



Prolonged follow-up of colorectal cancer patients after 5 years: to follow or not to follow, that is the question (and how)!

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It is estimated that in 2018 there were 1.8 million patients diagnosed with colorectal cancer (CRC) worldwide resulting in 862,000 deaths, which is an increase from 2012 by 33% and 24%, respectively (1). Surgical resection remains the standard of care for resectable, non-metastatic, CRC. Following complete resection, more than 90% of recurrences occur in the first 5 years with most occurring in the first 3 years (2). Beyond 5 years, however, there are currently no clear recommendations. There are some studies with up to 10 years of follow-up after surgery that have reported late recurrences after 5 years (3), thus the utility of prolonged follow-up after the initial 5 years is an important question. To address this knowledge gap, Kong *et al.* investigated the efficacy of prolonged follow-up beyond 5 years using a retrospective cohort of 1,054 CRC patients who underwent radical resection from 1980 to 1996 at their institution (4). The patient cohort consisted of 15% right-sided colon tumors, 18% left-sided colon tumors, and 62% rectal tumors. Pathological stages included 14% stage I, 56% stage II, and 31% stage III. Patients were followed every 3 months for the first 2 years, every 6 months in the following 3 years, and then yearly. To detect local or distant recurrence, the authors utilized a physical exam, ultrasound, X-ray, and computed tomography. The authors found significant associations between survival and the following variables: age ($P=0.026$), tumor site ($P<0.001$), and pathologic stage ($P<0.001$). Compared to patients who died within 5 years of surgery, patients who survived past 15 years had a higher

proportion of colon cancer relative to rectal cancer and stage I/II disease. Furthermore, 91% of relapses occurred in the first 5 years after surgery, whereas less than 1% of patients relapsed after 15 years of surveillance.

Since the mid-1980s, the death rate from CRC has declined resulting in a large number of CRC survivors (5). Of the 13.7 million cancer survivors living in the United States as of January 2012, 9% were CRC survivors (6), therefore determining an optimal surveillance protocol for CRC survivors is necessary due to the significant burden follow-up can pose on patients, physicians, and the healthcare system alike. The objective of follow-up programs for long-term CRC survivors is the early-stage detection of disease recurrence, at the point where it is amenable to curative resection. In their study, Kong *et al.* confirm much of the data already known—approximately 90% of CRC recurrences will occur in the first 5 years after resection and recurrence beyond the initial 5 years of follow-up is less common. In their cohort, less than 1% of recurrences occurred after 15 years. Perhaps the more relevant finding was the 6% recurrence rate that occurred between 5 and 10 years of follow-up which the authors failed to emphasize. Although a relatively small percentage compared to the 91% recurrence rate in the first 5 years after resection, a 6% recurrence rate is not insignificant. It would have been informative for the reader if a comparison had been performed of clinicopathologic characteristics between patients that recurred in the first 5 years versus

those that recurred after 5 years of resection. This information might have some clinical relevance in that it can help identify patients that are still at risk of recurrence after the initial 5 years of surveillance. After 15 years of surveillance, the authors found a recurrence rate of 0.8% among their cohort. Given such a low recurrence rate, is it realistic that all CRC patients be followed for such extended periods of time? One important question not addressed by the authors is the burden this would put on healthcare systems, as it relates to costs of extended follow-up.

Currently the standard duration of follow-up after CRC resection is 5 years, on the basis of the American Society of Colon and Rectal Surgeons and American Joint Committee on Cancer, which provides surveillance practice guidelines including physical examination, CEA, CT scan, colonoscopy, and endorectal ultrasound (7). However, establishing an optimal length of follow-up in accordance with risk stratification assigned to each individual patient is ideal. Frontali *et al.* addressed this specific question in a recent study (8). The authors assessed the utility of prolonged follow-up more than 5 years after CRC resection in a cohort of patients without evidence of recurrence during the initial 5 years of surveillance. After 5 years, Frontali *et al.* noted a tumor recurrence rate of 7% with a higher incidence among rectal cancer patients versus colon cancer patients (11% *vs.* 2%, $P=0.014$). Among CRC patients with recurrences after 5 years, the authors noted high recurrence rates in colon cancer patients with pT3 tumors, in rectal cancer patients with ypT0 to ypT2 tumors, and in rectal cancer patients with ypN0 tumors (8). Given the findings by Frontali *et al.*, it might be reasonable to follow all rectal cancer patients and select colon cancer patients with locally advanced disease for longer than 5 years after curative resection. Some of the data presented by Frontali *et al.* is corroborated by Kong *et al.*, however the study by Kong *et al.* lacks some granularity. Kong *et al.* concluded that surveillance can perhaps end at 15 years of follow-up but fail to provide the reader with specific patient cohorts that might benefit from a more extended follow-up protocol. Additionally, although clinicopathologic characteristics have been linked to recurrence, incorporating molecular markers for prognostic prediction, as has been applied in a wide array of cancer types (9), might improve our ability to successfully stratify patients after resection. In CRC, microsatellite instability and mutation status in *KRAS*, *NRAS*, and *BRAF* have been proposed as potential prognostic factors (10,11). Ultimately, clinicopathologic and genomic data will help guide not only adjuvant therapy

assignment but they will tailor surveillance protocols at the individual patient level.

There are a few areas where the study by Kong *et al.* is lacking some important details. The authors do not provide any information regarding neoadjuvant or adjuvant therapy. This information is important for the reader but also allows proper stratification of patients at risk for recurrence as has been previously reported (12). Additionally, the authors fail to account for the impact total mesorectal excision (TME) may have had on the outcomes of rectal cancer patients in their study. Although TME was first described in 1979, it did not become standard of care until the 2000s. TME has been shown to impact local recurrence and is a big advancement in the management of rectal cancer patients, which comprised a majority of the patient cohort in the study by Kong *et al.* Furthermore, the authors do not provide information regarding routine CEA labs or colonoscopy during follow-up, which are, in addition to routine computed tomography and physical exams, currently accepted surveillance modalities (13,14). In comparing clinicopathologic characteristics between patients surviving less than 5 years and over 15 years, the authors failed to differentiate between right- and left-sided colon cancers, which are known to have differing prognostic values (15). Additionally, the authors identified an association between tumor site and survival, however they failed to provide median overall survival and time to recurrence by tumor type. This additional data would provide more insight regarding the patient population and the inherent pathologic characteristics of the CRC cohort. Finally, and most importantly, the authors failed to discuss how recurrences in their cohort were detected. Were recurrences detected by CEA, colonoscopy, or radiographic imaging? This is an important datapoint to include in a study of long-term follow-up because it can provide insight into the optimal long-term surveillance protocol after the initial 5 years of follow-up after resection.

There is increasing evidence that select CRC patients should be followed closely past the initial 5 years of surveillance after curative resection. Unfortunately, guidelines to aid the physician in selecting patients that will benefit from prolonged follow-up are lacking. Large multi-institutional studies are needed to identify appropriate and applicable surveillance guidelines after the initial 5 years of surveillance following CRC resection.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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