functional Reserve Evaluation in Donor

- Graft viability depends on hepatocellular function
- Size determination alone by CT scan (volumetric) not reliable in cirrhotic livers.
- **Tc-99m-DTPA-GSA** and **HBS (hepatobiliary scan)** allow functional estimation
- Helps determine **resectability** or **transplant candidacy.**

Tc-99m-GSA Scintigraphy

- It Binds to **asialoglycoprotein** receptors on hepatocytes
- Provides:
    1. **LHL15** (hepatic uptake)
    2. **HH15** (blood clearance)
- Advantages: Objective, reproducible, noninvasive method

(Graaf 2010)

Quantitative Imaging – GSA Indices

- **LHL 15**: Liver to heart ratio at 15 min
- **HH15**: Heart retention at 15 min

- **High LHL15** (>0.9) **/ Low HH15** → Good Hepatic function

- Can guide <u>timing of surgery </u>or <u>listing</u>

Tc-99m-GSA Clinical Application

- Used pre-transplant to assess **remnant liver function in donor**
- Influences transplant candidacy and surgical approach
- Particularly useful in **cirrhotics or small-for-size liver in *donors.***

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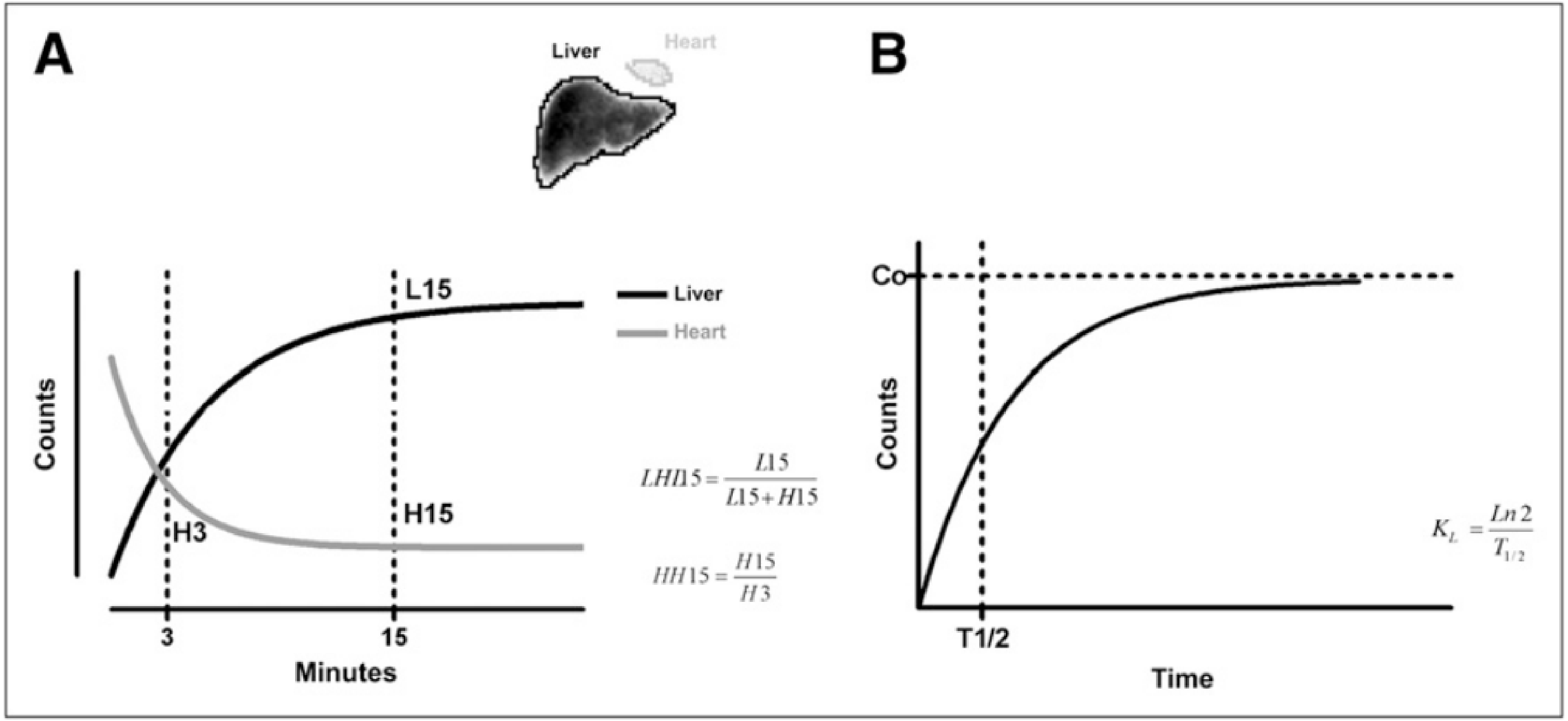

Planar dynamic 99mTc-GSA scintigraphy.

(A) LHL15 and HH15 are calculated from 99mTc-GSA time–activity curves from heart (gray) and liver (black).

(B) Blood clearance constant (KL) is calculated from liver uptake curve using clearance half-time (T1/2)

Living Donor Transplants

- Small-for-size syndrome risk
- GSA scintigraphy critical for graft sizing
- Avoids postoperative liver failure
- Common in Asia + increasingly in Western centres

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Hepatobiliary Scintigraphy (HBS)

- **Radiotracer**: Tc-99m mebrofenin or HIDA analogues
- **Assesses**: hepatocyte uptake, biliary excretion, transit times
- Quick, bedside-compatible, dynamic phase is useful .

(Monica Rossleigh 1988)

HBS Pre-Transplant Utility in recipient

- Identifies delayed uptake = hepatocellular dysfunction
- Delayed excretion = cholestasis or bile flow impairment
- Assists in MELD exception decisions.
- Dynamic uptake curves can be quantified

When to Use GSA vs HBS

GSA (Tc-99m-GSA)	HIDA/Mebrofenin
Receptor binding	Hepatobiliary flow
Quantitative reserve	Leak/obstruction
Pre-op, graft viability	Post-op, biliary issues

- Combining both enhances diagnostic accuracy

Semi-Quantitative Functional Assessment

Dynamic HBS provides semi-quantitative evaluation of liver function.

Key parameters:

- Hepatocyte Extraction Fraction (HEF) by **deconvolution analysis**
- Excretion half-time ($T_{1/2}$) using nonlinear least squares fitting

Semi-QuantitativeHepatic Functional Assessment

Interpretation:

- In hepatocellular dysfunction:
  - HEF decreases
  - T1/2 excretion time increases
- In biliary disease:
  - T1/2 excretion time increases
  - HEF remains normal

