INTERNATIONAL ACADEMY OF PATHOLOGY
JORDAN 14th-18th OCTOBER 2018

A REVIEW OF 345 CONSECUTIVE NEOPLASTIC LIVER BIOPSIES WITH IMMUNOHISTOCHEMICAL DIAGNOSTIC ALGORITHMS

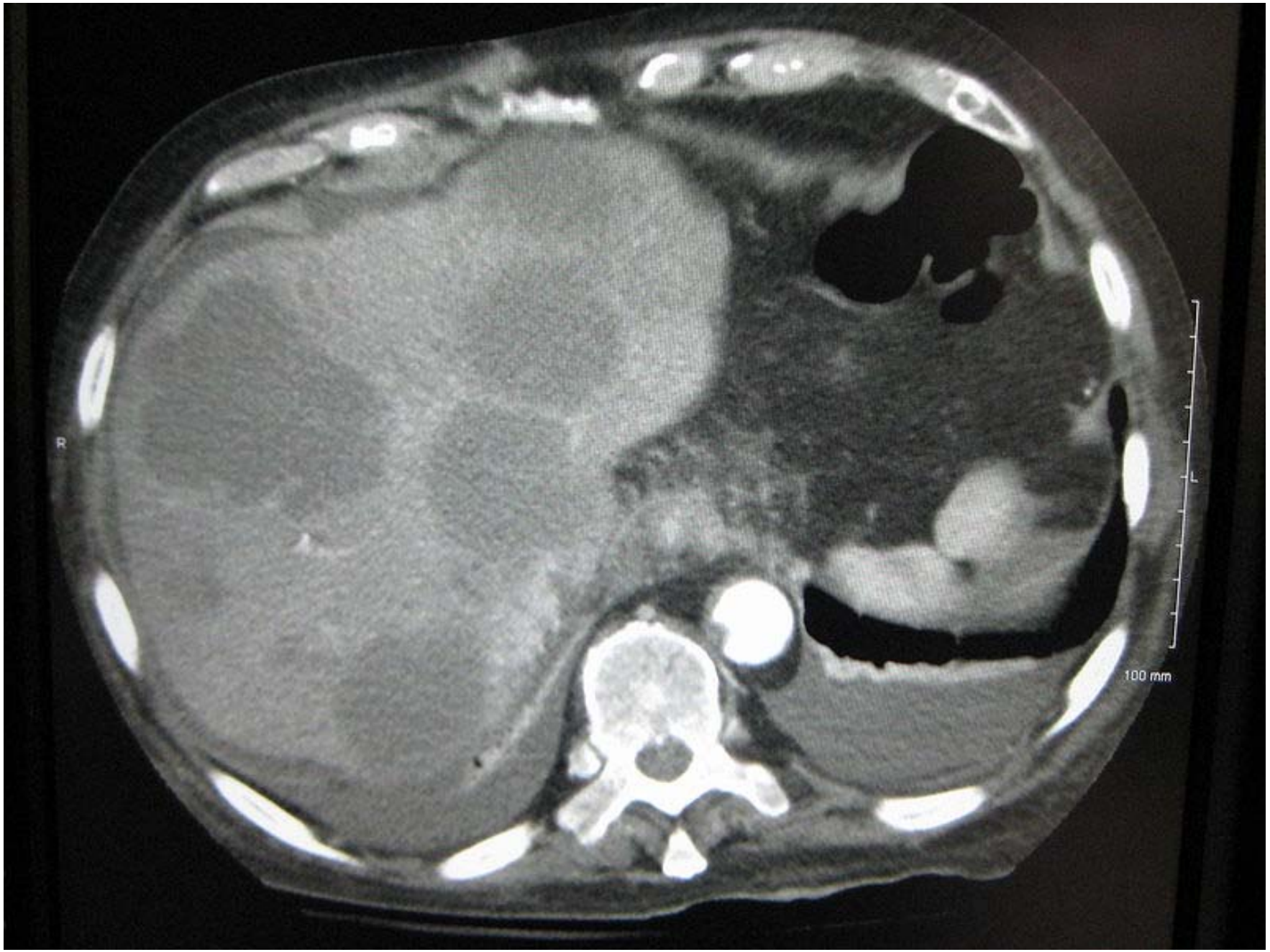
***Rani Kanthan and Selliah Kanthan**

**Dr. Rani Kanthan MBBS, MS, FRCS, FRCPC, FCAP, M.Ed.*

Professor, Dept. of Pathology & Laboratory Medicine

University of Saskatchewan

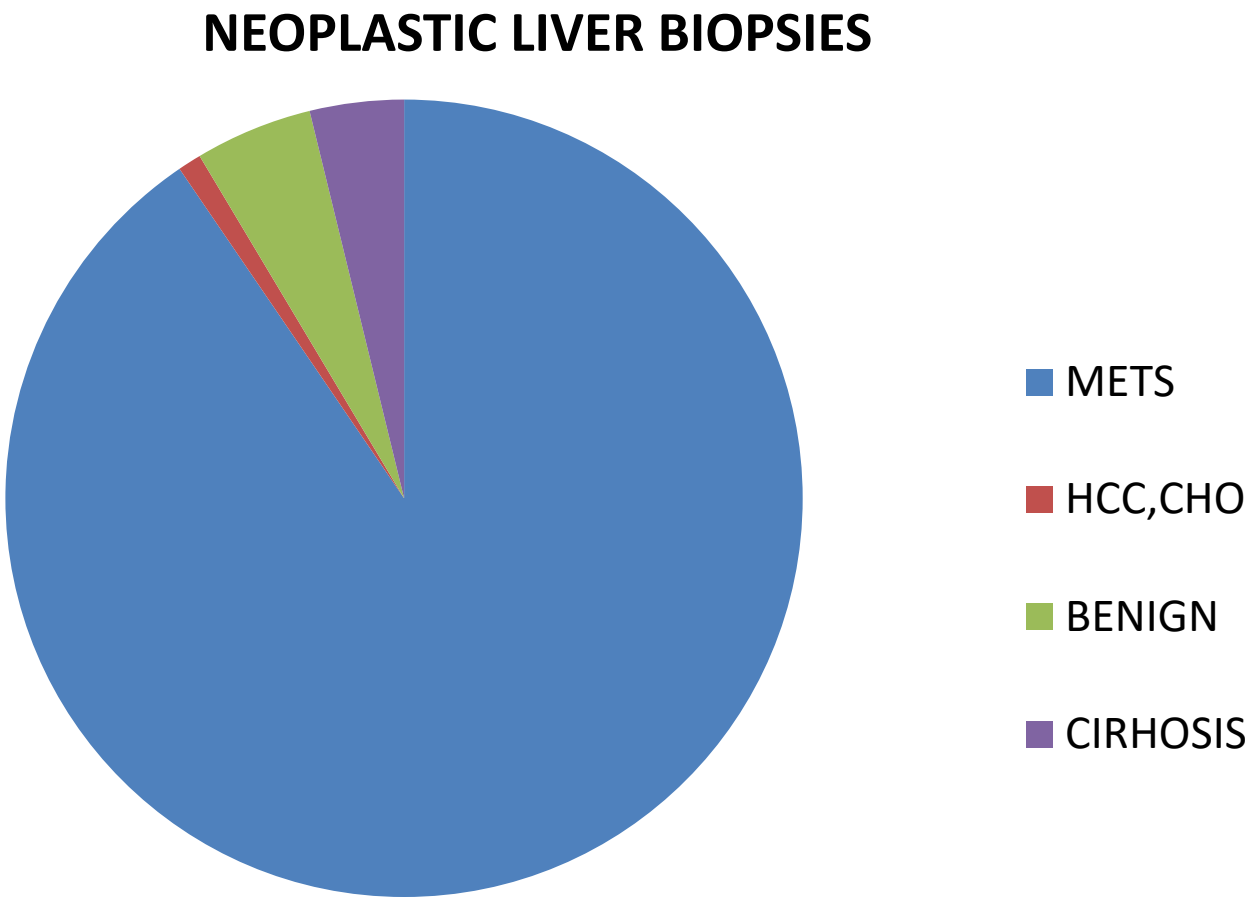
