METASTATIC COLORECTAL CANCER

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Colorectal cancer (CRC) is the 4th most common cancer diagnosed in the United States, and the second most deadly malignancy after lung cancer.

The incidence of CRC in the overall US population is declining, due in part to an increase in screening colonoscopies, but the rate of CRC is rising in young adults, and 20.5% individuals with newly diagnosed CRC are younger than 55 years of age. From 2000-2013 the incidence of CRC for individuals less than age 50 rose by 22% mostly by tumors of the distal colon and rectum.

Several population-based studies have explored the prognostic relevance of laterality in CRC with conflicting results; a recent meta-analysis found inferior survival for patients with right side colon cancer, several other reports have also found inferior survival among patients with right-side metastatic CRC especially if RAS-wild type tumors. Studies have shown that patients with right side colon cancers are older, more likely female, initially have more advanced tumor stage and poorly differentiated cancers. Studies also have found a higher rate of diploidy, mucinous histology, microsatellite instability and BRAF mutations in the right side tumors and more frequent p53 and KRAS mutations in the left side tumors. Recent studies noted that microbiome may also have a role in CRC, and differences in the flora from the proximal and distal colon may results in different biology and prognosis for the CRC.

The median survival of pts with metastatic CRC not able to have surgery is less than 3 years, the survival improves with surgically resectable disease to a 5 years survival rate of 26% to 40%. When treatment with curative intent is not possible patients are generally given a combination of cytotoxic chemotherapy with target therapy. The medication options have been limited in the last 15 years and remain 5-fu based combinations as FOLFOX, and FOLFIRI, with some options with targeted agents introduced in the 2000s like anti VEGF (bevacizumab), VEGF receptor 2 (ramucirumab), and EGFR (cetuximab and panitumumab), a fusion protein that targets VEGF A and B and placental growth factor (aflibercept), an oral angiogenic inhibitor (regorafenib) and an oral cytotoxic agent (trifluridine-tipiracil); with this option the median overall survival (OS) for patients with metastatic CRC has increased from 12 months in 1990 to more than 30 months in 2015. Now in the last couple years, the advances in Immunotherapy have open potential new treatments.

85 % of CRCs develop from chromosomal instability due to allelic losses, loss of heterozygosity, chromosomal amplifications and translocations, and 15 % of the CRCs have defective DNA **mismatch repair system (MMR)**. This produces hypermutations and **microsatellite instability (MSI).** The main function of the MMR system is the maintenance of the genomic stability and microsatellites are short DNA areas (1-6 bases) that are repeated throughout the genome and are particularly prone to replication errors resulting in genetic instability so defects in MMR lead to MSI. MSI is tested in CRC to classify it as **microsatellite instability high (MSI-H)** or **low (MSI-L)**. Individuals that are MSI-H should be referred for further genetic testing for Lynch syndrome. Also, MSI-H status in patients with stage II and III colon cancer has prognostic impact with a better 5 years survival and do not have improvement in survival with the 5-Fu based therapy, only the MSI-L benefit

from adjuvant chemotherapy. Studies that have compared the genetic profiles of primary VS recurrent CRC have found significant intratumoral heterogeneity and a higher mutational burden in recurrent cancers

MSI-H has become a target for treatment using immunotherapy. Checkpoint inhibitors against PD-1 and PD-L1 have demonstrated activity in metastatic CRC MMR -deficient/HSI-H tumors because these tumors are hypermutated. Currently, the National Comprehensive Cancer Network recommends pembrolizumab and nivolumab in the treatment of CRC in the 2nd and 3rd line for patients with MMR/MSI-H. Also, the FDA recently approved the use of pembrolizumab for any cancer MSI-H or MMR deficient that has progressed on standard therapy. Unfortunately, only 5 to15% of the metastatic CRC are MSI-H/MMR deficient these patients are the potential beneficiaries of immunotherapy with check point inhibitors. An area of active research is the use of immunotherapy on MSI-L or MSS CRC alone or in combination with agents that enhance antigen presentation. Molecular profiling in metastatic CRC is important in guiding therapy like the use of anti-EGFR receptor therapies for KRAS-Wild type patients, and finding new drug targets for BRAF mutations, HER 2 mutations, MMR deficiency etc. We still have a lot to learn to better understand tumor biology because the molecular heterogeneity of CRC affects treatment options and outcomes for patients with metastatic disease.

References

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