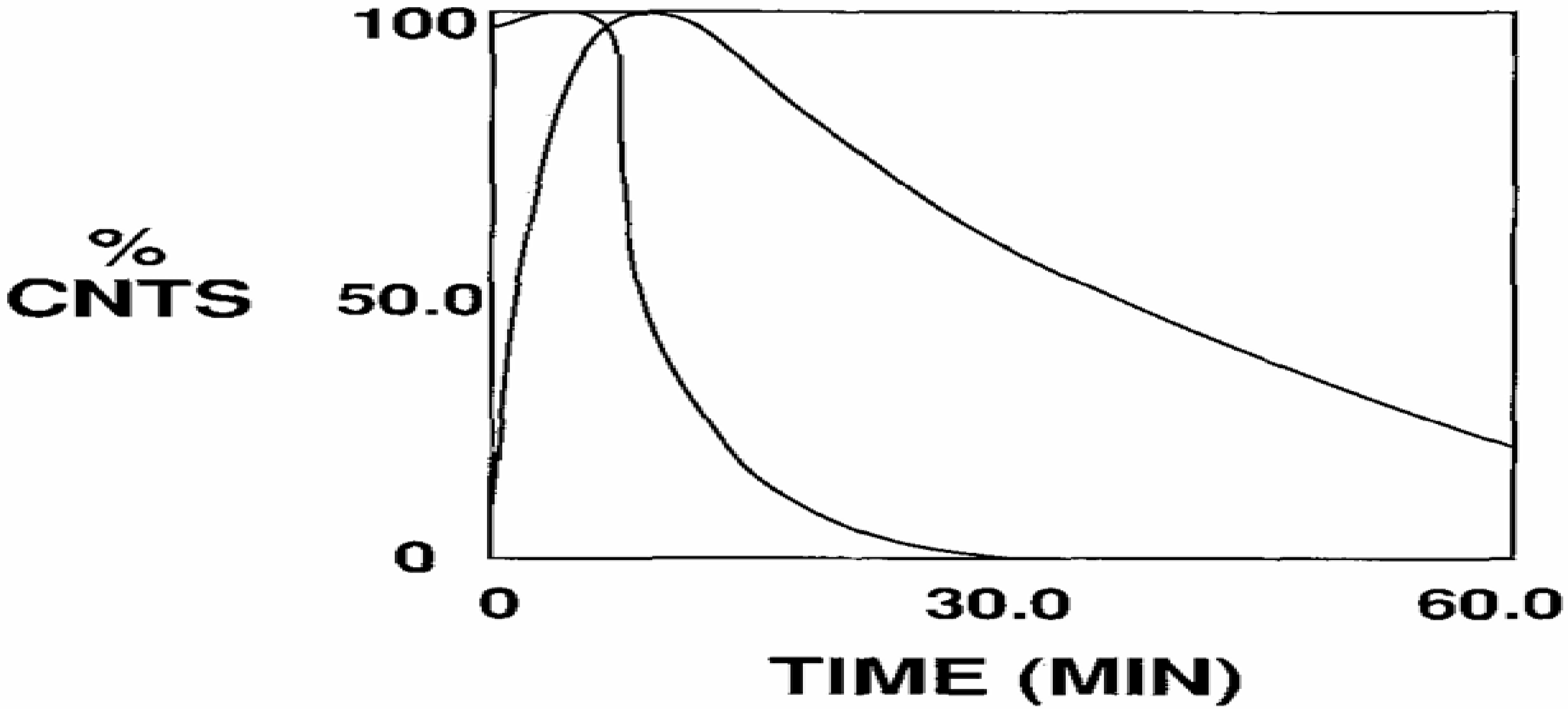
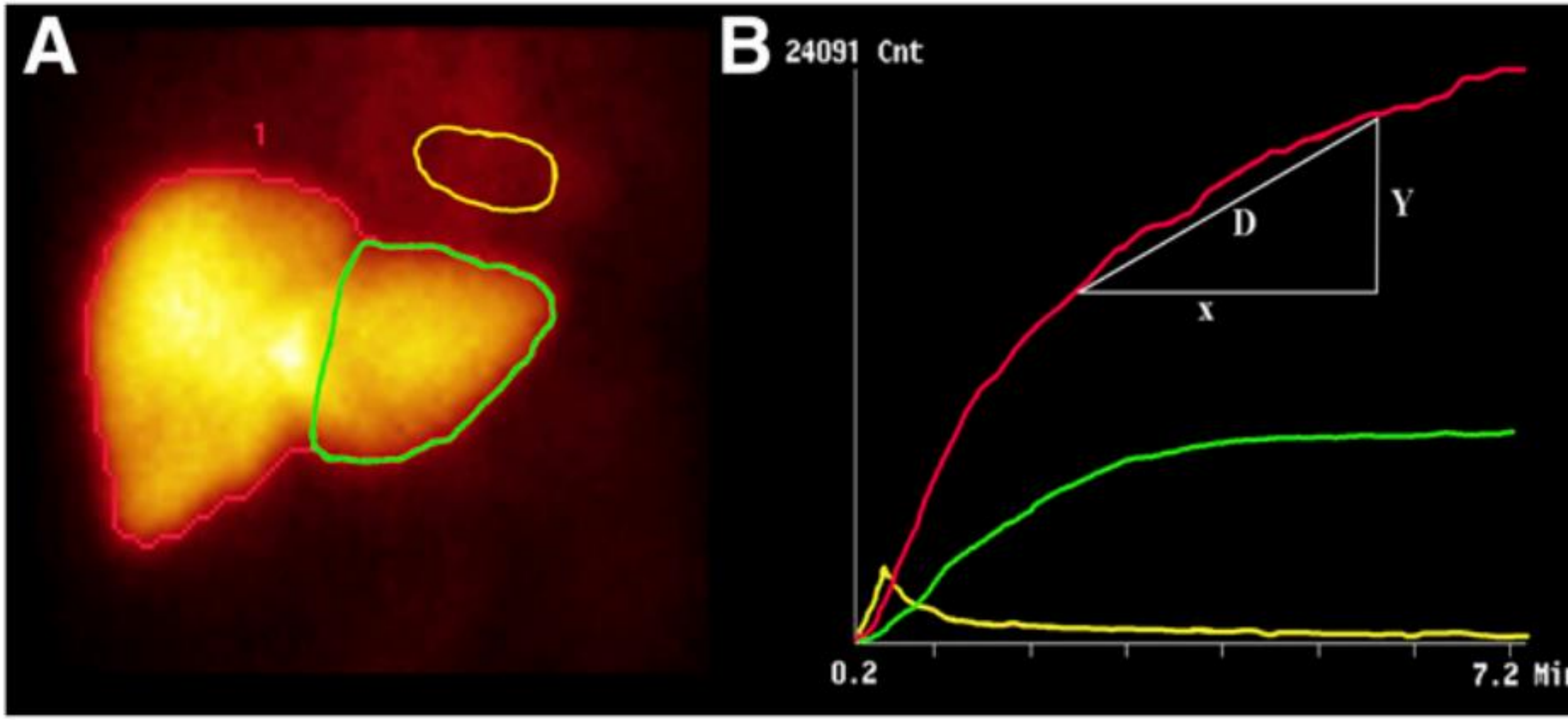


Fig 11. Quantitative hepatobiliary scintigraphy in three showing normal hepatocyte extraction fraction (HEF) and T½ excretion. (Courtesy of Dr Eva Dubovsky.)

Dynamic image of planar HBS



(A) Example of summed HBS images from 150 to 350 s after intravenous injection of 99mTc-mebrofenin. ROI is drawn around entire liver (red line), mediastinum (blood pool; yellow line), and FRL (green line).
(B) Blood-pool–corrected liver uptake time– activity curve. Liver uptake of mebrofenin is calculated as increase of blood-pool–corrected 99mTc-mebrofenin uptake (y-axis) per minute over a period of 200 s

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Hepatic Blood Flow Quantitative Studies

Quantitative studies help assess hepatic perfusion and function in transplant candidates.

Essential Nuclear medicine techniques:

- *Tc-99m sulfur colloid scintigraphy*:
  - Measures total hepatic blood flow.
- Tc-99m DTPA –GSA :
  - Evaluates venous and portal blood flow extraction fractions.
- Tc-99m DISIDA
  - Assesses hepatocyte extraction efficiency.

Juni et al.

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Quantitative Hepatic Blood Flow Studies

Interpretation:

- **DISIDA extraction efficiency <0.68** suggests
  - hepatocellular dysfunction.
- **Portal blood flow fraction >0.64** supports
  - hepatocellular injury without rejection.
- **Portal blood flow fraction <0.65** predicts
  - graft rejection.

Post-Transplant Complications

Post-Transplant Complications

based on etiology:

- Surgical complications: vascular, biliary, and parenchymal issues
- Graft-related complications: primary non-function, acute or chronic rejection
- Infectious complications: bacterial, fungal, and viral infections
- Neoplastic complications: de novo malignancies, post-transplant lymphoproliferative disorder (PTLD)

Post-Transplant Complications

based on timing:

- Early complications: occurring within the **first 6 months** post-transplant
- Late complications: occurring **after 6 months**

Vascular Complications After Liver Transplantation

Key vascular complications:

- **Hepatic artery thrombosis (HAT):**
  - The most serious vascular complication.
  - Incidence: approximately **15%** in adults and 12% in children.
  - High risk of graft loss and mortality if not promptly diagnosed and managed.
  - Best detected using Doppler ultrasound imaging.
- **Portal vein thrombosis:**
  - Incidence: approximately **9%.**
  - Associated with increased risk of graft dysfunction and re-transplantation.

Other vascular issues:

- Hepatic artery **stenosis**
- Venous outflow **obstruction**
- Development of **pseudoaneurysms**

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Biliary Complications After Liver Transplantation

Occurring in 10–25% of recipients.