Saskatoon, Saskatchewan


R
L
100 mm

HEPATIC METASTASES

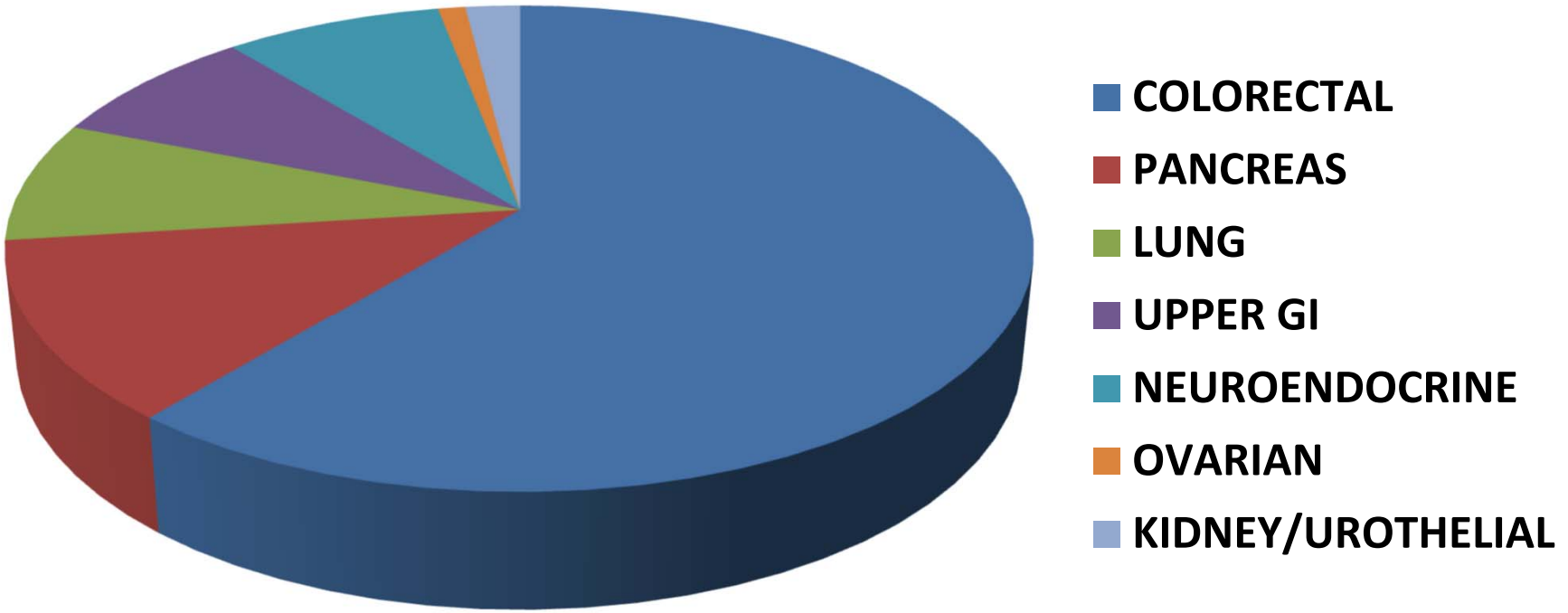
- Commonest organ to inherit metastases due to its rich dual blood supply
- Common sites of origin of these metastases are from colorectal, lung, breast, pancreatic, stomach, melanoma, neuroendocrine
- Herewith we share our approach to
  - Unknown primary
  - Awareness of uncommon hepatic metastases
    -unusual primary sites

