

## Hepatic Metastases

Metastatic neoplasm in the liver is a common sample in the pathology laboratory. Often, the primary site is known or highly suspected. Sometimes, a liver mass(es) is identified due to imaging for pain or poorly localized symptoms, or is identified incidentally for imaging of an unrelated medical process. Most diagnostic samples are obtained by image guided diagnostic needle biopsy, but therapeutic resections are also performed in the setting of hepatic metastases. Each of the above presentations and samplings requires a different diagnostic approach.

### BIOPSY OF METASTASIS, KNOWN PRIMARY

The primary purpose of liver mass biopsy in the setting of known or strongly suspected primary site is commonly confirmation of lesion identity before starting definitive therapy. However, a common secondary aim of the biopsy is to obtain predictive markers for therapy. In either event, CONSERVATION OF TISSUE for ancillary predictive studies, anticipated and UNANTICIPATED, can allow oncologists to investigate potential treatment pathways and save patients problematic repeat procedures.

Example: 62 year old woman presents with hemoptysis; negative smoking history. Imaging shows large lung mass, hilar adenopathy and multiple liver masses. A liver mass is identified. Biopsy demonstrates a moderately differentiated adenocarcinoma featuring irregular gland formation and scattered cytoplasmic mucin droplets.

In this example, the tissue obtained clearly needs to both confirm the diagnosis of pulmonary adenocarcinoma and to fulfill the significant ancillary testing needs of such a case. It is easy to envision the importance of having the clinical history to inform the immunohistochemical workup; focusing on positive TTF1 and key negative markers (ER, GATA3, cdx2) with preservation of tissue for EGFR, ALK, PDL1, ROS testing.

Other examples could include patients with history of breast cancer looking for a change in hormone receptor status, GIST with CD117 downregulation, or known primary with some disease free interval. This latter group is very broad. Hopefully, we would all obtain the primary pathology specimen for direct comparison of histomorphology in these situation.

In our system, the biopsy sample is divided into two blocks in an attempt to optimize tissue availability. A Filemaker Pro program has been set up by one of our members to drive the appropriate testing, including auto-emails to the molecular and cytogenetics labs involved downstream assays. While no doubt common practice, our final report in cases of metastatic neoplasm always contains a

statement on the background nonneoplastic liver tissue, even if that statement is that there is no liver tissue present. Before instituting this routine, we too often found ourselves in a tumor board presentation unable to comment on the background liver tissue, or its presence.

## BIOPSY OF LIVER LESION, UNKNOWN PRIMARY

The differential diagnosis in this setting, whether there is one mass or multiple masses, includes cholangiocarcinoma and hepatocellular carcinoma. As all experienced pathologists know, the tumor histomorphology will drive the specific immunohistochemical workup – no one size fits all. A useful construct is to place the neoplasm into one of several overarching categories. To each their own, but the following roughly works for me, with accompanying **starting** immunohistochemical panel (these are starting panels):

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 unstaineds 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 cloacagenic carcinoma).

Well differentiated neuroendocrine carcinoma: Cytokeratin cocktail, synaptophysin, chromogranin, hepar, cdx2, TTF1.

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!

## METASTASIS TO CIRRHOTIC LIVER

The obvious: most masses in cirrheses are hepatocellular carcinoma. In fact, hepatocellular carcinoma in cirrhosis does not require biopsy for diagnosis unless

imaging findings are very unusual. Also, hepatocellular carcinoma can be multifocal. Further, the rule of thumb is no metastasis to cirrhotic liver.

Nonetheless, metastases do rarely occur. Small cell carcinoma is most common in my personal experience, with well differentiated neuroendocrine tumors and GI adenocarcinomas rarely occurring. The circulation of cirrhosis may make it less likely, the patient's decreased life expectancy may decrease the probability of developing metastatic disease, or a combination of these two factors. In any case, metastasis will rarely occur to a cirrhotic liver.