Types of biliary complications:

- **Bile leaks:**
  - Typically an early complication, often within the first few weeks.
- **Anastomotic strictures:**
  - Typically a late complication occurring months to years after transplant.
- **Non-anastomotic strictures:**
  - Associated with ischemia (ischemic cholangiopathy).
- **Biloma formation:**
  - Encapsulated bile collection due to leakage.
- **Biliary stones or sludge formation.**
- **Sphincter of Oddi dysfunction.**

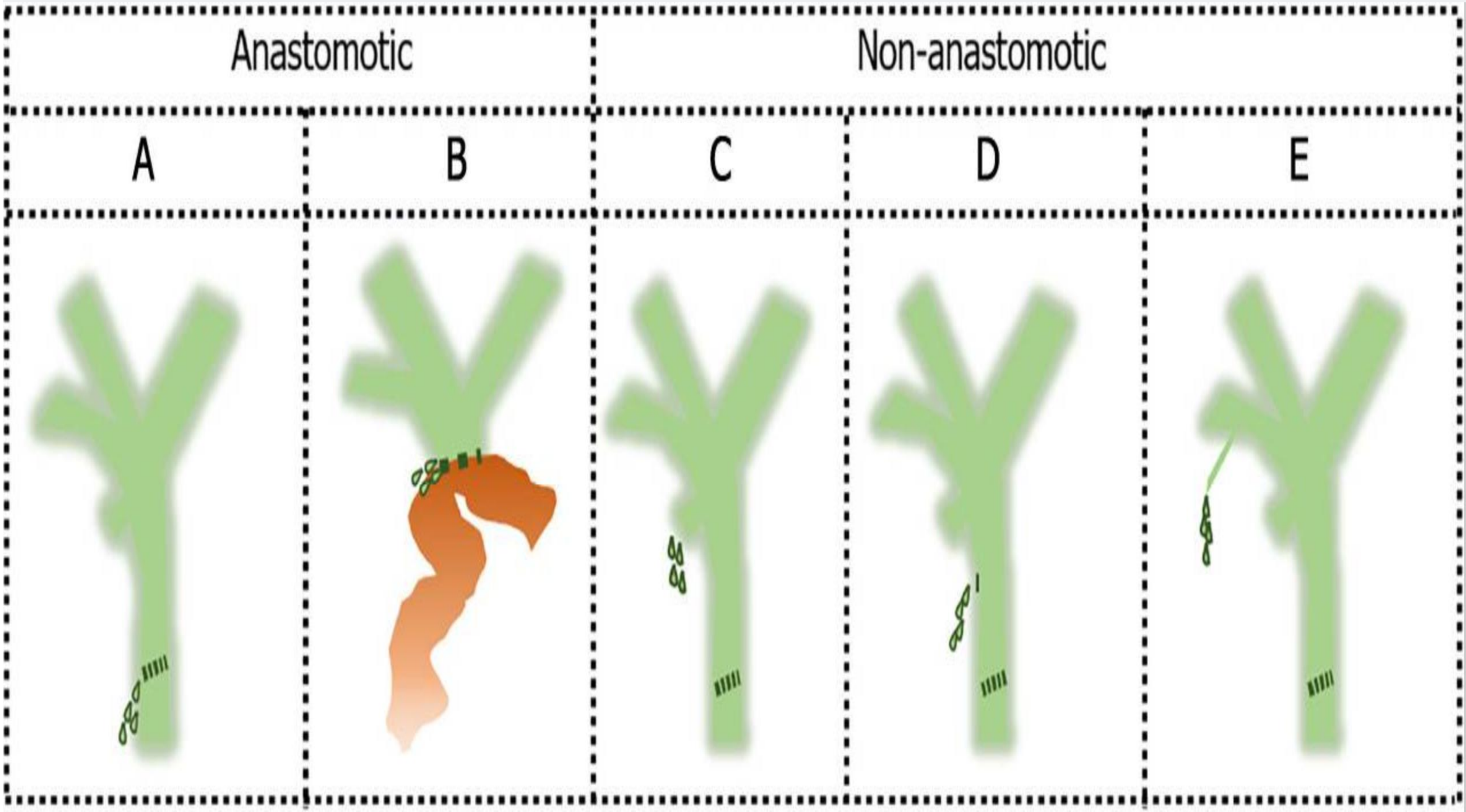
Timing and Types of Biliary Complications

Early biliary complications

- Bile leaks
- Early **anastomotic** strictures
- Biloma formation

Late biliary complications :

- Late anastomotic strictures
- **Non-anastomotic** strictures (ischemic cholangiopathy)
- Biliary stones or sludge
- Sphincter of Oddi dysfunction


Anastomotic
Non-anastomotic
A
B
C
D
E

Diagnostic Approaches for Bile Leak

Invasive techniques:

- **ERCP**
  - Gold standard for diagnosis and therapeutic intervention.
  - Risks include pancreatitis, perforation, and infection.
- **PTC**
  - Used when ERCP fails or is not feasible.
  - Risks include bleeding, bile leakage, and infection.

Non-invasive techniques:

- **MRCP**
  - Provides a detailed anatomic view of the biliary system.
  - High sensitivity and specificity for strictures and obstruction.
- **Hepatobiliary scintigraphy (HIDA scan):**
  - Functional imaging to dynamically detect active bile leaks.
  - Highly sensitive even for subtle or early leaks.

Nuclear Medicine in Post-Transplant Evaluation

Early Post-Transplant Imaging

- **High risk period**: first 7 days post-op
- **Common complications**:
  - Hepatic artery thrombosis,
  - Biliary leak,
  - Poor graft function
- **Imaging** = early detection → graft salvage

Functional Imaging in Immediate Post-Op

- **Nuclear techniques:**
  - Perfusion imaging (GSA)
  - Hepatobiliary scintigraphy (HBS)
- Detect functional failure <u>before lab changes</u>
- SPECT and planar studies both useful

Hepatic Artery Thrombosis

- Most feared early complication
- **Risk**: ischaemia, infarction, graft failure, mortality
- **HBS shows** segmental absence of uptake

  Use in conjunction with Doppler US

Graft Dysfunction

- **Differentials:**
  - Acute rejection
  - Ischemic injury
  - Drug toxicity
- Labs often inconclusive
- Imaging offers early insight

Deconvolution Analysis in Graft Dysfunction

- Used in HIDA, Tc-99m-GSA
- Useful when lab tests are ambiguous
- **Scan Finding**:
  - Hepatic Extraction Fraction (**HEF**)
  - **T½** clearance
- Helps <u>avoid unnecessary biopsy</u>
- Improves specificity for dysfunction vs obstruction

HIDA Scan in Bile Leak Detection

- **Normal**: Radiotracer moves from liver → bile ducts → small intestine.
- **Bile leak**: Radiotracer extravasation outside the biliary tree into *peritoneal* or perihepatic spaces.

Advantages:

- High sensitivity for detecting active leaks.
- Can detect small leaks missed by MRCP or ERCP.
- Dynamic and functional imaging, not just anatomic.

Limitations:

- Planar imaging alone has limited anatomic detail.
  - Better localization with SPECT views

Planar Imaging vs SPECT/CT in HIDA Scintigraphy

SPECT/CT imaging:

- Improves localisation and characterization of bile leaks.
- Increases **diagnostic accuracy**: **65.6%** vs **96.8%**

Current recommendation:

- Whenever available, SPECT/CT should be performed along with planar imaging to improve bile leak detection and localization.

HIDA Scan Main features for Bile Leak

- **Early phase (0–30 minutes):** Normal hepatic uptake and excretion into bile ducts and small bowel.
- **Detection of bile leak:**
  - Appearance of radiotracer outside the expected biliary tract.
  - Progressive accumulation in perihepatic, subhepatic, or peritoneal spaces.
- **Delayed imaging (up to 4–6 hours)** is often necessary for detecting small or slow leaks.

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HIDA Scan Interpretation tips

- **Early** dynamic imaging improves **sensitivity**.
- **Delayed** imaging helps confirm **slow leaks**.
- Always correlate imaging findings with clinical signs (e.g., bilious drain output, rising bilirubin).

Free-flow Bile Leak vs Biloma on HIDA Scan

Free-flow leak:

- Radiotracer spreads diffusely within the peritoneal cavity.
- Accumulates along natural peritoneal recesses, such as:
  - Right paracolic gutter
  - Morison's pouch
  - Pelvic cavity

Free-flow Bile Leak vs Biloma on HIDA Scan

Biloma (encapsulated bile collection):

- Radiotracer accumulates in a localized, well-circumscribed area.
- No diffuse spread to other peritoneal spaces.
- May fill slowly on delayed images.

Limitations and Pitfalls in HIDA Scan Interpretation

Potential limitations and pitfalls:

- Very small or clinically **insignificant leaks may be missed**.
- Other fluid collections (ascites, hematoma, seroma, urine leak) may **mimic bile leak**.
- Bowel activity can cause **false positives** if misinterpreted.

