**UPDATES IN GASTROINTESTINAL PATHOLOGY**

**UPDATED HER2 TESTING GUIDELINES IN GASTROESOPHAGEAL ADENOCARCINOMA**

The incidence of gastroesophageal adenocarcinoma (GEA) has risen significantly in the past few decades in Western countries, particularly in men. Overall survival of patients with advanced disease is still poor, although treatment with trastuzumab, the only approved directed biomarker therapy available for such patients, has resulted in a modest, but statistically significant prolongation of overall survival in patients with HER2-positive tumors. HER2 is overexpressed in approximately 10-20% of GEAs, with expression more common in well to moderately differentiated intestinal-type tumors. Testing for HER2 expression may be performed by immunohistochemistry (IHC) or FISH.

Given the distinct differences in HER2 scoring and outcomes in GEA compared to breast carcinoma, an expert international panel recently convened to establish more formalized HER2 testing guidelines, which were published in November 2016. The impetus was to resolve such considerations as: 1) testing and scoring in biopsy versus resection specimens, especially given heterogeneity of HER2 expression in GEA tumor samples; 2) testing of primary tumor versus metastasis; 3) acceptability of FNA cell blocks; 4) order of testing (IHC or FISH); 5) best area within tumor to test; and 6) staining patterns (GEAs often show basolateral/lateral cell membrane staining as opposed to complete membranous staining that can be seen in breast carcinoma).

The key updated guidelines, which are based on systematic literature review of evidence-based findings by the College of American Pathologists (CAP), the American Society of Clinical Oncology (ASCO) and the American Society for Clinical Pathology (ASCP), are as follows:

**Recommendations for treating clinicians:**

- Testing in biopsy or resection specimens should be performed preferably prior to initiation of trastuzumab therapy if tissue is adequate.
  - Either the primary tumor OR a metastasis is acceptable for testing.
  - FNA specimens (cell blocks) are an acceptable alternative when no other specimen is available.

Current Concepts in Pathology is a newsletter provided by CoCoPath to keep our clinical colleagues updated on current topics in the field of pathology, and how they correlate with clinical practice.

In this edition, Dr. Nader Shihabi and Dr. Christine Cesca discuss HER2 testing in gastroesophageal adenocarcinoma, an important variant of GIST, a potential new instigator in Crohn’s disease, and the 8th edition of the AJCC Cancer Staging Manual.

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**Continued on page 2**
Biopsy or resection specimens used for HER2 testing should be rapidly placed in fixative, ideally within 1 hour (cold ischemic time) and fixed in 10% neutral buffered formalin for 6 to 72 hours (supporting data mainly from breast cancer literature).

In summary, HER2 testing in GEA differs from that in breast carcinoma in terms of actual scoring and staining pattern, distinct biopsy and resection specimen criteria, and requisite testing of lowest grade tumor morphology in GEA. Further, studies have shown good concordance of HER2 results in primary and metastatic GEA tumor samples - higher than for breast carcinoma overall.

HER2 testing should only be ordered when requested by the treating clinician for patients with advanced GEA who are potential candidates for treatment with trastuzumab.

**SDH-Deficient GISTs: A Distinct and Important Subtype**

Succinate-dehydrogenase (SDH) deficient GIST is an increasingly recognized variant showing an overall high rate of metastasis, albeit indolent, which cannot be predicted in terms of behavior and progression by conventional risk stratification. While most gastrointestinal stromal tumors (GISTs) harbor KIT or PDGFRA activating mutations, SDH-deficient GISTs (also called “wild-type” GISTs) show loss of function of succinate dehydrogenase (SDH, a mitochondrial enzyme complex).

SDH-deficient GISTs account for approximately 8% of GISTS, and a significant subset occur in the pediatric age group. Many patients have germline SDH mutations; somatic mutations may also occur due to hypermethylation of the SDHC promoter. These tumors occur exclusively in the stomach, and are often multifocal within the gastric wall at presentation, unlike conventional GISTs. Lymph node metastases are often present, however, long-term survival with SDH-deficient GISTs is not uncommon even with distant metastases, despite
the ineffectiveness of tyrosine kinase inhibitor therapy in these tumors.

SDH-deficient GISTs are characterized by distinctive histologic architecture, cytology and immunohistochemistry. These tumors display a characteristic multinodular/plexiform architecture, and have either an epithelioid or mixed epithelioid-spindle cell morphology. Importantly, these GISTs show diagnostic loss of SDHB protein expression by immunohistochemistry. Performing this stain is key in identifying this distinctive variant of GIST due to its managerial and genetic implications.

In the hereditary setting, germline SDH-mutated GIST may occur in association with paragangliomas (Carney triad or Carney-Stratkis syndrome) and occasionally, renal cell carcinoma. SDH-deficient renal cell carcinoma is also becoming an increasingly recognized entity, and in some patients has a protracted clinical course. These renal tumors, which are KIT negative, frequently demonstrate an oncocytic morphology and mimic other oncocytic renal neoplasms. Diagnosis is based on absence of immunohistochemical staining for SDHB. Screening patients with SDH-deficient GISTs for paragangliomas and renal cell carcinomas may therefore be reasonable in follow-up management, in addition to genetic testing and counseling.

**Crohn’s Disease: Role of Candida Tropicalis in Pathogenesis?**

Scientists have long postulated that the gut microbiome may play a major role in the development of Crohn’s disease. A recent study published in September 2016 (journal mBio) strongly suggests that a fungus may be a key contributing factor in this condition. An international team of researchers found that patients with Crohn’s disease had significantly higher levels of two types of bacteria – *E. Coli* and *Serratia marcescens* – as well as the fungus *Candida tropicalis*, than those without the disease. They suggest that these microorganisms may interact and “work together” to help precipitate Crohn’s disease. There are likely other factors in addition to microorganisms that are involved in the pathogenesis of Crohn’s disease, and further research is needed.

Nevertheless, this finding could potentially lead to new treatments for people with Crohn’s disease.

**New Edition of AJCC Staging Manual**

The 8th edition of the AJCC Cancer Staging Manual, originally announced to be distributed and effective January 1, 2017, has been deferred to an effective date of January 1, 2018. The AJCC’s decision to delay the date is largely to allow software vendors and laboratories time to adapt their cancer reporting systems, including IT worksheets, to the modifications.

The new edition, which has a pathologist as editor-in-chief for the first time, incorporates significant changes including multiple new staging categorizations (e.g. low grade appendiceal mucinous neoplasms), integration of molecular information, and an overall move to a more personalized approach to cancer classification than the traditional TNM system.

Key practical points in the implementation of the 8th edition of the AJCC Staging Manual include:

- The 8th edition has been published, but clinicians and pathologists will continue to use the 7th edition for staging and reporting of all new cancer patients through 2017.
- Clinicians can use the scientific content of the 8th edition immediately for patient care. Pathologists can include the new scientific content in their reports depending on their assessment of the specimen.
- New CAP cancer protocols will be released in the second quarter of 2017, with a noted implementation date of January 1, 2018 for required reporting and survey purposes.
In this edition, the concept of HGSC is examined with a focus on early diagnosis. Most of these carcinomas, approximately 90% in some series, arise from surface epithelial origin, and of these carcinomas, approximately 30% are of high grade serous carcinoma (HGSC).

While not quite as byzantine as the politics of Westerosi succession, the lymphoma (DLBCL) often raises similar concerns about the patient’s outcomes following standard therapy. More aggressive large B-cell neoplasms, colloquially designated as “triple-hit” (THL) lymphomas.