Metastatic Disease of the Liver: A common sense approach to a common problem

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    – Nearly half with adequacy assessment

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- Image guided (ultrasound, CT)
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  - Confirm, obtain ancillary predictive studies
- Unknown primary site
  - Broader evaluation; don’t forget liver primary
- Therapeutic resections, CRC
  - Therapeutic response evaluation

Hepatic Metastases - Adequacy
- Touch prep of US or CT needles
- Cytotechnologist where available
- Regional hospitals, scheduled when pathologist present for lab management
- Diff-Quik stain

Multiple masses, suspected unusual primary

Hepatic Metastases - General
- Common primary sites
  - Colorectal and upper GI
  - Pancreatobiliary
  - Lung
  - Breast
- Less common primary sites
  - Everything happens...
  - Melanoma, GYN, GU, soft tissue, hematolymphoid, etc

72 year old woman
Clinical Information Critical  
(and, anything can happen)

- 12 yrs ago, parotid tumor
- Resected, locally extensive, Rad Rx
- 5 yrs ago, local recurrence, add’l resection
- 1.5 yrs ago, local recurrence
- 0.5 yrs ago liver masses, one large, several small

Suspected / known primary site

- Confirmation, definitive therapy
- Ancillary predictive studies
  — Anticipated and unanticipated
  — Conserve tissue!!

Suspected / known primary site  
Example #1

- 47M, morbid obesity, T2 diabetes
- ED for 2 weeks left lower back pain
- CT, sigmoid colon thickening and multiple liver masses
- Liver biopsy was elected
- Plan for neoadjuvant chemotherapy
**Suspected / known primary site**

*Example #1*

- Metastatic adenocarcinoma c/w CRC
- Kras, nras, braf assays wildtype

*Suspected / known primary site*  

*Example #2*

- 89F, weight loss, cough, 30 pk-yr smoker
- 5.3 cm necrotic lung mass, extending into mediastinum
- 4.9 cm liver mass suspicious for met
- Image guided liver biopsy
Suspected / known primary site
Example #2
FMP system for ancillary studies

Example #2

- DIAGNOSIS
  - Liver: Non-small cell lung carcinoma (NSCLC), favor adenocarcinoma
- COMMENT
  - Immunostains were performed on this case. The results follow, and support the above interpretation.
- TTF1: Positive
- p40: Negative
- **LUNG ANCILLARY TESTING PROTOCOL**
  - Case number: Sxx
  - Patient name: xxxxx xxxxxx
- HISTOLOGIC TYPE
  - Non-small cell lung carcinoma (NSCLC), favor adenocarcinoma
- STAGE
  - IV
- STATUS
  - Histologically proven stage IV disease
- TISSUE BLOCK AVAILABLE FOR ANCILLARY TESTING
  - A1

Suspected / known primary site
Example #2b

- 71F, extensive perirectal abscess, sepsis
- Hospitalized, sequential imaging
- Large RML lung mass, multiple liver masses
- Image guided liver biopsy
**LUNG ANCILLARY TESTING PROTOCOL**

Case number: Sxxxxx  
Patient name: xxxxxxx

**HISTOLOGIC TYPE**  
Small cell carcinoma  
Stage IV

**TISSUE BLOCK AVAILABLE FOR ANCILLARY TESTING**

**COMMENT**  
This patient's sample does NOT meet Allina Lung Cancer Committee criteria* for reflex EGFR, ALK, ROS1, or PD-L1 (for pembrolizumab (Keytruda) eligibility) testing. The block identified above will be stored in pathology for 10 years for possible future ancillary testing. If you would like ALK, EGFR, or any other ancillary tests in the future, please call 612-863-4670 (option 2).

*Allina Lung Cancer Committee EGFR, ALK, ROS1, and PD-L1 reflex testing criteria:  
Stage IV disease (histologically proven or clinically suspicious)  
Adenocarcinoma or TTF-1 positive adenosquamous cell carcinoma for EGFR, ALK, ROS1, and PD-L1  
Squamous cell carcinoma or NSCLC, favor squamous cell carcinoma for PD-L1.

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**Suspected / known primary site**  
Example #2b

- Small cell carcinoma  
- Stage IV

**COMMENT**

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**Suspected / known primary site**  
Example #3

- 75F, ductal breast CA 2 years earlier
- Stage IIA, ER+, HER2 amplified
- Now develops 5.5 cm liver mass

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Known Primary, final points

- Conserve tissue
  - Consider splitting cores into separate cassettes
  - Minimize IHC, get history, compare
- Comment on background liver tissue, or “no background liver tissue present”

Unknown Primary

- Metastases to cirrhotic liver?
- Metastasis versus cholangiocarcinoma
- Broad workup issues, based on original histologic impression
- Review clinical record carefully

Unknown primary site

Example #1

- 62M, alcoholic cirrhosis, ascites, anasarca, SOB, thrombocytopenia
- Imaging notes multiple liver masses
Example #1

- 62M, alcoholic cirrhosis, ascites, anasarca, SOB, thrombocytopenia
- Imaging notes multiple liver masses
- IHC:
  - Positive: Chromogranin, synaptophysin, cdx2
  - Negative: Hepar

Unknown Primary

- Undifferentiated large cell malignancy
- Oncocytic large cell malignancy
- Small cell carcinoma/undifferentiated large cell neuroendocrine
- Well differentiated neuroendocrine carcinoma
- Adenocarcinoma
- Spindle cell lesion or overt hematopoietic neoplasm: See other conference!