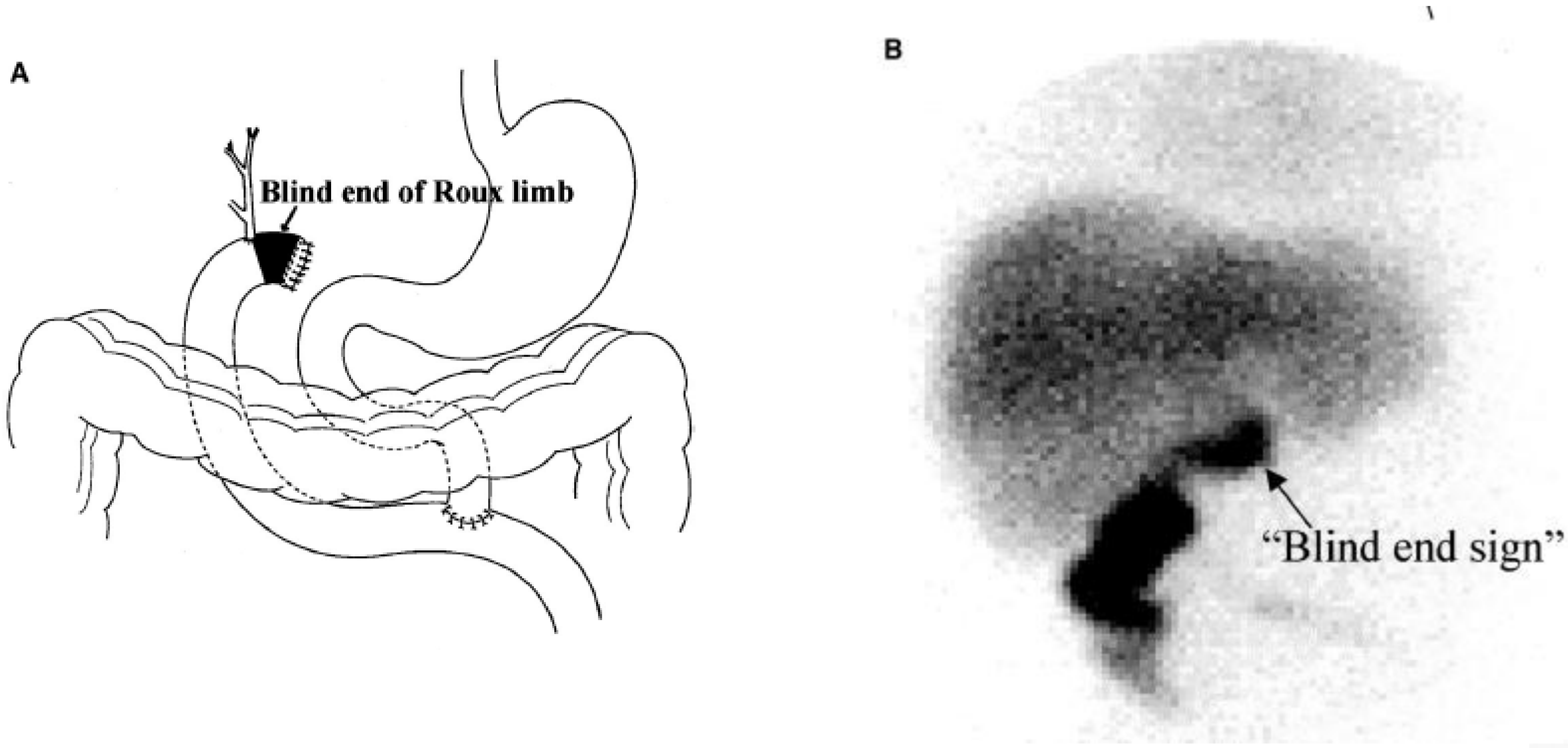
Strategies for better Interpretation :

- Dynamic (cinematic) review is essential — bile leaks increase in intensity while bowel activity moves distally.
- SPECT/CT helps clarify uncertain cases by providing exact anatomical correlation.
- Delayed imaging improves detection of subtle leaks.

Differentiating Leak vs Blind End

- True bile leak = constant shape, irregular
- Blind end = fluctuates, tubular, bowel-sized
- Delayed images is essential & avoid false positive diagnosis

The Blind End Sign – Schematic and Real Case



The “blind end sign” shown schematically (A,shaded area) and on a single image from a dynamic hepatobiliary scan (B).

Functional Assessment of Liver Graft Using Hepatobiliary Scintigraphy

- Beyond detecting leaks: **dynamic evaluation of graft function.**
- **Parameters analysed from deconvolution analysis:**
  - Hepatocyte Extraction Fraction (HEF)
  - Excretion half-time (T½).
- **Interpretation:**
  - **Normal graft**: high HEF, normal T½.
  - **Dysfunctional graft** (ischemia, rejection, cholestasis): reduced HEF, prolonged T½.

Normal HBS in Transplanted Liver

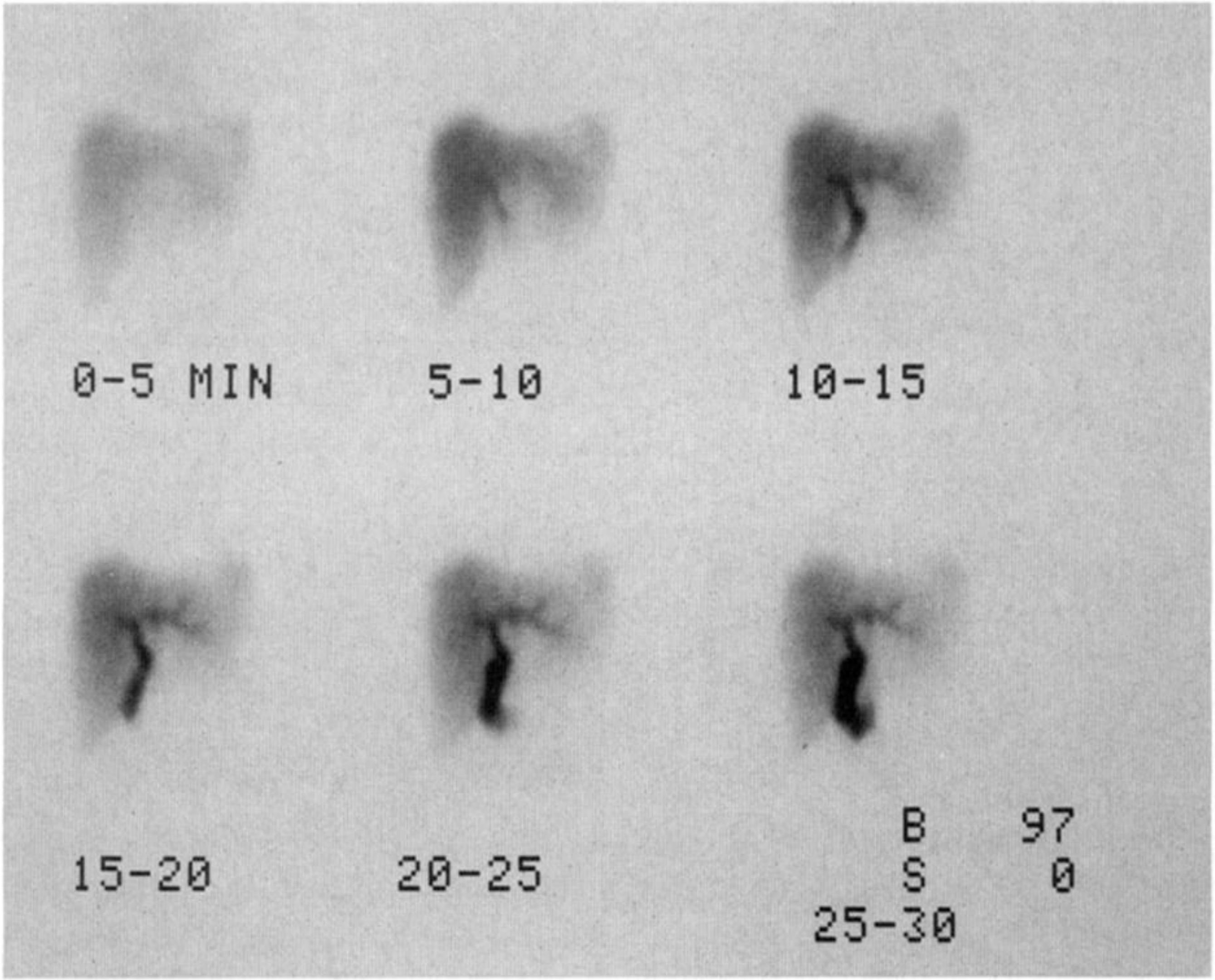


Fig 9. Quantitative hepatobiliary scintigraphy showing normal hepatocyte extraction fraction (HEF) and T1/2 excretion. (Courtesy of Dr Eva Dubovsky).