345 consecutive LIVER BIOPSIES



NEOPLASTIC LIVER BIOPSIES

METASTATIC LIVER LESIONS



LIVER METASTASES

Commonest

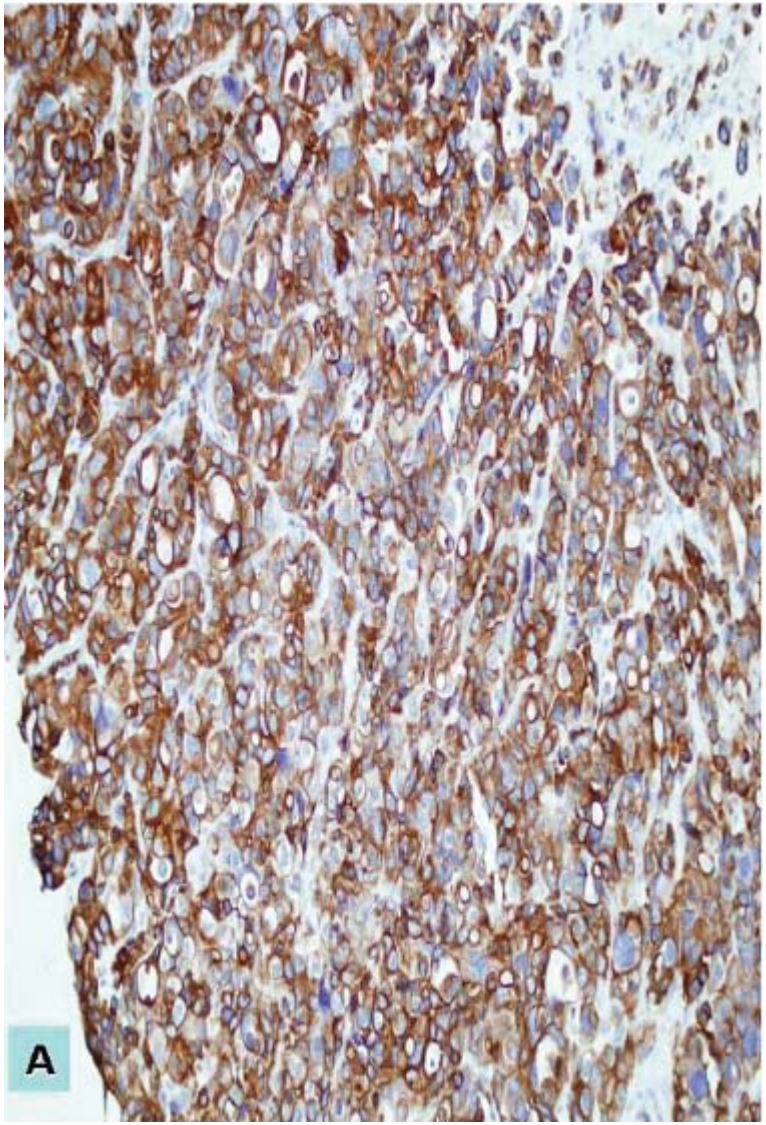
- **Adenocarcinoma [GIT, Breast, Lung, Pancreas]**
- **Neuroendocrine tumors [GIT, Pancreas, Lung]**
- **Melanoma**
- **Lymphomas**
- **Rarely soft tissue sarcomas**

PATHOLOGISTS ROLE

- Identify tumor versus non tumorous lesions
- Differentiate benign versus malignant lesion
- Identify tumor type
  - Primary hepatic malignant tumor
    - Malignant Epithelial Tumor [HCC, Cholangio]
    - Malignant Mesenchymal Tumor [Angiosarc, EHE, etc]
    - Others –melanomas, lymphomas
  - Secondary hepatic malignant tumor –as above Epithelial, mesenchymal}
- Identify primary site of origin

DIAGNOSTIC CHALLENGES AND ROLE OF IMMUNOHISTOCHEMIOSTRY IN METASTATIC LIVER DISEASE

- **NO specific singular panel of IHC markers**
- **Selection of IHC marker is based on**
  - **Sex – Male versus female**
  - **Morphological features seen on histopathology**
  - **Clinical history**
  - **Radiological findings**
  - **Any other relevant investigations such as**
    - **Increasing serum markers CEA**



A: IHC OF HCC – DIFFUSE HEPAR POSITIV

Hep Par 1

Strengths	Limitations
High sensitivity and specificity (>80%)	Negative: 50% of poorly differentiated, scirrhous HCC
Most adenocarcinomas are negative	Focal staining 10-20%
Other polygonal cell tumors often negative	Positive: 20-30% lung, esophageal, gastric adenoCA
Well studied in different tumors	

Glypican-3

Strengths	Limitations
High sensitivity in poorly differentiated, scirrhous HCC (>80%)	Low sensitivity in well (<50%) and moderately differentiated HCC
Negative in adenoma and most high-grade dysplastic nodules	Positive in occasional cirrhotic nodules
	Positive in other tumors: yolk sac, melanoma, some adenocarcinomas

Needle biopsy for HCC

No stains necessary

- Bile production
- Cirrhotic liver: characteristic features
  - Trabecular pattern
  - Fat and/or Mallory hyaline

'Mesothelioma' approach

2 hepatocellular markers	2 'adenocarcinoma' markers
Arginase-1 Glypican-3 Hep Par 1 Polyclonal CEA	MOC31 CK19 CK7

Other markers	Clinical setting
TTF-1, CDX-2, ER/PR etc	If appropriate
2 marker approach Arg-1, MOC31	Limited material

	Arginase-1	MOC31
Group 1	+	-
Group 2	-	+
Group 3	+	+
Group 4	-	-

GROUP 1- HCC

GROUP 2- ADENOCARCINOMA- RENAL , NE TUMORS…

GROUP 3- ADENOCARCINOMA/NET

Arginase – MOC31 –

Pancytokeratin +	Pancytokeratin -
HCC	Melanoma
Adenocarcinoma	Adrenocortical CA
NE tumors, RCC	Angiomyolipoma
Urothelial CA	Sarcomas with
Squamous cell CA	epithelioid pattern

NON HEPATIC /METASTATIC ADENOCARCINOMAS

Table 6. Differentiation of Colorectal Adenocarcinoma From Pulmonary and Endometrioid Adenocarcinomas*

	Colorectal	Pulmonary	Endometrioid
CK7	−	+	+
CK20	+	−	−
CEA (monoclonal)	+	−	−
CDX-2	+	−	−
TTF-1	−	+	−
ER	+/−	−	+
CA 125	−	−	+
Vimentin	+/−	+/−	+

Table 2. Cytokeratin Expression in Various Types of Adenocarcinoma

CK7+/CK20+	CK7+/CK20-	CK7-/CK20+	CK7-/CK20-
Urothelial carc	Breast	Colorectal	Prostate
Pancreas	Lungs		RCC
Biliary tract	Esophagus/stomach		HCC
Cholangiocarc	Pancreas		ACC
Eso/stomach	Biliary tract		
Mucinous carc	Cholangiocarcinoma		
	Ovary, Endometrium		

RCC, Renal cell carcinoma; HCC, Hepatocellular carcinoma; ACC, adrenal cortical carcinoma; *ovarian, colon, mucinous brochoalveolar

	HCC	NET
Arg-1, GPC-3, Hep Par 1	Positive	Hep, GPC-3 rarely positive
MOC31 CK19, CK7	5-20%	Usually positive
Chromogranin Synaptophysin CD56	Negative Rare positive Variable	Positive Positive Positive