Unknown Primary

- Undifferentiated large cell malignancy:
  - Cytokeratin cocktail (AE1/AE3/Cam 5.2), CD45, S100, HMB45, CD117, synaptophysin. Others based on individual features and/or initial immunohistochemistry. May be useful to optimize tissue utilization by pre-cutting additional unstained sections for immunohistochemistry.

- Oncocytic large cell malignancy:
  - Cytokeratin cocktail (AE1/AE3/Cam 5.2), Hepar, arginase, S100, HMB45, CD117, synaptophysin, inhibin.

- Small cell carcinoma/undifferentiated large cell neuroendocrine:
  - Cytokeratin cocktail (AE1/AE3/Cam 5.2), TTF1, CK7, CK20, synaptophysin, chromogranin. Consider anorectal squamous carcinoma (aka cloacogenic carcinoma).

- Well differentiated neuroendocrine carcinoma
- Adenocarcinoma
- Spindle cell lesion or overt hematopoietic neoplasm: See other conference!
Unknown Primary

- Undifferentiated large cell malignancy
- Oncocytic large cell malignancy
- Small cell carcinoma/undifferentiated large cell neuroendocrine
- Well differentiated neuroendocrine carcinoma
- Adenocarcinoma:
  - CK7, CK20, cdx2 &/or CDH17, TTF1. If woman, GATA3, estrogen receptor. Some use CK17 & CK19 as an adjunct for cholangiocarcinoma (negative & positive, respectively, in many cases) versus metastasis. When the primary is likely upper GI or pancreatobiliary, there is typically a comment regarding likelihood of specific primary site. Of note, cholangiocarcinoma often presents with multiple masses.
- Spindle cell lesion or overt hematopoietic neoplasm: See other conference!

Unknown primary site

Example #2

- 72F, f/u high grade invasive urothelial CA
  - 5 years ago, treated by TURB & chemo
  - Imaging shows 4.5 cm liver lesion, gastrohepatic LNs
- EUS FNAB, liver mass and LN
- Cystoscopy and CT => normal bladder
**Unknown primary site**

Example #2

- 72F, f/u high grade invasive urothelial CA
  - 5 years ago, treated by TURB & chemo
  - Imaging shows 4.5 cm liver lesion, gastrohepatic LNs
- EUS FNAB, liver mass and LN
- Cystoscopy and CT => normal bladder
- Normal upper, lower endoscopy
- CPC most c/w cholangiocarcinoma

**Therapeutic Resection, CRC**

- Confirm CRC
- Evaluate margins
- Evaluate chemorads effect
- Chemotherapy ass’d liver injury

**Therapeutic Resection, CRC**

TRG

- Tumor Regression Grade:
  - TRG1: Absence of tumor cells, replaced by fibrosis
  - TRG2: Rare scattered tumor cells, abundant fibrosis
  - TRG3: Significant residual tumor, predominant fibrosis
  - TRG4: Tumor cells predominating over fibrosis
  - TRG5: Almost exclusively tumor cells without fibrosis

*Annals of Oncology 2007;18:299-304*
Tumor Thickness at Tumor-Normal Interface:
"The focus in which the maximum contiguous tumor cell thickness was observed at the TNI (perpendicular to TNI in mm) was measured by a ruler. This focus was composed of uninterrupted layers of tumor cells without admixed fibrotic stroma, acellular mucin, or nonneoplastic liver parenchyma."


Radiologic response - RECIST

Pathologic response - TRG

Pathologic response - untreated
Therapeutic Effect, Liver CALI

Sinusoidal dilatation:
SOS 0 - absent
SOS 1 - mild (centrilobular involvement limited to one-third of the lobular surface)
SOS 2 - moderate (centrilobular involvement limited to two-thirds of the lobular surface)
SOS 3 - severe (complete centrilobular involvement)

Nodular Regenerative Hyperplasia:
NRH 0 - absent
NRH 1 - nodules present but indistinct
NRH 2 - nodules present but only occasionally distinct
NRH 3 - nodules distinct in most examined areas

Fatty Liver Disease:
Steatosis %
Grade steatohepatitis (Brunt 0-3)
Stage steatohepatitis (Brunt 0-4)

Therapeutic Resection, CRC

• Confirm CRC
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• Evaluate chemorads effect
• Chemotherapy ass’d liver injury

Cytokeratin

CD45 (CD20)
CD338

Lambda ISH

Kappa ISH