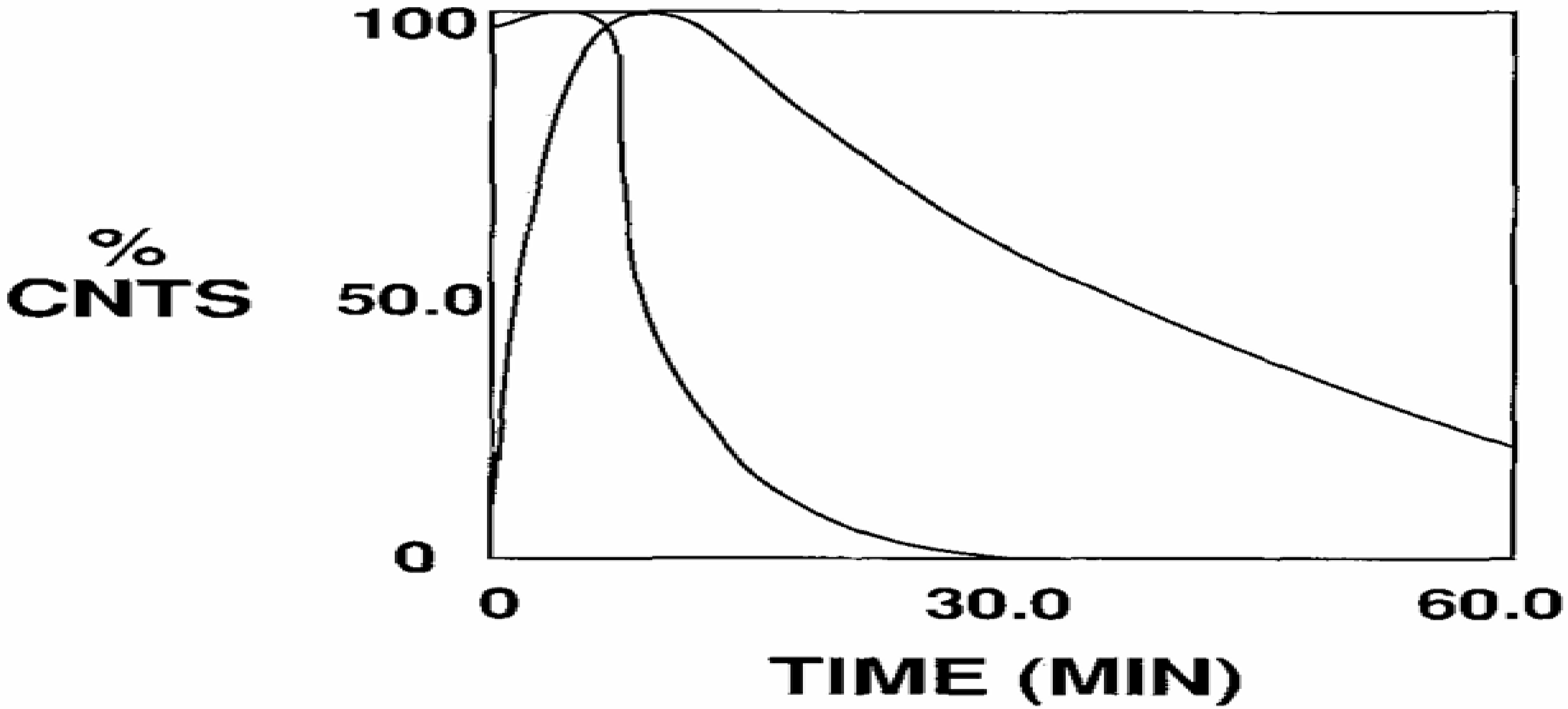
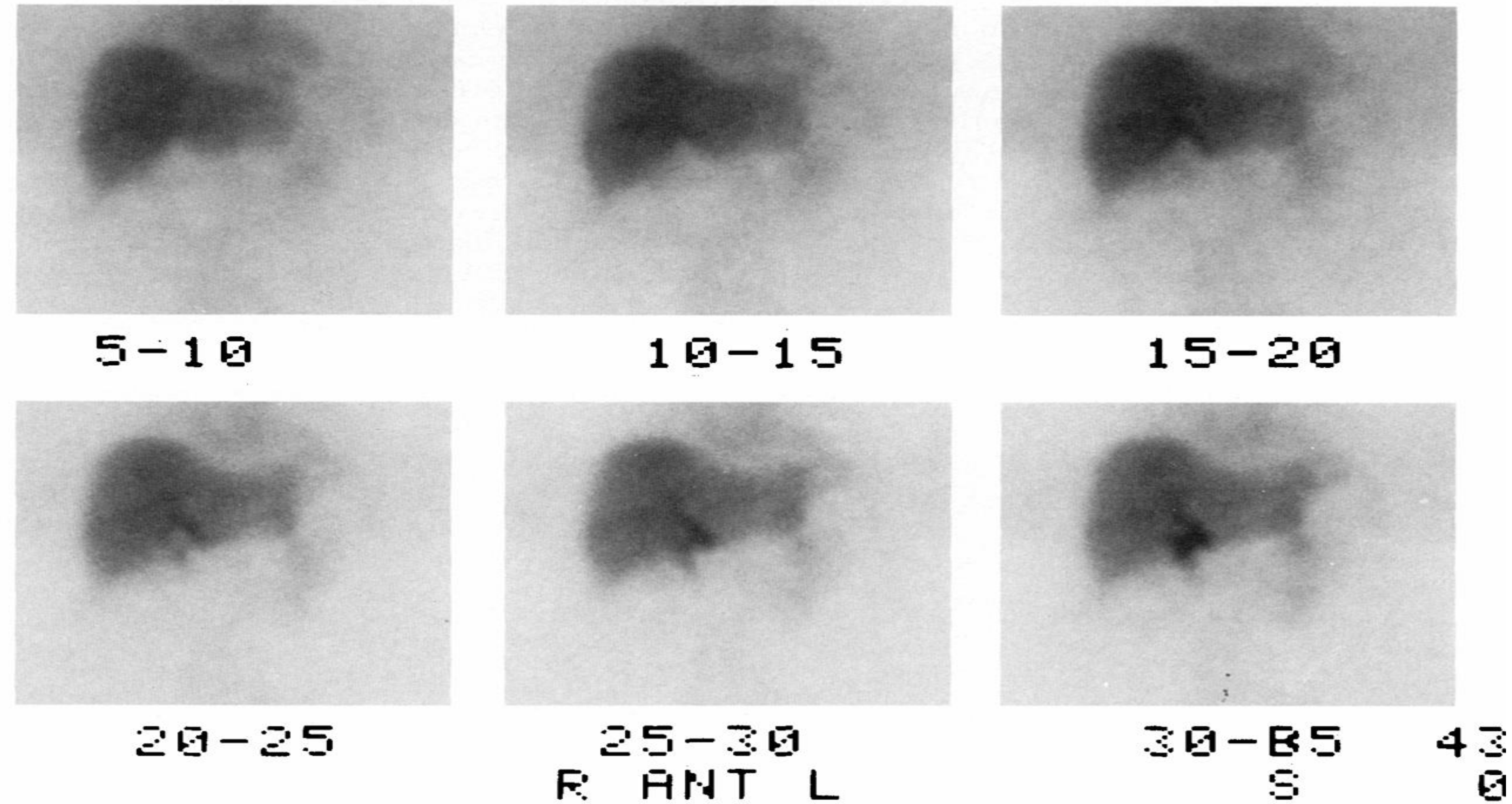


Fig 11. Quantitative hepatobiliary scintigraphy in three showing normal hepatocyte extraction fraction (HEF) and T½ excretion. (Courtesy of Dr Eva Dubovsky.)



Quantitative hepatobiliary scintigraphy showing **poor hepatocyte extraction fraction** (HEF) and **delayed T½ excretion** in biopsy proven **acute rejection.** (Courtesy of Dr Eva Dubovsky.)

