Pilot Study on Interval Colon Cancer: Missed Colon Cancer or Fast Growth from a Serrated Polyp?

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Results

Ten out of twenty-five (40%) of the patients with invasive colorectal carcinoma had a BRAF V600E mutation (Figure 4a). 80% of these patients were female (Figure 4b), and 90% of the patients were over the age of 70 (Figure 4c). 70% of the tumors with the BRAF mutation were located in the right ascending colon (Figure 4d).

Materials and Methods

**Microscopic localization of tumor**

The diagnosis of invasive carcinoma was confirmed by histologic criteria (Figure 3a). The H and E slides were reviewed and areas representing tumor/invasive adenocarcinoma were marked for paraffin block macro-dissection. Paraffin blocks with designated tumors were cut at 5 sections, 10 microns each.

**DNA extraction:**

The cut sections were submitted for DNA extraction (using the Qiagen protocol) and subsequent PCR amplification for BRAF detection.

**BRAF detection:**

The Entron Braf Mutation Analysis Kit was used. It is intended for the detection of the following BRAF mutations in human genomic DNA at codon 600:

- GTG → GAG (V600E)
- GTG → AAG (V600K)
- GTG → GAT (V600D)

- The BRAF mutation analysis real-time assay is based on mutation-specific PCR. Mutation-specific PCR uses primers that are 100% complementary to mutant variants of the gene. The assay also amplifies an internal control gene in order to ensure that sufficient amount of DNA is available for amplification.

- The detection of the amplification product is done by using fluorescent hydrolysis probes. Each probe contains a fluorophore (FAM™ for the mutant variant of the BRAF gene or VIC® for the internal control gene).

- The probes are complementary to the regions of interest and hybridize to the template DNA. During the amplification process, DNA polymerase cleaves off the fluorophore and the quencher from the probe. Upon separation from the quencher, the fluorescence signal increases dramatically, which is seen by the instrument detectors.

- The PCR detection instrument used in the study is the Roche LightCycler 480.

- Sensitivity of the assay: the assay is able to detect 1% mutation in a background of wild-type DNA.

**Conclusion and Future Direction**

The data from our institution is in accord with previous publications and demonstrates the propensity of interval colorectal cancer to occur within the right side of the colon. It also highlights the association of these cancers with BRAF mutation, the sessile neoplasia pathway, older age, and female gender7. The study also supports the hypothesis that interval colorectal carcinoma following a negative colonoscopy might indicate a missed SSP as the precursor lesion in the right side of the colon in a significant subset of the cases. Future direction is aimed at improving the screening process for colorectal carcinoma. Additional testing includes the possibility of serologic screening and better preparation/visualization of the right side colon, which may facilitate early detection of precursor lesions. Enhanced clinical experience with colonoscopies and awareness of the subtle nature of these precursor lesions may also establish a better preventive strategy in a subset of the patients.

**References**

6. 8. Microscopic images produced by Dr. Shereen Gheith and Dr. Jillian Grau (Figures 1 and 3a). 21 Jul 2016.

**Patient Age and Mutation Distribution**

- Total Wild Type vs. Mutant.

**Patient Gender**

- Total Female vs. Male.

**Tumor Location**

- Right ascending colon
- Cecum
- Hepatic flexure
- Rectum
- Right transverse colon
- Left descending colon
- Sigmoid colon
- Rectosigmoid colon

**DNA Extraction**

- Normal colon mucosa (yellow arrow) transitioning to an invasive adenocarcinoma (blue arrow). Hematoxylin and Eosin stain, original magnification x 10.
- Inset: Invasive adenocarcinoma, original magnification x 40.

**Patient Age**

- 55-59
- 60-64
- 65-69
- 70-74
- 75-79
- 80-84
- 85-89
- 90-94

**Tumor Location**

- Right ascending colon
- Cecum
- Hepatic flexure
- Rectum
- Right transverse colon
- Left descending colon
- Sigmoid colon
- Rectosigmoid colon

**Mutation Gender**

- Male 55%
- Female 45%

**Mutation Tumor Location**

- Right transverse colon 55%
- Sigmoid colon 30%
- Left descending colon 15%

**Conclusion**

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