ALBERTA PRECISION LABORATORIES

Leaders in Laboratory Medicine

Laboratory Bulletin

Date: **December 16, 2019**

To: **All APL Pathologists, Endocrine Surgeons, Nuclear Medicine/Radiologists, Endocrine/Neuroendocrine Oncologists (Cross Cancer Institute, Tom Baker Cancer Centre, Regional Cancer centres including Central Alberta Cancer Centre (Red Deer), Grande Prairie Cancer centre, Jack Ady Cancer Centre, Margary E.Yuill Cancer Centre, Community Cancer Centres including Barrhead, Bonnyville, Bow Valley, Camrose, Drayton Valley, Drumheller, Fort McMurray, High River, Hinton, Lloydminster, Peace River.**

From: **Provincial Endocrine Special Interest Group (SIG), Laboratory Services**

Re: **Reflex MIB-1/Ki67 ordering on Neuroendocrine Tumours (NET)**

PLEASE POST OR DISTRIBUTE AS WIDELY AS APPROPRIATE

Key Message:

- NETs although relatively rare are increasing in incidence in recent years.
- There is an established role of grading of NET for prognosis, treatment, theranostic and clinical trial enrolment purposes in NET patients ([1, 2]) using BOTH mitotic index and proliferation rate using MIB-1/Ki67 and BOTH are required although the current College of American Pathologists synoptic protocols indicates these are “and/or” elements in reporting. Ki67 is an essential biomarker in NET Patients. Please see reference below, including AHS cancer guidelines.

Recommendation:

- At this time, Ki67 immunohistochemistry ***must be ordered*** on all NETs of the gastroenteropancreatic system (including mesenteric metastases, appendix, esophagus, stomach, duodenum, ampulla, jejunum, ileum, colorectum, anal canal, pancreas, liver and intrahepatic bile ducts, gallbladder and extrahepatic bile ducts) on resection and biopsy specimens. The ***percentage of Ki67 positivity and method used should also be reported***. Visual estimation/”eyeballing”; manual count – including positive cells and the total number of cells counted; or automatic/software-assisted counting – including software/system can be utilized.
- As per the CAP Cancer checklist guidelines (“Ki67 index is reported as percent positive tumor cells in area of highest nuclear labeling (“hot spot”), although the precise method of assessment has not been standardized**.** A number of methods used to assess Ki67 index, including automatic counting and visual estimation.[3,4] Automated counting is not widely available and requires careful modification of the software to circumvent the inaccuracies.[3] Visual estimation can be used for most tumors; however, for tumors with Ki67 index close to grade cut-offs, it is recommended to perform the manual count on the print of camera-captured image of the hot spot. It has been recommended that a minimum of 500 tumor cells be counted to determine the Ki67 index, and a notation is made if less cells are available. Grade assigned based on Ki67 index is typically higher than that based on mitotic count, and the case is assigned to the higher of the two if both methods are performed), please see Reid et al reference below[4]. Other recommended methods include: 1) digital print out of hotspot field with manual counting of Ki67 positive tumour cells over at least 500 (ideally 2000) total tumour cells, or 2) use of validated image analysis software. These counts should ideally also be attached to or stated in the original report.

For reports which omit this index, clinicians will be instructed to call the pathologist of record to correct this omission.

- Confirmation of Neuroendocrine differentiation is also recommended using synaptophysin, chromogranin, INSM1, CD56, somatostatin receptors, OR neurolysin whichever immunostain is available to the primary pathologist.
- A synoptic protocol for NET biopsy specimens has recently been developed. Implementation planning is in progress and will be available once the template is finalized and published.

References:

1. https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-endo003-octreotide-nets.pdf
2. https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-endo001-targeted-therapies-pnets.pdf
3. Tang LH, Gonen M, Hedvat C, Modlin I, Klimstra DS. Objective quantification of the Ki-67 proliferative index in neuroendocrine tumors of gastroenteropancreatic system: a comparison of digital image analysis with manual methods. *Am J Surg Pathol*. 2012;36(12):1761-1770.
4. Reid MD, Bagci P, Ohike N, Saka B, Erbarut Seven I, Dursun N et al. Calculation of the Ki67 index in pancreatic neuroendocrine tumors: a comparative analysis of four counting methodologies. *Mod Pathol.* 2015; 28(5):686-9411.

For questions and assistance with interpretation of Ki67 immunostain, please contact any of the members of the Provincial Endocrine Pathology Special Interest Group:

- Martin Hyrcza: Martin.Hyrcza@albertaprecisionlabs.ca
- Moosa Khalil: Moosa.Khalil@albertaprecisionlabs.ca
- Steve Gorombey: Steve.Gorombey@albertaprecisionlabs.ca
- Julinor Bacani: Julinor.Bacani@albertaprecisionlabs.ca

This bulletin has been reviewed and approved by the Provincial Endocrine Special Interest Group and Anatomical Pathology Discipline Council.