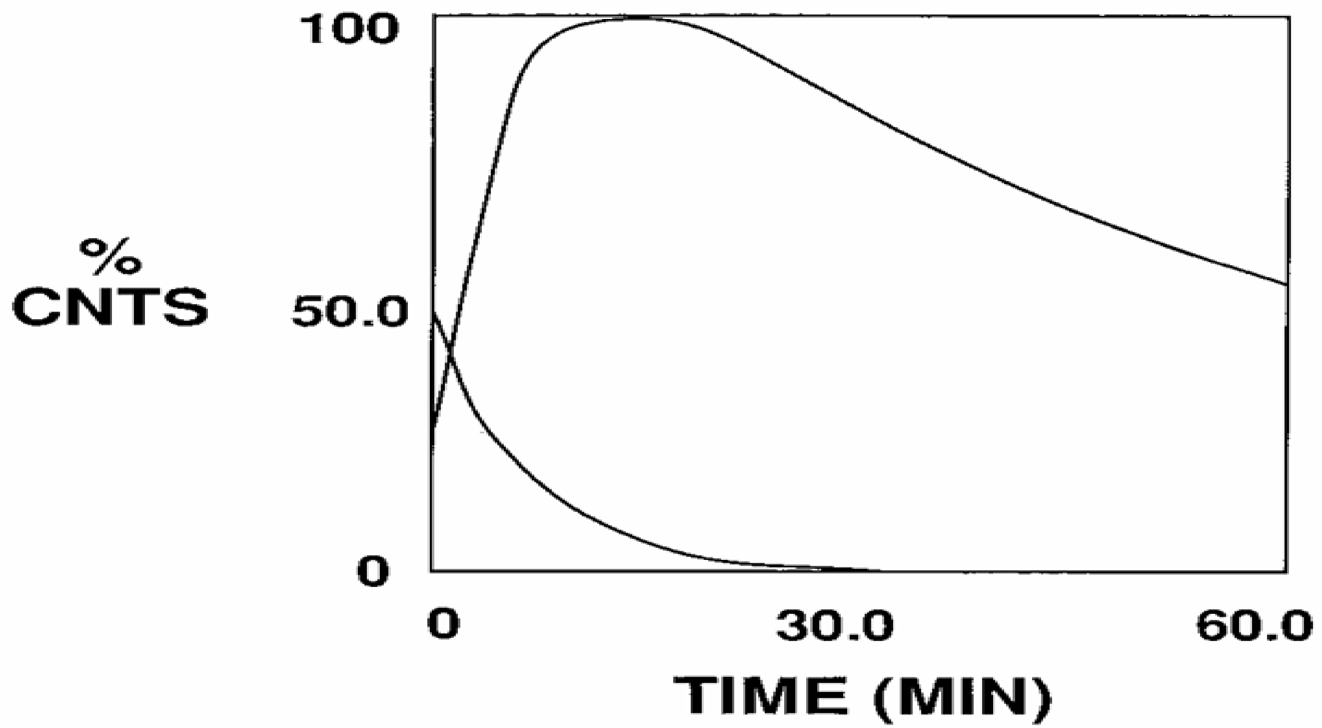
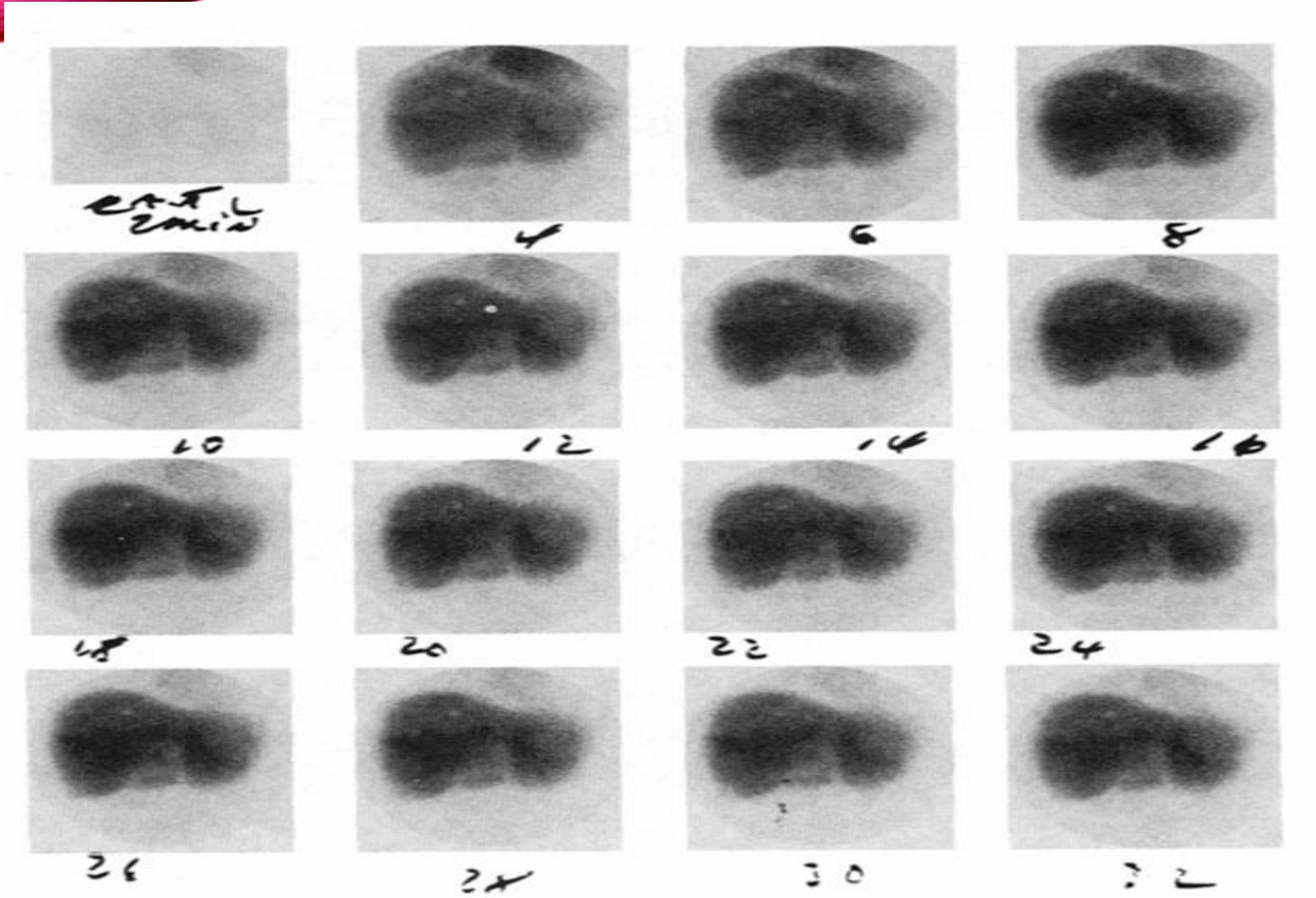


Fig 14. Quantitative hepatobiliary scintigraphy showing poor hepatocyte extraction fraction (HEF) and delayed T½ excretion in a biopsy proven acute rejection. (Courtesy of Dr Eva Dubovsky.)



Quantitative hepatobiliary scintigraphy showing poor hepatocyte extraction fraction (HEF) and **markedly delayed T½ excretion** suggestive of **high-grade obstruction** confirmed by cholangiography.

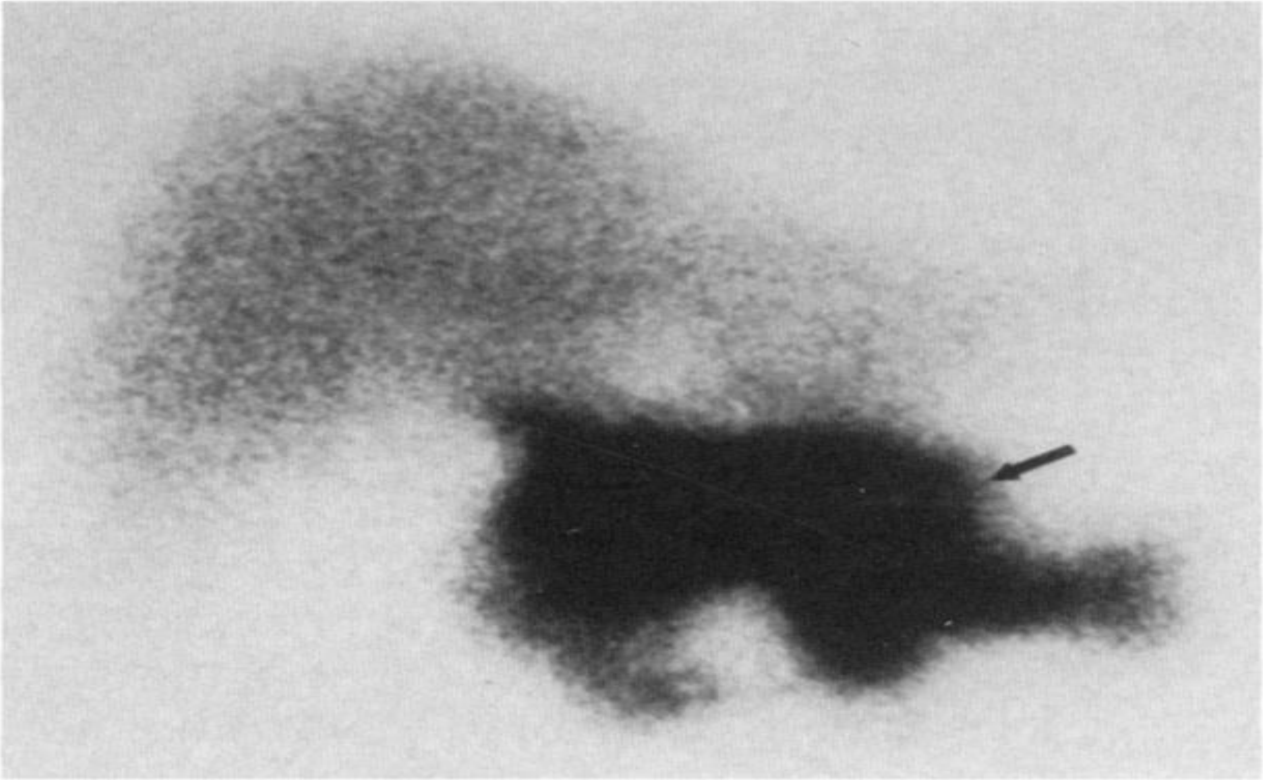
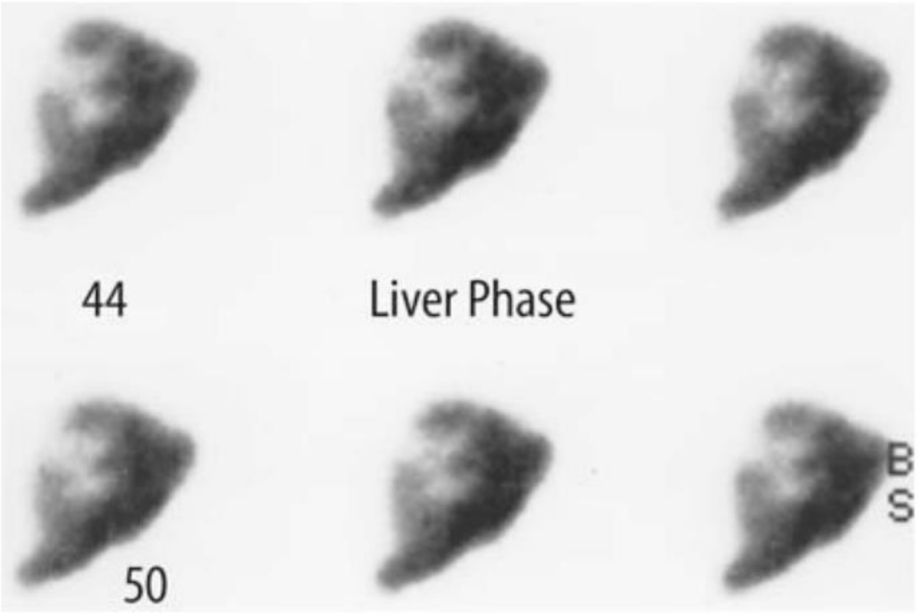