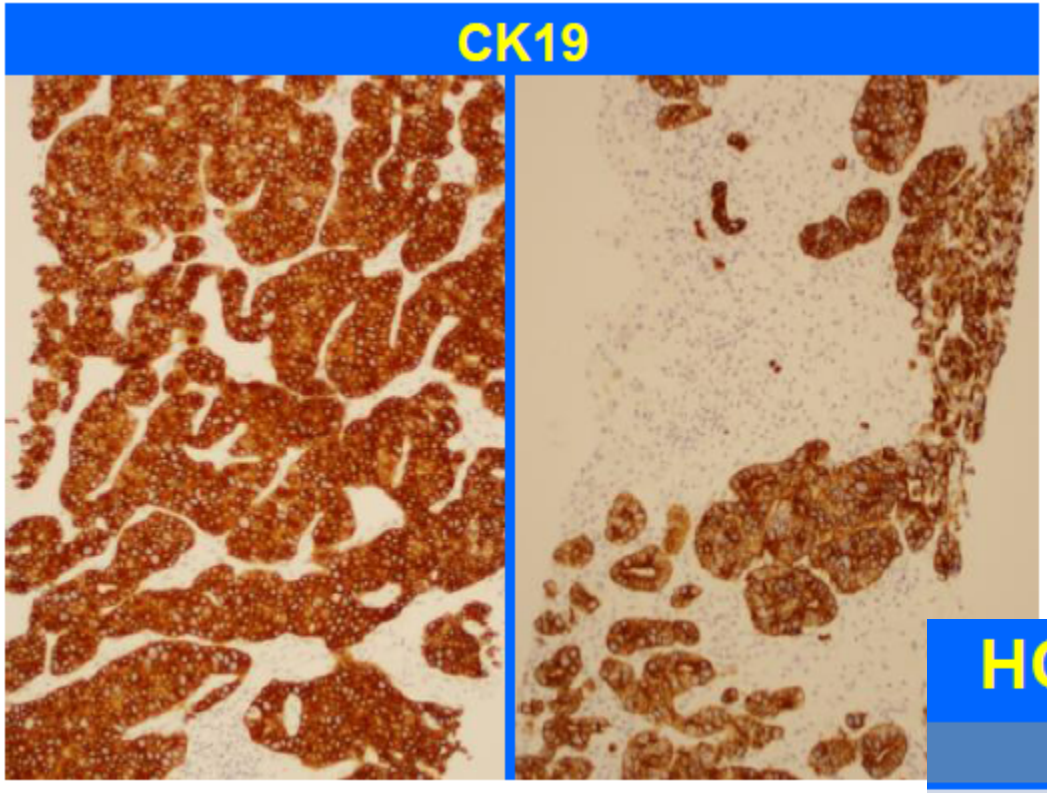
Marker	HCC	Clear cell RCC
Arg-1, GPC-3	Positive	Negative
Hep Par 1	Positive	Negative
PAX-2 or PAX-8	Negative	Positive Other GU/GYN tumors
RCC marker, EMA, vimentin	Negative	Positive
CD10	Canalicular	Membranous

Two-stain approach for clear cell tumors:
Arg-1 and PAX-2/PAX-8

HCC vs. polygonal cell tumors

Polygonal cell tumor	Marker
Adrenocortical CA	Inhibin Melan A
Epithelioid angiomyolipoma	SMA HMB-45, Melan A
Melanoma	SOX10, S-100 HMB-45, Melan A

Arginase, Hep Par 1: negative
GPC-3: melanoma



62year old woman with a 5cmLIVER MASS and no clinical evidence of chronic liver disease

?HCC _pseudoglandular pattern

?Cholangio- Poorly differentiated

Combined HCC +CHolangio

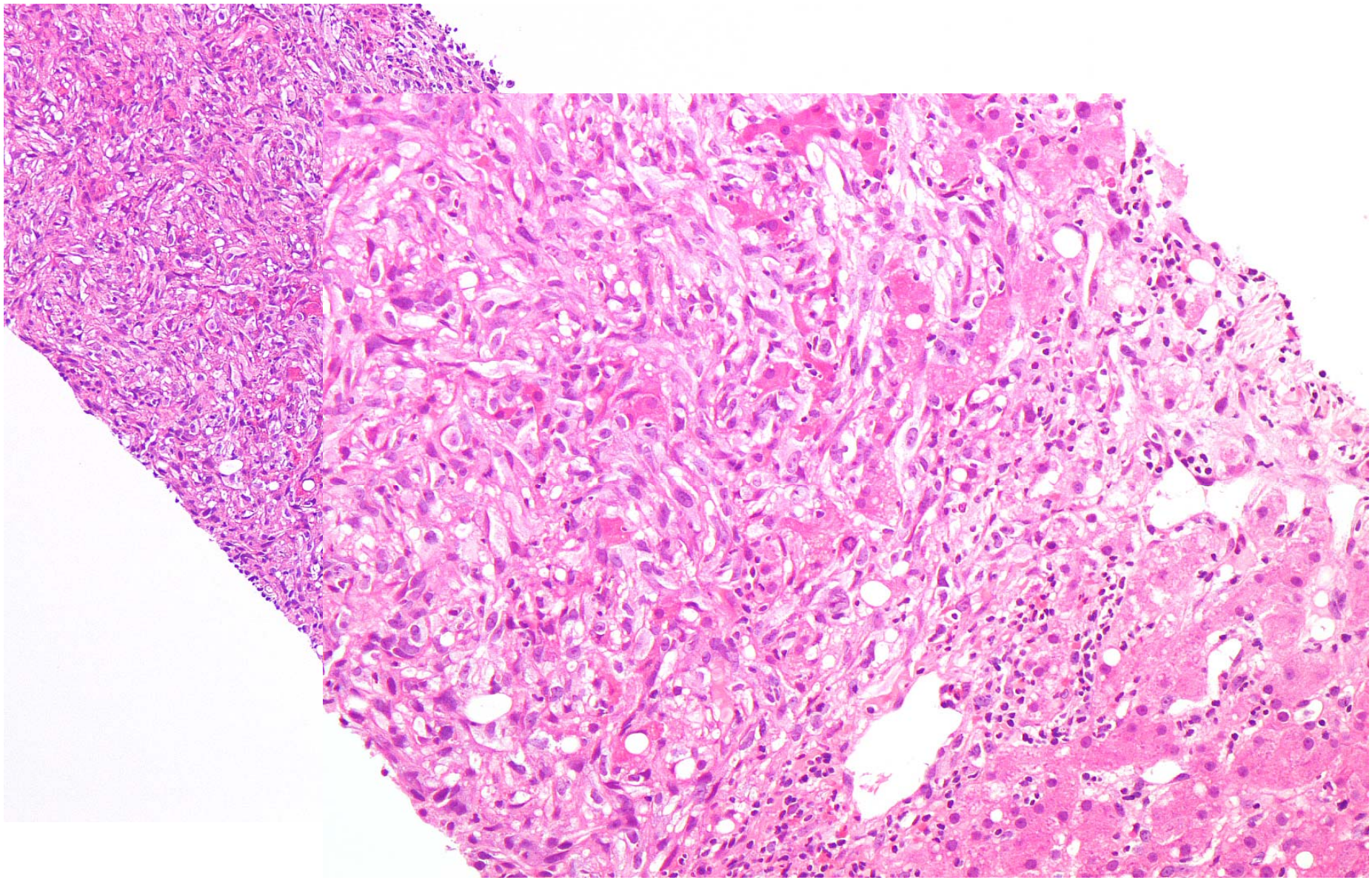
HCC or CC: clinical impact

HCC	CC or Combined HCC-CC
Lymph nodes may not be removed	Lymph node dissection is routine