## PATHOLOGIC EVALUATION OF RESECTED COLORECTAL METASTASIS

The obvious goals for a surgical pathologist evaluating a resected CRC metastatic deposit is to confirm the diagnosis and evaluate the margin of resection. But let's consider the oncologist's dilemma as to whether to continue the same treatment or change regimens going forward. Information regarding treatment effect on the resected tumor can provide such information. Also affecting treatment decisions is potential adverse treatment effects. This section deals with chemoradiation therapeutic effects on the neoplasm and the background benign liver (chemotherapy-associated liver injury, CALI).

In the evaluation of treatment effect on metastatic deposits, one multifactorial evaluation demonstrated tumor cellularity and fibrosis to be significant indicators of treatment response. Referred to as Tumor Regression Grade (TRG), this has been validated and used in additional investigations. (1-3)

### Tumor Regression Grade:

TRG1- Absence of tumor cells, replaced by abundant fibrosis

TRG2- Rare scattered residual tumor cells and abundant fibrosis

TRG3- Large amount of residual tumor with predominant fibrosis

TRG4- Tumor cells predominating over fibrosis

TRG5- Almost exclusively tumor cells without fibrosis

A separate indicator of treatment effect has also been proposed and evaluated, but is less commonly used. (4-5) Tumor Thickness at Tumor-Normal Interface (TNI) has been defined as, "The focus in which the maximum contiguous tumor cell thickness was observed at the TNI {perpendicular to tumor-normal interface 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."

We added both of these parameters to our reports on resected CRC metastases. We highlighted several internal issues within our group upon instituting these parameters as part of our uniform reporting:

1. Minimum sampling suggested is > 1 section per cm. Sections should include both center and edge of the metastasis, with some emphasis on tumor-normal interface. Gross heterogeneity should be sampled. Applies to each mass resected.
2. We should attempt to find pretreatment radiographic measurements and compare them with our careful gross tumor size measurements. This allows the clinician a single place in the medical record to look at both size change as well as change in tumor composition.
3. Fibrosis, not necrosis, has been shown to be a key treatment-response feature.

Finally, sinusoidal dilatation, nodular regenerative hyperplasia and fatty liver disease have been associated with chemotherapy-related liver injury. (6-7) We, therefore added these parameters to each of our CRC metastatectomy reports based on the following criteria.

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)

Building our CRC metastatectomy reports around the elements of TRG, TNI and CALI put forth in the literature has allowed our oncologists to optimize the information they have going forward for selection of chemotherapeutic agents.

## REFERENCES

### Tumor Regression Grade (TRG)

1. Rubbia-Brandt L, Giostra E, Brezault C, et al. Importance of histological tumor response assessment in predicting the outcome in patients with colorectal liver metastases treated with neo-adjuvant chemotherapy followed by liver surgery. *Annals of Oncology* 2007;18:299-304.
2. Loupakis F, Schirripa M, Caparello C, et al. Histopathologic evaluation of liver metastases from colorectal cancer in patients treated with FOLFOXIRI plus bevacizumab. *British J of Cancer* 2013;108:2549-56.
3. Reddy SK, Parker RJ, Leach JW, et al. Tumor Histopathology Predicts Outcomes After Resection of Colorectal Cancer Liver Metastases Treated With and Without Pre-Operative Chemotherapy. *Journal of Surgical Oncology* 2016;113:456-462.

### Tumor Normal Interface (TNI)

4. Maru DM, Kopetz S, Boonsirikamchai P, et al. Tumor thickness at the tumor-normal interface: a novel pathologic indicator of chemotherapy response in hepatic colorectal metastases. *Am J Surg Pathol* 2010;34:1287-94
5. Blazer DG 3rd<sup>1</sup>, Kishi Y, Maru DM, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. *J Clin Oncol* 2008;25:5344-51.

### Chemotherapy Associated Liver Injury (CALI)

6. Viganò L, Capussotti L, De Rosa G, et al. Liver resection for colorectal metastases after chemotherapy: impact of chemotherapy-related liver injuries, pathological tumor response, and micrometastases on long-term survival. *Ann Surg* 2013;258:731-42
7. Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. *Annals of Oncology* 2004;15:460-6.