Fig 3. Hepatobiliary scintigraphy showing accumulation of tracer in the left subhepatic space (solid arrow) in a 49-year-old man 6 days after liver transplant.



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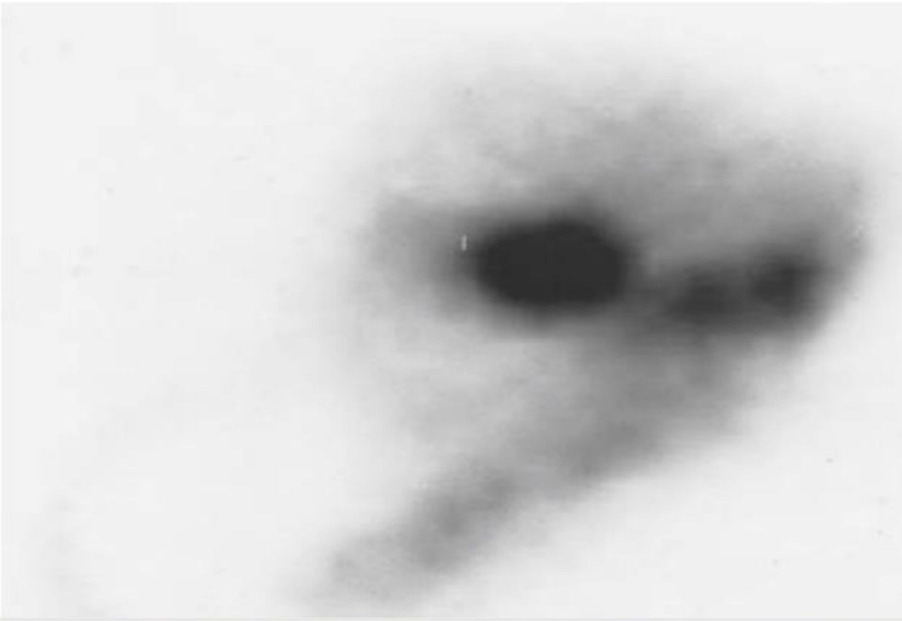

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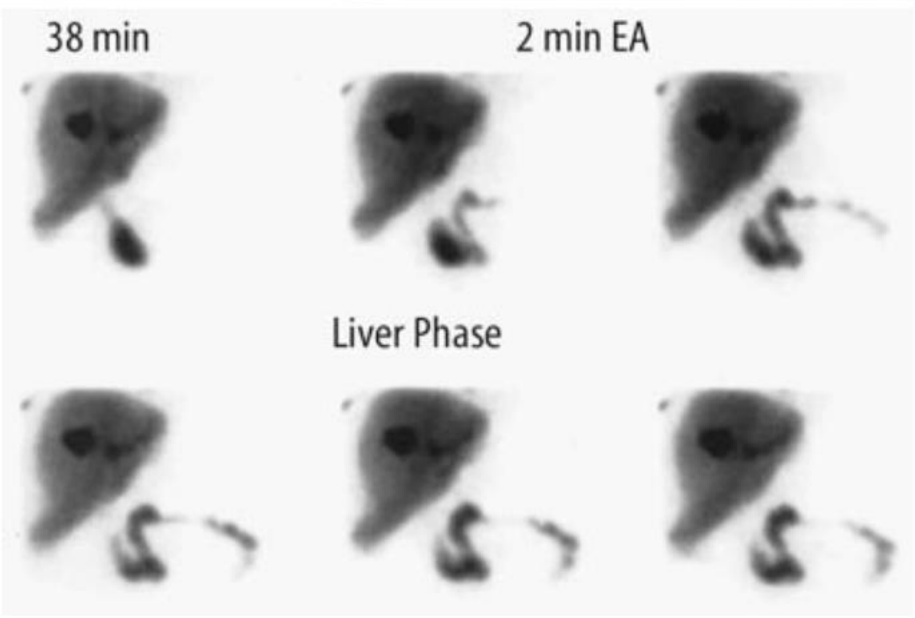
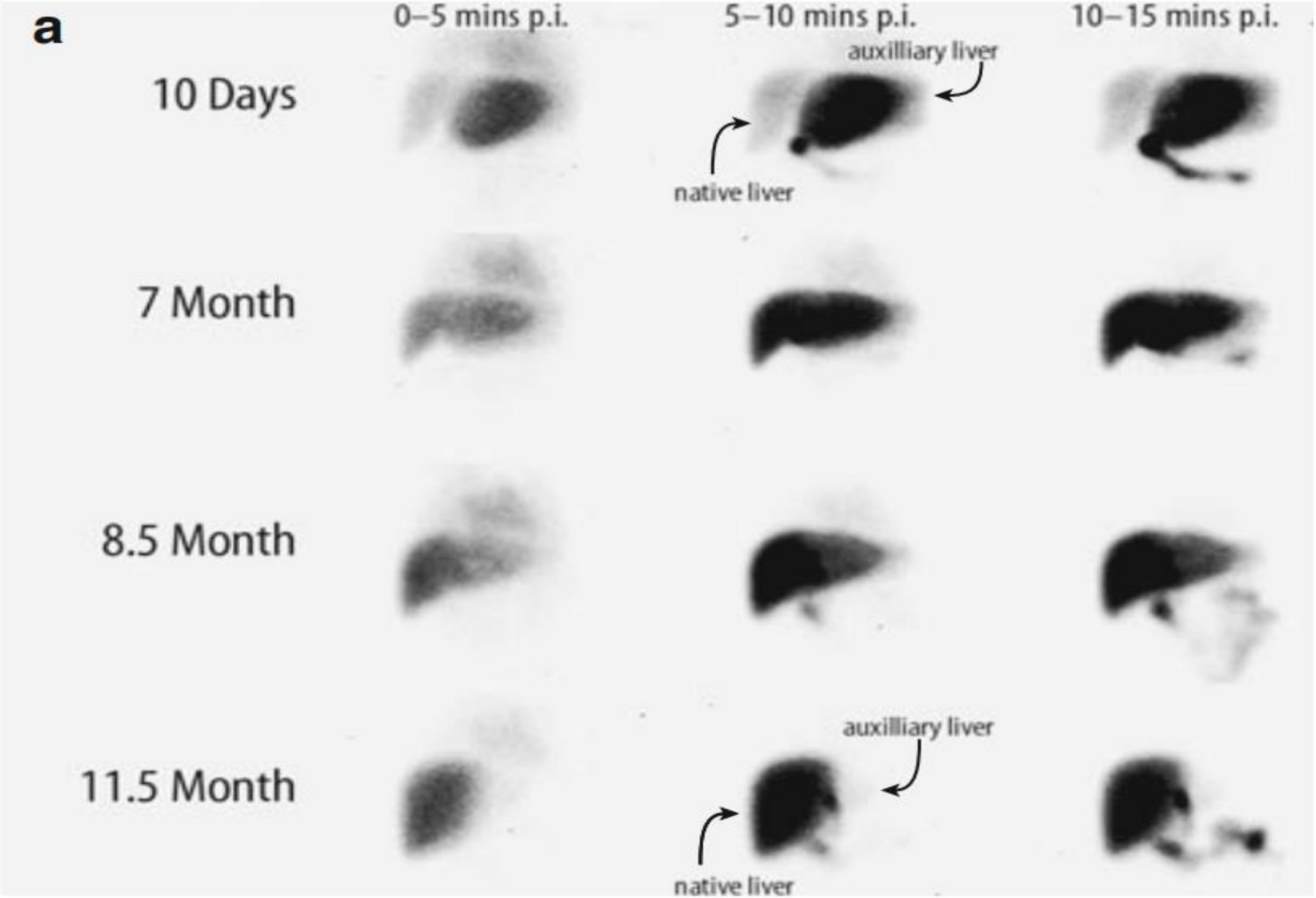


