Importance of Genetic Testing for Patients with Multiple Colorectal Cancer Primaries

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BACKGROUND
- Individuals with hereditary colorectal cancer (CRC) may be at increased risk for a second primary CRC.
- A personal history of multiple CRCs and/or early onset CRC may be considered an indication for genetic testing.
- Since hereditary CRC has various genetic etiologies, clinicians often opt for multi-gene panel testing (MGPT).
- Identifying patients with inherited colorectal cancer susceptibility can help to guide medical management and aid in cancer prevention.

Genes included in testing:
- Colon cancer genes (n=7046, 100% of cohort): APC, BMPR1A, CDH1, CHEK2, EPCAM, GREM1*, MSH1, MSH2, MSH6, MUTYH, PIK3, POLD1*, POLQ*, PTF1, SMAD4, STK11, and/or ATM.
- Additional genes (n=145, 2.0% of cohort): ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH4, CCR2, MRE11A, NBN, NFI, PALB2, RAD50, RAD51C, RAD51D, SMARCAD1, and/or ATM.

RESULTS
- Individuals with a history of multiple CRCs (see right) had an overall positive rate of 23.8% (n=72), as compared to 12.4% (n=836) in those with a history of one CRC (see left).
- OR=2.2; p=1.16-7; 95%CI=[1.653,2.907].

STUDY AIM & METHODS
- Here, we aim to evaluate the diagnostic yield of MGPT among patients with multiple CRC primaries.
- MGPT tests and age at CRC diagnoses were reviewed for 7,046 CRC patients who underwent testing from March 2012 to June 2016.
- Depending on the panel ordered, analysis of 14 to 49 genes associated with CRC and/or other cancers was performed.
- The diagnostic yield and ages at CRC diagnoses were compared between patients with a history of one CRC (n=836) and those with two or more CRCs (n=307).

Genes without any positives in the multiple CRC group are not pictured; percentages calculated based on # of individuals tested.

Multiple CRC Group
Single CRC group

MUTATION DISTRIBUTION

AGE AT DIAGNOSIS

27.4% 22.6%

20.4% 40.7%

59.3%

Multiple CRC group
Single CRC group

Potential Implications of Positive Results

- Recommendations to address increased risks for colon cancer:
  - Surveillance: consider early colonoscopy in mutation carriers for APC, BMPR1A, CHEK2, EPCAM, GREM1, MSH1, MSH2, MSH6, MUTYH, PIK3, POLD1*, POLQ*, PTF1, SMAD4, STK11, and/or ATM.
  - Chemoprevention: aspirin may decrease the risk for colon cancer in patients with Lynch syndrome.

- Consider total abdominal colectomy with ileorectal anastomosis and total proctocolectomy with ileal pouch-anal anastomosis as options for patients with Lynch syndrome to prevent metastatic lesions.
- Consider total abdominal hysterectomy and/or bilateral salpingo-oophorectomy (i.e. BRCA1/2, Esophagastroduodenoscopy (EGD), early mammogram/BRCA1/2, CHEK2, PALB2, PNI, STK11, TP53).
- Proliferative masticectomy, thyroid sonography, annual urinalysis, etc.

Take-home points:
- Overall, individuals with multiple CRCs were about twice as likely to be mutation-positive than those with one CRC, specifically, for LS (OR 3.39) or another CRC genetic (OR 2.4).
- Those in the multiple CRC group diagnosed with their first CRC before 50 were about three times as likely to be mutation-positive than those with one CRC.
- Genetic testing for those with multiple CRCs/early onset CRC captures a significant number of patients/relatives who may benefit from consideration of strategies to reduce their risk of developing an additional CRC or extra-colic cancers.

REFERENCE