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One Colon Lumen but Two Organs

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The colon is a remarkable organ in that it manages the final products of digestion after nutrient assimilation, and packages it as waste to expel. The colon has the highest bacterial load of any organ, with commensal bacteria occupying a niche that prevents noncommensal organisms from expanding, and some bacteria producing vitamins that can be utilized. It is the colon, with its local environmental influences on intrinsic stem cells and an individual's genetic background, that makes this organ the third most common site for cancer in men or women and the site with the second highest cause for cancer deaths overall.[1] Because of the risk for cancer, early detection is key, and men and women are screened according to the latest guidelines to detect cancers and its precursor lesion, the adenoma, in hopes of reducing the cancer incidence and to intervene early to save lives.[2] The relatively high risk for colon cancer in the population has led to the development of multiple tests that can either detect adenomas and/or cancer, with each having variable sensitivities and specificities.[2] Colonoscopy in particular has been advocated because of its relative high sensitivity, and its diagnostic and therapeutic capabilities for both adenomas and cancer. Although it is the gold standard for colonic neoplasia detection, colonoscopy can miss lesions that may be related to the endoscopist's expertise or thoroughness,[3] although other factors may be related to the biology and growth characteristics of neoplasia that occur within the colon.

Fundamentally, the colon is 1 organ, but develops from 2 different embryonic areas of the primitive gut: the midgut, which gives rise to the small intestine through to the proximal two thirds of transverse colon, and the hindgut, which gives rise to the distal third of the transverse colon through the upper anal canal.[4] Functionally, the proximal colon absorbs most of the remaining water from the incoming digestive contents utilizing effective haustral shuttling, whereas the remainder of the colon utilizes peristalsis as its primary motility characteristic, and lubricates the remaining waste as it becomes more solid while progressing toward the rectum. The right colon "sees" bile acids and other metabolites that have escaped the small intestine's reuptake or detoxifying mechanisms, and in a form before colonic bacterial action on the metabolites. Genetic profiling of normal right and left colon confirm major differences between sites of this endodermally derived organ: There are >165 genes showing >2-fold and 49 genes showing >3-fold differences in gene expression between the adult human right and left colon.[5]

The development of neoplasia likewise differs by site within the colon. As we age, a left-to-right colon cancer shift ensues between the seventh and eighth decades of life.[6] Females are more likely to develop proximal cancers whereas males develop more distal cancers,[4] suggesting the possibility of hormonal influences on incidence. African Americans have higher prevalence of adenomas >9 mm proximally compared with Caucasians, and have a higher prevalence of proximal cancers.[7,8] Adjuvant and neoadjuvant treatment of colon cancer is different based on site, with rectal cancers being treated at earlier stages (stage II) with addition of radiation treatment to chemotherapy, compared with more proximal stage III cancers and no radiation.[9] Treatment responses indicate biological behavior differences for site-specific colon cancers.[10]

Morphologic and genetic differences of colonic neoplasia are observed based on site within the colon. Laterally spreading tumors, a type of superficial "flat" spreading neoplasm, are commonly found in the right colon, and can be difficult to detect without enhanced endoscopic methods.[11] These lesions are much more likely to contain cancer than their polypoid counterparts,[11] and their lack of exophytic growth has been attributed to lack of *KRAS* mutation.[12] Microsatellite instability (MSI), seen in up to 20% of sporadic cancers and prevalent in proximal cancers, is caused by hypermethylation of the DNA mismatch repair gene *hMLH1* (through the CpG island methylator phenotype [CIMP] pathway), and these tumors lack mutated *KRAS* but contain the V600E *BRAF* mutation.[10,13] Sessile serrated adenomas are associated with and progress to right-sided colon cancers, have *BRAF* mutation, and often manifest MSI from methylation of *hMLH1*, strongly suggesting that these mutations drive the development of these morphologically low profile and proximally located MSI tumors.[13] All of these morphogenetic findings are likely unified in defining a pathogenic pathway in the right colon. One ascertained clinical consequence is that either the presence of CIMP or MSI in a patient's colon cancer predicts a lack of improved survival response with 5-fluorouracil–based chemotherapy.[14–16] Detection of proximal serrated polyps appears to be endoscopist dependent,[17] and their presence at screening increases interval neoplasia during surveillance.[18]

Are there screening differences for mortality based on colonic site? The best evidence suggests that there is.[19,20] At worst, colonoscopy does not improve mortality from proximal cancers,[19] and at best, it improves it markedly but to a lesser extent than from distal cancers.[20] Perhaps the colon should be considered 2 organs matching its embryonic origin, with varying approaches for site-specific screening based on the observed morphologic, genetic, racial, gender, age, detection, and mortality differences of proximal colonic neoplasia compared with distal lesions. Akin to unseen moisture on the road after it freezes, right-sided lesions progressing through neoplastic development may be the "black ice" of the colon. Strategies to better recognize and detect right-sided lesions (eg, optical, dye based, genetic, etc) may need to be pursued in a broader fashion for these apparently more difficult to identify lesions, in order to make the impact on par with the beneficial effect observed with screening for left-sided lesions.

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