Abscess in a transplant liver. (**False Positive)**

(a) An abscess causes a large filling defect within liver parenchyma
(b) and fills with bile at 4.5 h

(c)A repeat study 3 months later shows shrinkage of the abscess, but fistula persists



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0–5 mins p.i.
5–10 mins p.i.
10–15 mins p.i.
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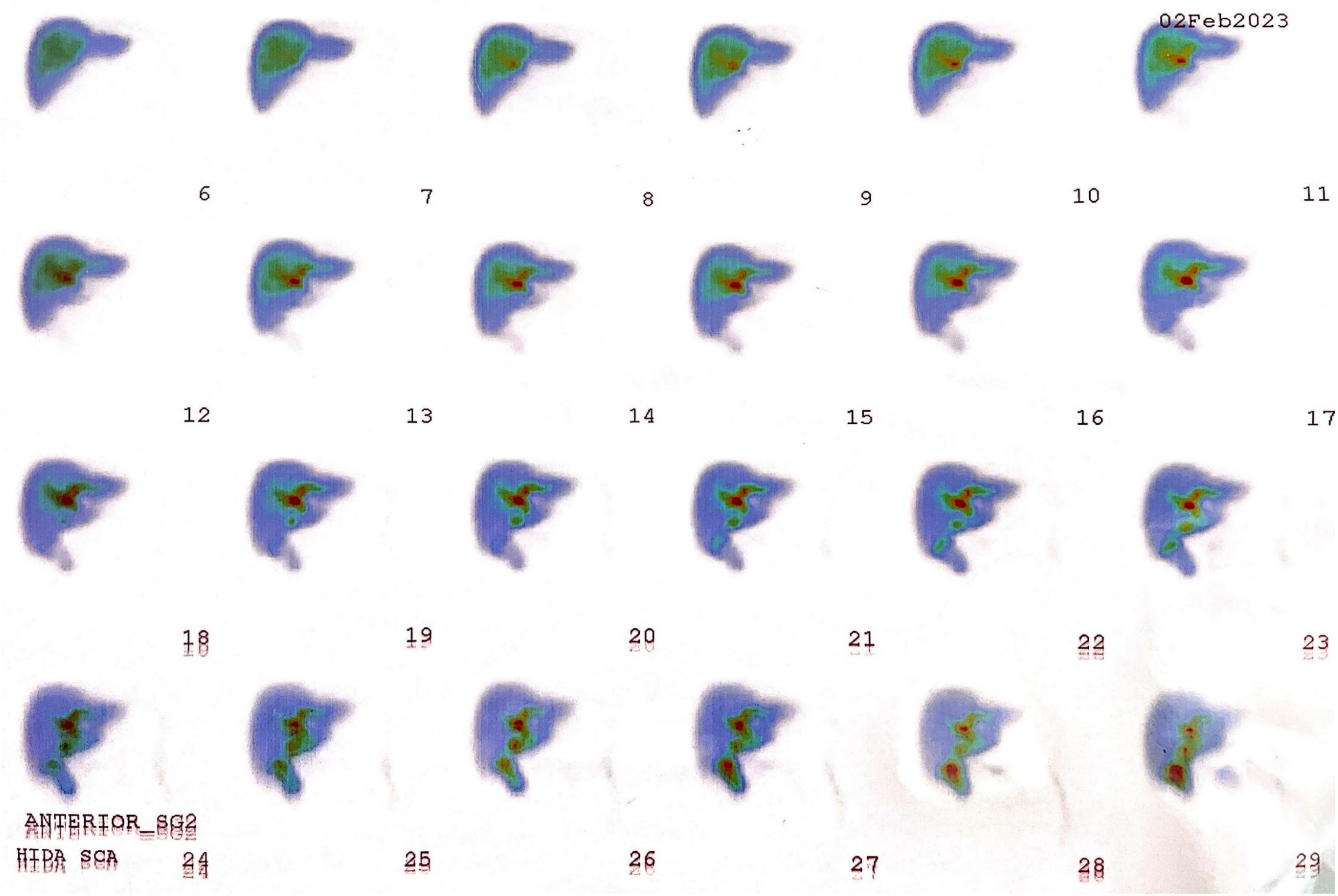
auxilliary liver
native liver
7 Month
8.5 Month
11.5 Month
auxilliary liver
native liver

Case Report
(Firouzgar Hospital)

- 16-year-old female, day 7 post-orthotopic liver transplantation
- Clinical Suspicion for biliary leak.
- **CT scan**: Biloma or Infectious Hematoma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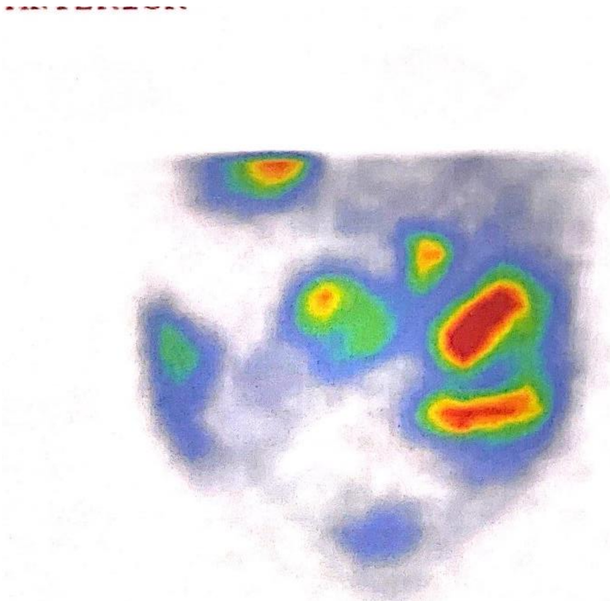
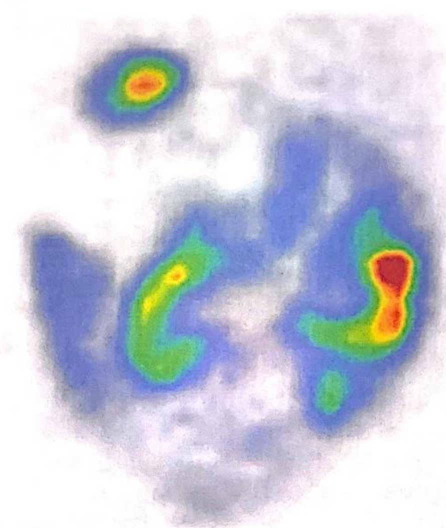
Anterior View, Delayed



2 Hrs



6 Hrs

Newer Trends

Theranostics in Liver Transplantation

- Combines diagnosis + therapy
- Common in **HCC**:
  - Y-90 radioembolization (SIRT)
  - FDG-PET (confirming tumour control)

- **Bridges** patients to transplant
- Used for downstaging tumors to meet transplant criteria

PET in Liver Transplant Oncology

- FDG-PET for guiding transplant eligibility:
  - Excluding extrahepatic **metastases**
  - Assessing **tumour response**
- Better risk stratification in borderline cases

Summary and Key Takeaways

- **Biliary complications**, particularly bile leaks, remain a major cause of morbidity post-transplant.
- **Early detection** of bile leaks is critical to prevent graft loss and improve outcomes.
- Hepatobiliary scintigraphy (**HIDA** scan) is a highly sensitive, dynamic tool for identifying bile leaks.
- **Nuclear medicine** plays a vital role in both preoperative evaluation and postoperative management of liver transplant patients.

Clinical Practice Recommendations

- Use **GSA scans** in pre-op functional reserve estimation
- Deploy **HIDA** or **Mebrofenin HBS** early in post-op period
- Train teams to recognise **blind end** vs true bil leaks

Thank You

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