CMS CLASSIFICATION AND SURVIVORSHIP

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Dr. Jason Willis does not have any relevant financial relationship to disclose.

CASE

48 YEAR OLD WOMAN WITH STAGE IIA (T3 N0 M0) ADENOCARCINOMA OF THE SIGMOID COLON PRESENTS FOR ADJUVANT THERAPY RECOMMENDATIONS

- ECOG Performance Status: 0
- Past medical history: gastritis, non-smoker
- Family history: osteoporosis (mother), diabetes (father). No known family history of gastrointestinal, genitourinary, or gynecologic cancers.
- ROS: negative (including no neuropathy)

Pathology findings:

- Moderately differentiated
- Negative LVI or PNI
- Negative for carcinoma in 14 resected lymph nodes
- Microsatellite status: stable (by IHC)
- CEA: undetectable post-operatively

ECOG, Eastern Cooperative Oncology Group; LVI, lymphovascular invasion; PNI, perineural invasion; ROS, reactive oxygen species; IHC, immunohistochemistry; CEA, carcinoembryonic antigen

- **What additional molecular testing should be ordered?**

COLORECTAL CANCER CLASSIFICATION: CONSENSUS MOLECULAR SUBTYPES

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- **14%: CMS1** (microsatellite instability immune), hypermutated, microsatellite unstable and strong immune activation
- **37%: CMS2** (canonical), epithelial, marked Wnt and Myc signaling activation
- **13%: CMS3** (metabolic), epithelial and evident metabolic dysregulation
- **23%: CMS4** (mesenchymal), prominent transforming growth factor–β activation, stromal invasion and angiogenesis

- **13%:** Samples with mixed features possibly represent a transition phenotype or intratumoral heterogeneity

CMS, consensus molecular subtype

Guinney J, et al. Nature Medicine. 2015;21(11):1350.

CONSENSUS MOLECULAR SUBTYPES OF COLORECTAL CANCER

- Gene expression-based signatures that correlate with meaningful clinical outcomes and tumor biology
- Prognostic value has been validated in multiple retrospective studies

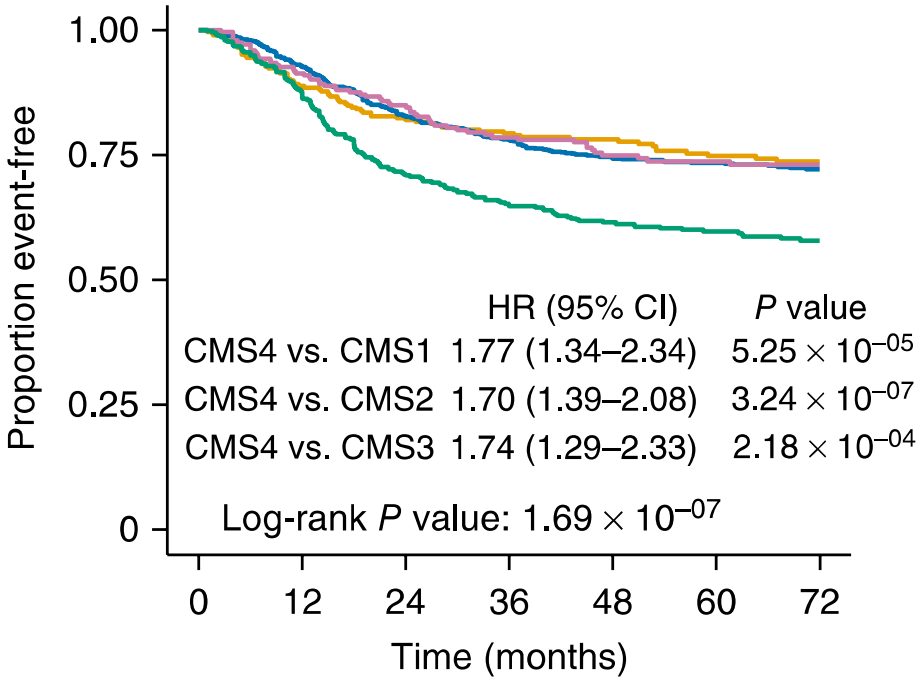

Figure represents: Prognostic value of CMS1 (orange), CMS2 (blue), CMS3 (pink) and CMS4 (green) with Kaplan-Meier survival analysis in the aggregated cohort for relapse-free survival (n = 1,785)[1]

CI, confidence interval; CMS, consensus molecular subtype; HR, hazard ratio; MSI, microsatellite instability

[1]Guinney J, et al. Nature Medicine. 2015;21(11):1350.

RECOMMENDED MOLECULAR TESTINGS

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KRAS, *NRAS*, and *BRAF* Mutation Testing

- All patients with metastatic colorectal cancer should have tumor tissue genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations individually or as part of a next-generation sequencing (NGS) panel. Patients with any known *KRAS* mutation (exon 2, 3, 4) or *NRAS* mutatio (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab.[44-46] *BRAF* V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor.[47-49]
- Testing for *KRAS*, *NRAS*, and *BRAF* mutations should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform *high-complexity* clinical laboratory (molecular pathology) testing. No specific methodology is recommended (eg, sequencing, hybridization).
- The testing can be performed on formalin-fixed paraffin-embedded tissue. The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the *KRAS*, *NRAS*, and *BRAF* mutations are similar in both specimen types.[50]

Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing

- Universal MMR* or MSI* testing is recommended in all patients with a personal history of colon or rectal cancer. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
- The presence of a *BRAF* V600E mutation in the setting of MLH1 absence would preclude the diagnosis of Lynch syndrome in the vast majority of cases. However, approximately 1% of cancers with *BRAF* V600E mutations (and loss of MLH-1) are Lynch syndrome. Caution should be exercised in excluding cases with strong family history from germline screening in the case of BRAF V600E mutations.[51]

MLH-1, MutL homolog 1

CASE *(CONTINUED)*

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- **The patient is followed on surveillance. She enquires about her risk of disease relapse and measures she can take (if any) to adjust that risk**

- What type of molecular testing should be ordered?
- Should adjuvant chemotherapy be offered?

- **What type of molecular testing should be ordered?**
  - Based on current standards of care, molecular testing for early-stage disease should include microsatellite status by pCR or IHC
- **Should adjuvant chemotherapy be offered?**
  - Having stage IIA disease with no high-risk features, the patient is unlikely to benefit from adjuvant chemotherapy.
  - **Would CMS classification change your recommendation?**

IHC, immunohistochemistry; pCR, pathologic complete response