Molecular characterization of colorectal tumors in young patients compared with older patients and impact on outcome

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**BACKGROUND**

- Colorectal cancer (CRC) is increasingly diagnosed in adults <60 years old, often at an advanced stage and with a worse prognosis.
- Limited data suggests tumors that develop in a younger cohort show distinct genetic changes that are different from classic CRC in older adults. It is unclear how these differences affect clinical outcomes.

**AIM:** To compare profiles of genetic alterations and clinical variables between younger and older patients to further elucidate differences and impact on survival.

**METHODS**

- Molecular profiles of 4,821 tumors from young (<45 years; n=1,277) and old (>65 years; n=3,544) CRC patients were obtained from Caris Life Sciences.
- Protein expression (IHC), gene amplification (ISH), sequencing (NGS and Sanger), and fragment analysis were performed to generate profiles.
- Fisher’s exact two-tailed tests were used to determine molecular differences between the two age groups.
- CRC cases from 2005 to 2015 at the Lombardi Comprehensive Cancer Center with associated Caris Life Sciences tumor molecular profiles were analyzed to identify young (<45 years) and old (>65 years) patient cohorts for the clinical outcome correlation portion of study.
- Forty-seven patients <45 years old and twenty-seven patients >65 years old were identified.

**RESULTS**

- As seen in Table 1, a significantly higher number of younger patients were metastatic at time of diagnosis.
- Older patients had higher rates of BRAF, APC, and KRAS mutations and higher microsatellite instability (MSI) rates (p=0.002). Other mutations and biomarker expression between age groups were similar.
- Younger patients without significant ERCC1 expression experienced lower overall survival rates.
- There were no significant differences in sex, race, or primary site of disease between age groups.
- Other patients had higher rates of BRAF, APC, and KRAS mutations, whereas younger patients had higher overall expression of HER2, 2/neu, and MGMT and an increased number of BRCA1/2 mutations.
- Younger patients without significant ERCC1 expression experienced lower overall survival as compared with the older cohort. No additional differences in overall survival based on biomarker expression or mutation status in patients with clinical outcome data were revealed.
- Our findings suggest there are distinct genetic differences in younger patients as compared to older patients with CRC. In our limited clinical cohort, however, these genetic differences did not appear to impact survival.
- Continued efforts are needed to further understand the significance of these differences to allow for the development of tailored screening and treatment strategies for both age groups of CRC patients.

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**Figure 1. Overall Survival, <45 years old at diagnosis compared to >65 years old**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean Age</th>
<th>Younger (&lt;45)</th>
<th>Older (&gt;65)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (OS)</td>
<td>51.1 months</td>
<td>26%</td>
<td>56%</td>
<td>0.076</td>
</tr>
</tbody>
</table>

- Median overall survival (OS) in the younger cohort was 51.1 months versus not reached (NR) in the older cohort (p=0.076).
- As seen in Table 1, there was a significantly higher number of younger patients were metastatic at time of diagnosis.

**Figure 2. Overall survival stratified by age group in ERCC1 negative patients**

<table>
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- No statistically significant difference in overall survival were noted with biomarker expression or mutation status within each age group.
- Evaluating biomarker expression positivity or mutated gene and impact on survival between age groups, no statistically significant differences were found.
- Evaluating lack of biomarker expression or mutated gene and impact on survival between age groups, ERCC1 underexpression was associated with lower overall survival in the younger cohort (p=0.045).

**Figure 3. Biomarker frequency in Caris cohort**

- The most frequently mutated genes included TP53, APC, KRAS, PIK3CA, SMAD4, and ERCC1.
- Mutations rates for BRAF (p<0.001), APC (p=0.0034), and KRAS (p=0.025) were higher in older patients.

**Figure 4. Genetic mutation frequency in Caris cohort**

- Twelve genes with the highest mutation rates were HER2, 2/neu, and MGMT in the younger group. A significant number of BRCA1/2 mutations were observed.

**CONCLUSIONS**

- Younger CRC patients were more likely to present with metastatic disease and had a trend toward lower overall survival.
- There were no significant differences in sex, race, or primary site of disease between age groups.
- Microsatellite instability occurs at similar frequencies in the young and older cohorts. Interestingly, MSI high was seen exclusively in older patients.
- Older patients had higher rates of BRAF, APC, and KRAS mutations, whereas younger patients had higher overall expression of HER2, 2/neu, and MGMT and an increased number of BRCA1/2 mutations.
- Younger patients without significant ERCC1 expression experienced lower overall survival as compared with the older cohort. No additional differences in overall survival based on biomarker expression or mutation status in patients with clinical outcome data were revealed.
- Our findings suggest there are distinct genetic differences in younger patients as compared to older patients with CRC. In our limited clinical cohort, however, these genetic differences did not appear to impact survival.
- Continued efforts are needed to further understand the significance of these differences to allow for the development of tailored screening and treatment strategies for both age groups of CRC patients.