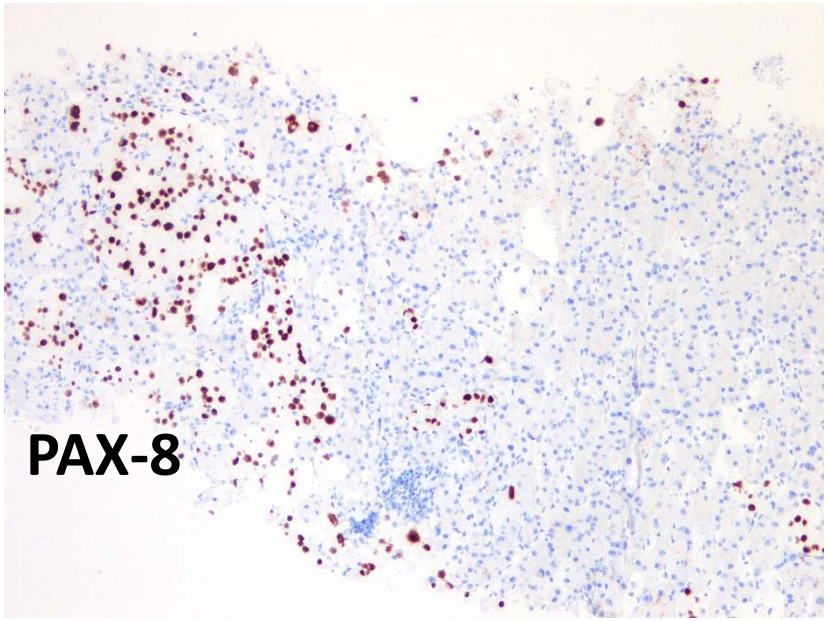
HCC	CC or Combined HCC-CC
Sorafenib, transarterial chemoembolization	Gemcitabine-based or fluoropyramidine-based

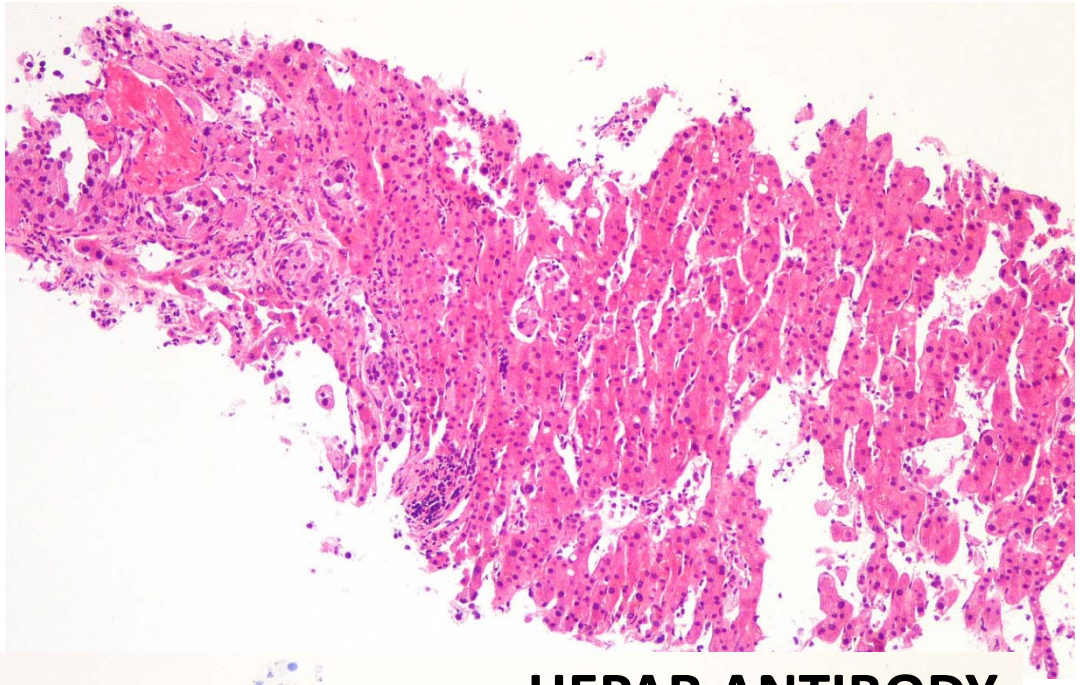
HCC	CC or Combined HCC-CC
Liver transplant: Milan/UCSF criteria	Likely denial

