Why Do We Need to Care About Tumor Location in the Patient with Colorectal Cancer?

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Colorectal cancer is one of the most common cancers and, with an increasing incidence, also one of the biggest cause of cancer death.

Developing histologically through stages ranging from adenoma to adenocarcinoma, approximately 65% of colon cancers are located distal to the splenic flexure detected by sigmoidoscopy, whereas 35% from the proximal to the sigmoid and are not detected by flexible sigmoidoscopy. As the first cancer to be elucidated as a model of carcinogenesis by Vogelstein – with the development from inflammation, polyp to become cancerous and involving various molecular factors - it is one of the most studied.

The formation of the adenoma is known as tumor initiation while the progression of the adenoma to carcinoma what we know as tumor progression. Molecular genetic studies have provided some of the strongest experimental support for the adenoma-carcinoma hypothesis, thus colorectal cancer is probably the best understood complex cancer in terms of molecular site.

From the aforementioned studies, it was found that the progression from adenoma to carcinoma is the result of an accumulation of molecular genetic alterations involving, among other changes, activation of oncogenes, inactivation of tumor suppressor genes, and participation of stability genes.

The development of colorectal cancer occurs simultaneously associated with mutations in several genes. A large body of evidence demonstrates that colorectal cancer is associated with an accumulation of genetic changes. On the other hand, there are significant differences both in terms of clinical molecular tumor to between one race with other races. Clinical and molecular differences also occur between one location and another location. As a clinician, it is important to ascertain the location of the tumor and make predictions about the clinical course of these tumors.

Several researchers have conducted the orientation of the location as well the difference between age and gender. The proximal colon cancer is frequently observed in females and older patients while distal colon cancer is dominant in males and younger patients.

Molecular studies have realved the difference between the distal and proximal colon. Proximal colon cancer is more likely to be positive for microsatellite instability with wild type p53 while distal site cancer is dominated by chromosomal instability with a mutated p53.

For hereditary colorectal cancer, there are two dominant locations of cancer, distal and proximal. Distal colorectal cancers have aneuploid DNA, harbor mutations in the adenomatous polyposis coli (APC), p53, and K-ras genes. These genes actually behave more aggressively. Proximal colorectal cancers are more likely to have diploid DNA, possess microsatellite instability, harbor mutations in the mismatch-repair genes. These genes actually behave less aggressively, as in
hereditary nonpolyposis colorectal cancer.6

Further evidence found that only 40% of proximal tumours showed allelic losses at chromosomal regions in 17p, 18 and 5q. For proximal tumours, almost 80% are found to be diploid compared to only 40% of distal tumours. Left-sided tumours have been shown to express higher levels of growth factors. These growth factors include IGFI192 and EGF/TGF-alpha. The cyclooxygenase COX-2 is overexpressed in 90% of rectal tumours, while it is only overexpressed in 20% of colonic tumours.4

A mutation that may differ between distal and proximal tumors is the microsatellite instability (MSI). The microsatellite instability phenotype has been reported to be up to 10-fold higher in frequency as seen in sporadic proximal compared to distal tumours.7 The location of familial cancer syndrome is also different, hereditary nonpolyposis coli (HNPCC) arise from proximal colorectal cancer, while FAP arise first from rectum and distal colon before extending.3

Genetic structural differences between the distal and proximal colorectal cancer also affects the effects of chemotherapy. Various studies have shown that MSI+ associated with chemotherapy sensitive, patients with MSI+ have a better survival rate. By looking at the presence or absence of MSI, also the location of the tumor, the clinician can relate to the response of chemotherapy. Proximal colorectal patients could have a better prognosis than patients with distal colorectal cancer if they receive a 5 FU-based chemotherapy.3

Finally, colorectal cancer is rather unique in that finding out the location of tumor and determining its molecular characteristics is important and we might be albe to predict whether it commonly occurs in these patients by looking at age and sex. This data also can help the clinician to predict the clinical course and response of chemotherapy.

REFERENCES