EDITORIAL

Rectal Cancer: Age Matters in the Affairs of Stage

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““Aging is not lost youth but a new stage of opportunity and strength.””

—Betty Friedan

The American Cancer Society estimates that 132,700 new colorectal (CRC) cases will be seen in 2015 (1), making CRC one of the top three most common cancers in the United States as well as a major health burden worldwide. It is encouraging that in the United States CRC incidence rates appear to be leveling off, even declining in recent years (2). This decline is largely attributed to the success of colonoscopic screening in patients over the age of 50 years. It allows for the early detection and removal of colorectal polyps before they progress to cancer and is the mainstream of CRC prevention efforts. However, recent literature suggests a worrisome trend of rising incidence of CRC in young individuals (3–6), a population that is not included in current population screening guidelines. These observations have important public health implications, but these studies suffer from a lack of uniformity in defining young CRC with studies including patients under the age of 40 or 50 years, with the majority of these studies being done at single centers, making it difficult for policy makers to fully appreciate the public health implications. The heterogeneity in studies has led to conflicting results as to what clinicopathological features are prognostic in young CRC patients, if any.

It is in this context that the article by Meyer et al. in this issue of the Journal is timely (7). The authors used the population-based data from the US Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute to compare clinicopathological characteristics among patients with young rectal cancer (defined as age <50 years) diagnosed between 1988 and 2008. They included patients with stage I-III disease, without any history of prior radiotherapy and at least one lymph node examined with a standard rectal cancer operation, to help ensure that patients had received similar perioperative care. One in 10 patients included was under the age of 50 years, with 2.1% under the age of 40 years, and 7.5% age 40 to 49 years. The approximately 10% incidence of young rectal cancers is consistent with that of other studies (8). Adjusting for factors such as number of lymph nodes harvested and other clinicopathological factors, the authors found age to be statistically significantly predictive of lymph node positivity (LN+). For each T stage, LN+ was inversely associated with age. Intriguingly, for patients under the age of 40 years compared with patients age 60 to 69 years (the majority of cases), they were 2-fold, 1.5-fold, and 1.3-fold more likely to be LN+ for T1, T2, and T3 disease, respectively.

A study using population-based data such as the SEER database is limited by available clinical data. As the authors acknowledged, it is not known how these patients came to diagnosis—were they discovered on diagnostic or screening evaluations? Older patients are far more likely to have their rectal cancers detected presymptomatically as part of screening, and there are studies to suggest their doctors are also less likely to ignore early symptoms compared with the young. Although the authors account for this by stratifying by T stage, reporting that age is predictive of LN+ status regardless of T stage, it remains unclear how late presentation in younger patients could affect these results, except to attribute to different underlying biology. Regardless of these limitations, the results of this study have significant clinical implications. Given the higher propensity amongst young rectal cancer patients to be occult LN+ even for T1 disease, this will need to be taken into account for choice of surgical intervention. Although preoperative neoadjuvant chemoradiotherapy is recommended for the management of resectable rectal cancer, it is not uniformly practiced and the results here give further impetus for this to be standard of care in fit young rectal cancer patients.

Given the results from this article and others, there is certainly a growing consensus that “young CRC” is a clinical entity in need of both research and health policy attention. To aid future research into this area, it will be important that future studies address this issue by first addressing what uniform definitions we will use. Amongst the definitions to be defined, what age should be considered the threshold for “young CRC”? A review of studies

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up to 2003 revealed that approximately 70% of references defined “young” as patients younger than age 40 years (9), but this trend appears to be reversing with increasing numbers of studies using younger than age 50 years (10), which is the cutoff used by the Amsterdam criteria for identifying patients who may be at risk of Lynch Syndrome (LS). In another recently published study, and an important one, the authors using SEER data divided patients into three age groups to better understand what cutoffs would be useful. They grouped the case patients as age 21 to 40, age 41 to 50, and older than age 50 years (11). In this study, they included all CRC patients and found that patients with CRC diagnosed at age 21 to 40 years had later stage presentation and more aggressive pathological features but better survival. CRC patients age 41 to 50 years had the best CRC survival, in contrast to patients in the other two age groups. What this study highlights is that there is certainly heterogeneity in CRC patients under the age of 50 years and perhaps future CRC studies would need to look at the three groups separately rather than as a single cutoff.

Is “young CRC” a good catchall for both young rectal and young colon-only cancers? Should we consider them similarly with regards to biology and management? As the authors highlight, we do not yet understand the molecular differences between CRCs seen in young vs elderly patients and between “young rectal” vs “young colon” cancers. Important host-environ-
ment factors remain to be interrogated and understood, including the interaction of host genetics with innate immunity, the tumor and its microenvironment, and the gut microbiome, in disease initiation and progression.

What we do know is that approximately 5% of all CRCs are due to a heritable cause. Indeed, LS accounts for approximately 3% of all incident cases of CRC. Almost certainly, part of the 10% “young CRC” in this study have an inherited cancer syndrome. What of the rest? It is important that all these patients also be assessed for cancer predisposition syndromes. For LS, universal testing of the molecular phenotype of mismatch gene repair deficiency through either microsatellite instability or immunohistochemist-
ry has been shown to be a cost-effective screening tool for detection of LS (12–14). For the other hereditary CRC syndromes, it remains challenging, and clinicians will need to pay particular attention to family history as well as detailed personal history for all CRC patients under the age of 50 years to identify who might require referral for genetic risk assessment (15). A recent study found a high prevalence of hereditary cancer predisposition syn-
dromes in patients under the age of 35 years and recommend that any CRC patient age 35 years or younger receive genetic testing in the setting of genetic counseling (16). Of the 193 patients with evaluable data, 35% had an identifiable hereditary cancer syndrome, including 23 with Lynch Syndrome, 22 with mutation-negative Lynch Syndrome, 16 with familial adenomatous polyposis, two with constitutional mismatch repair deficiency, two with biallelic MUTYH mutations, and one with Li-Fraumeni Syndrome.

While knowing the index case’s mutation will allow family members to undergo predictive testing such that only those affected need receive increased surveillance starting at an early age, unfortunately, the majority of young CRC patients do not have a family history (17). An absence of family history therefore does not preclude early onset CRC in an individual, nor does it exclude de novo occurrence of heritable cancer. This underscoring the need for further research to better understand the etiology of early-onset CRC. Apart from LS and the other hereditary CRC syndromes, we have, at present, no other means of rapidly identifying those at increased genetic risk, which leads to the last question. How should we best screen these patients without adding substantial burden to the healthcare system? In this era of value-based healthcare in the era of genomic medi-
cine, the answer may lie in using molecular multtarget DNA-based stool screening to first identify that subset that requires colonoscopy (18). 

“Age is opportunity no less, Than youth itself, though in another dress, And as the evening twilight fades away, The sky is filled with stars, invisible by day.”

-- Henry Wadsworth Longfellow, Monturi Salutamus, 1875

Notes

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