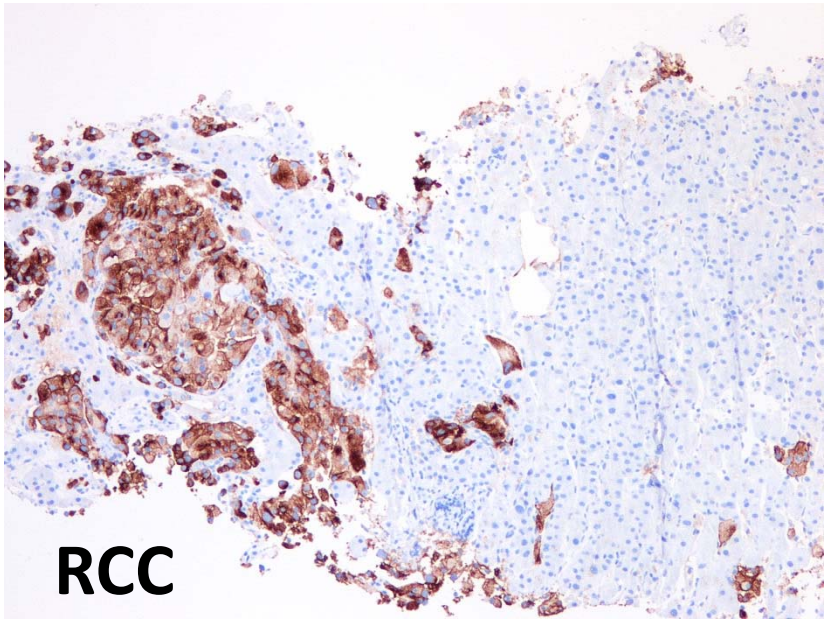
HEPATIC METASTATIC MENINGIOMA

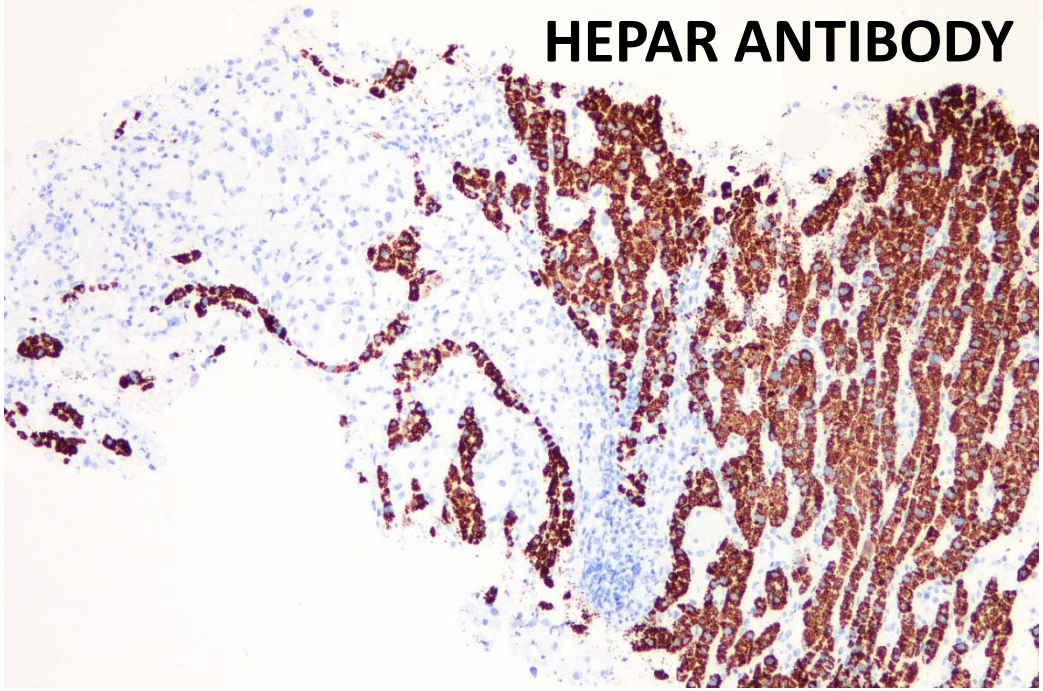


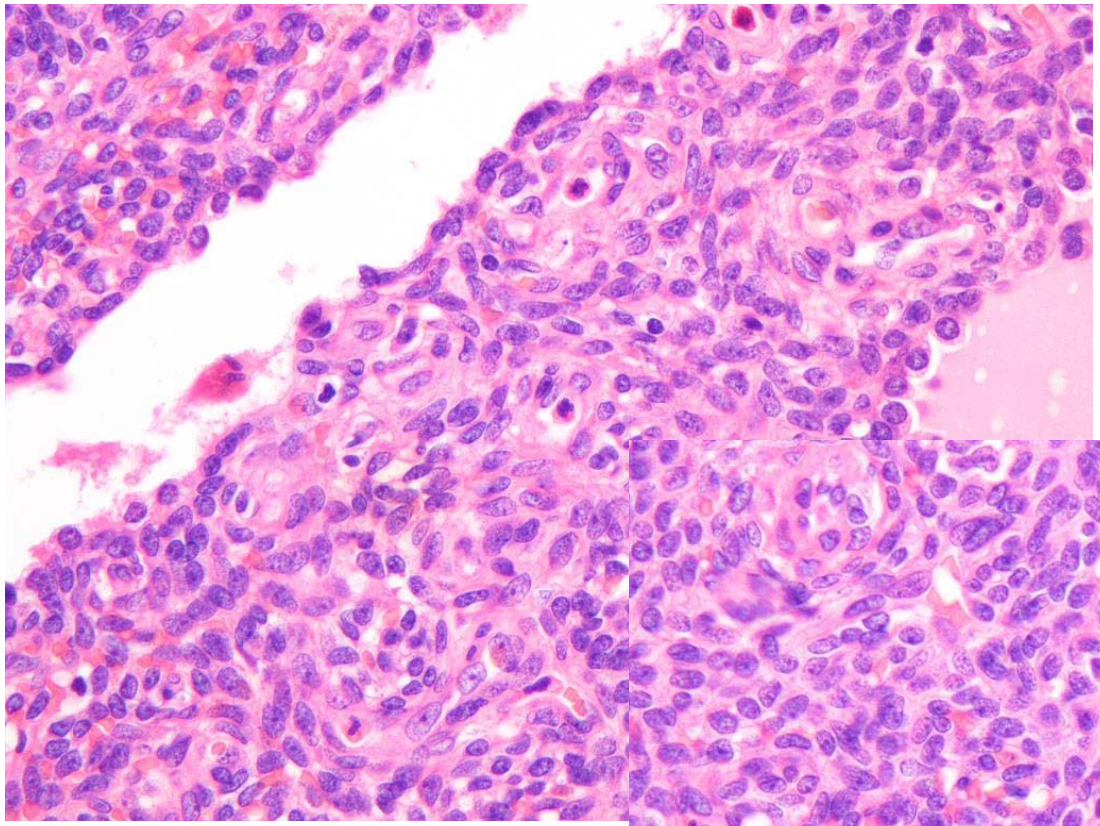
HEPATIC METASTATIC RENAL CELL CARCINOMA



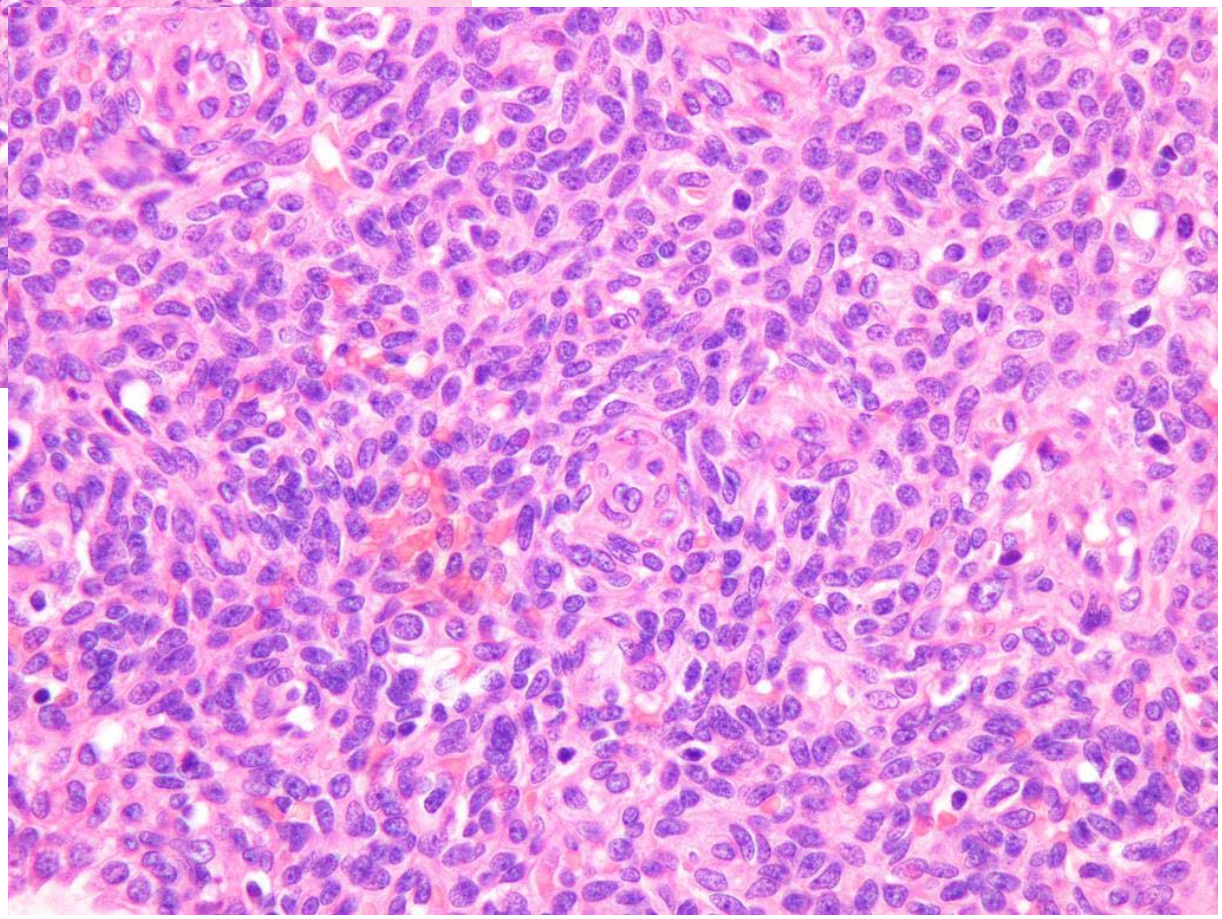






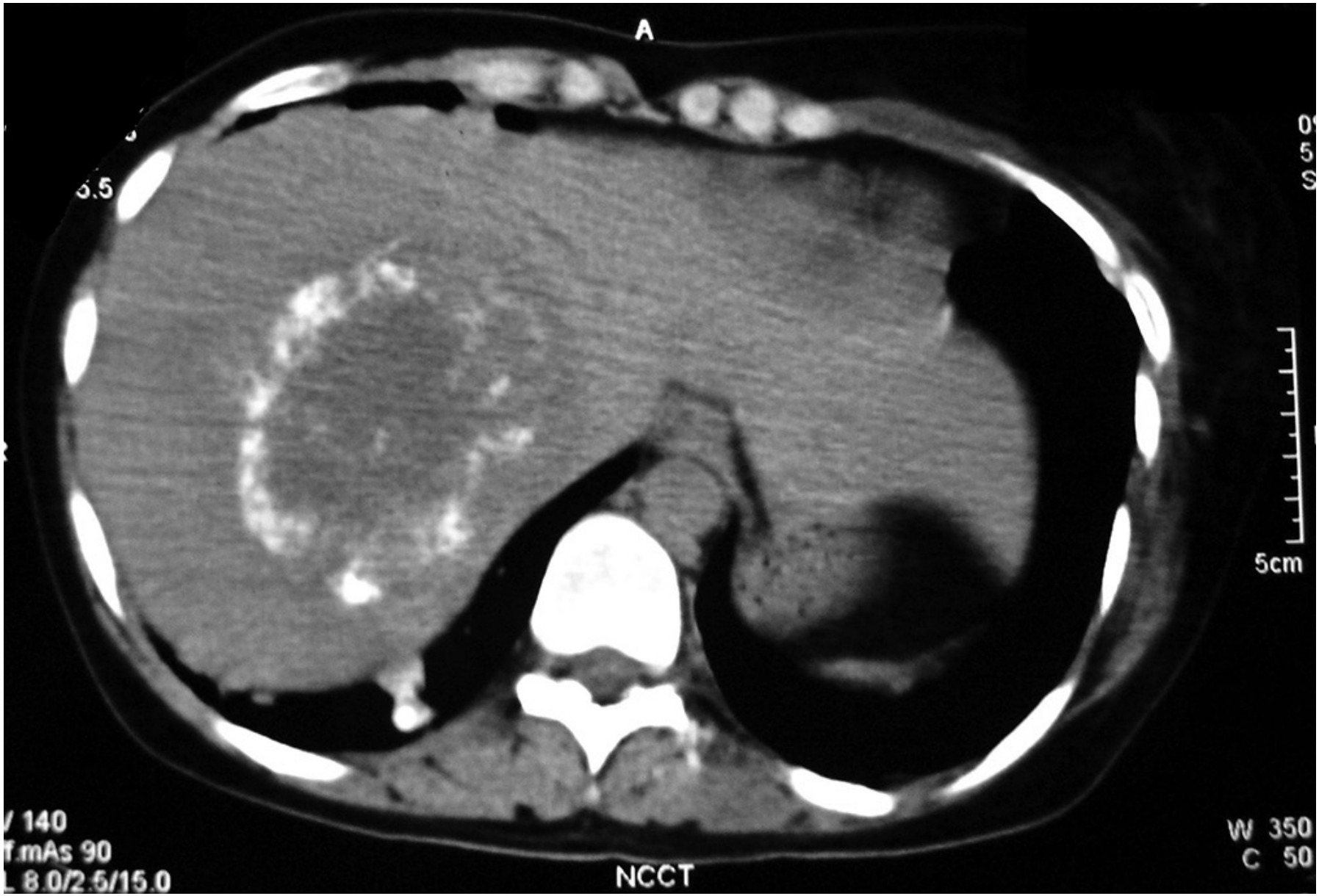


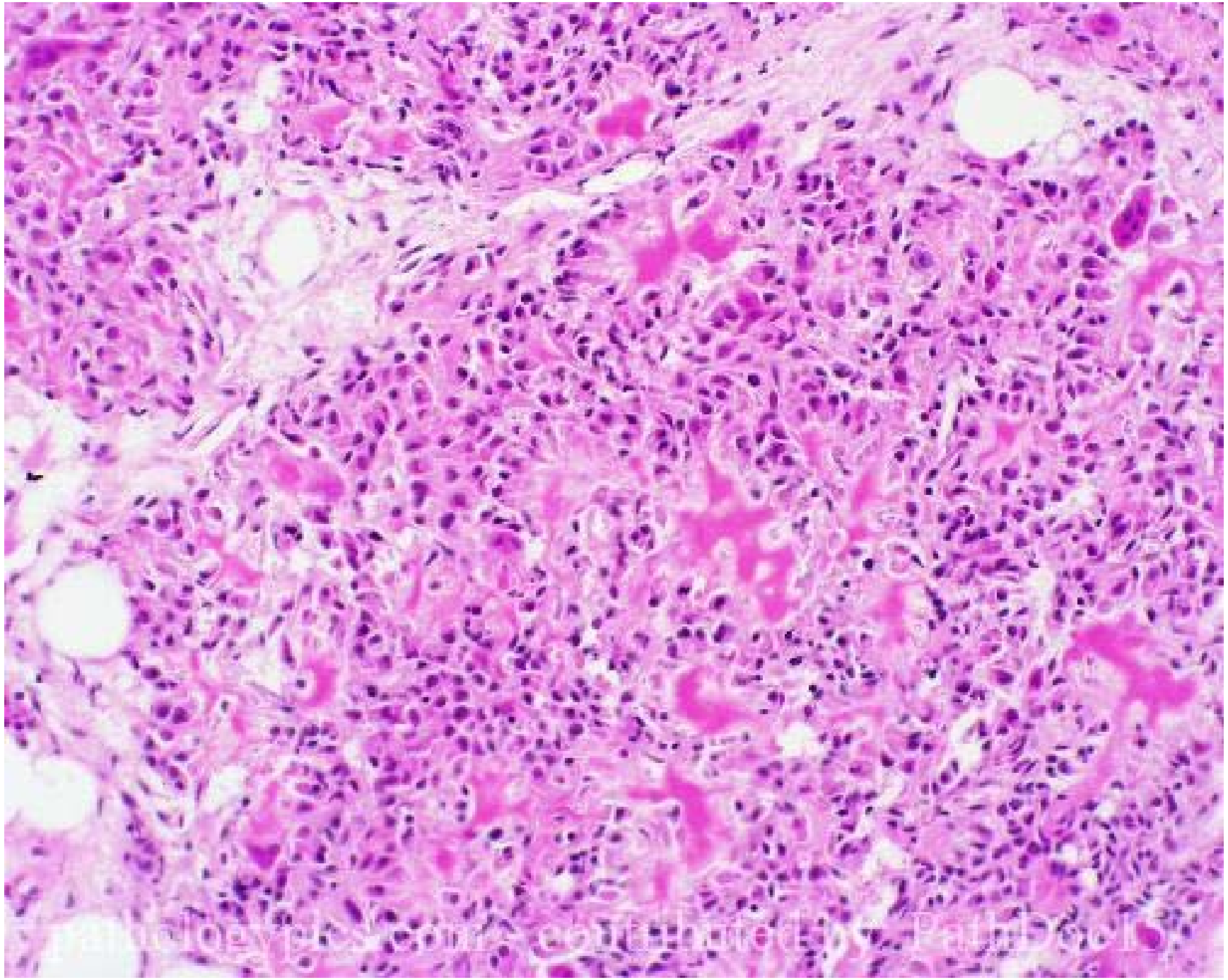
Monotonous ovoid to spindly cells with minimal cytoplasm intimately associated with prominent arterioles, closely resembles proliferative endometrial stroma



METASTATIC ENDOMETRIAL STROMAL SARCOMA

15 year old known malignancy with liver lesion





LIVER METS – UNKNOWN PRIMARY

- SOPHISTICATED IMAGING
- IMMUNOHISTOCHEMICAL TESTING
- MOLECULAR PROFILING

LINEAGE RESTRICTED TRANSCRIPTION FACTORS

RECOGNITION OF TUMOR PHENOTYPES

- SATB2 –colorectal, appendix
- GATA3- urothelial/breast
- NKX3-1-androgen depend-restricted to prostate
- PAX8- Mullerian , Kidney,
- TTF1- Lung /thyroid
- SF1-Adrenal cortical
- CDX2- intestinal phenotype
  - Metastatic mucinous versus primary ovarian
  - Gastric signet ring versus lobular breast cancer
  - *Never use a single marker – always a panel to confirm or negate your working diagnosis*

  - **LIMITATIONS**
    - Tissue antigenicity,
    - Tissue heterogeneity,
    - Inadequate sample

MOLECULAR PROFILING- TISSUE OF ORIGIN

- DNA Microarray
- Rt-PCR Assay
- M-RNA /microRNA
- NGS

Molecular genomic signatures

- Kidney profile
- Lung profile
- Breast profile
- Ovarian profile
- Colorectal profile

TREATMENT IN THE GENOMIC ERA

- Targeted therapies instead of blind blanket of platinum based chemotherapy
- Identify driver mutations of the cancer-personalized therapy

CONCLUSIONS

- **Liver is the common site for metastases.**
- **Accurate identification of the type of metastases**
- **Diagnostic accuracy is important in todays era of precision medicine –tumor specific targeted therapy**
- **Tumor mutational analysis –increasing for treatment**
- **Think of unusual sites if the histology is unusual and does not fit the norm .**
- **Liver metastases can be the initial primary presentation ,…accurate diagnosis needed.**
- **Despite IHC, history, clinical investigations ….we do have cases of a liver metastases-unknown primary [upto 5%]**

shukraan jazilaan

شكرا جزيلا

ANY QUESTIONS?