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The New Screening Guidelines for Colonic Neoplasms in Patients with Cystic Fibrosis; Are They Enough?

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Editorial

Cystic fibrosis (CF) is the most common lethal autosomal inherited disease of Caucasians[1,2]. The defect in CF transmembrane conductance regulator (CFTR) results in various degrees of disrupted ion and fluid transport across epithelial cells, affecting respiratory, digestive, and reproductive systems. Manifestations includes recurrent lung/sinus infections, pancreatic insufficiency, constipation, and biliary dysfunction[1-3], with lung complications being the leading cause of morbidity and mortality in these patients[4]. Previously CF was not considered a cancer syndrome, as these patients used to haveshort life span in past and long-term complications were not studied[5]. However survival has improved, to be specific, one cohort study reported increase in the median age of survival from 31.9 years in 1990, to about 49.7 years in 2012 in cases of CF [6]. Contributing factors include early detection, better nutrition, and newer treatment options [4,6]. With increased survival now, a predisposition to digestive tract malignancies has been identified in these patients[4].

Genetic studies have suggested that CFTR is in fact a tumor suppressor gene. In one study, colonic and small intestinal tumors developed in the mice after intestinal CFTR gene was knocked off in them [7]. It is hypothesizedthat the alterationin the luminal environment caused by CFTR dysfunction leads to various changes that may ultimately lead to chronic inflammation with its related risk of cancer, since CFTR normally plays important physiologic role in various digestive tract organs[7,8]. In addition, various effects of the disease process (like deficiencies of protective vitamins) could play a role in increasing the risk for cancer [2,8]. At the same time, interestingly and for unknown reasons, the risk of melanoma is shown to be decreased in these cases, although the risk of digestive cancers is increased [3]. Abdul Karim et al. reported the first case of digestive tract cancer (biliary adenocarcinoma) in CF patient in 1982 [9]. Neglia et al. performed retrospective cohort study on over 38,000 patients with CF from national databases in the US, Canada, and Europeover a 7-year period [2], and despite no increased risk of other cancers, the risk of digestive tract cancers was significantly increased, with an observed to expected risk ratio of 6.5. In this study, most patients who developed digestive tract cancers were in their thirties and 23% of thosewere colon cancers, making colon cancer the most prevalent. Mayer et al. studied the risk in post-transplant CF patients and found a high risk of fatal colon cancer even in 3rd and 4th decades of life [10]. A study by Sheldon et al. involving 412 CF patients showed an increase in pancreatic and small intestinal cancers in these cases [5].

Therapy related immunosuppressive effect (post lung and/or liver transplant) may potentially accelerate the cancer development process in CF. A 20-year US study followed 41,188 CF patients and confirmed the risk of digestive tract cancers, particularly in post-transplant patients [3]. The observed to expected risk ratio for digestive tract cancers was 3.5 (17.3 in post-transplant patients). For the colon and small intestinal cancers analyzed separately, the observed risk was 6.2 and 11.5 (30.1 and 52.2 in post-transplant patients), respectively. Patients who had homozygous deletion mutations for F508, had the highest risk for bowel cancers compared to those with other genetic alterations in CF. This was especially high among those who held the diagnosis of distal intestinal obstruction syndrome (impaction of inspissated stool in distal intestines) which preceded cancer diagnosis by 9 years in many, but no similar increased risk was observed in association with other CF complications. Their data also showed higher frequency of cancers in right colon.

In general, colon cancer is one of the more preventable cancersin the general population through efficient screening andearly detection of premalignant adenomas and non-invasive cancers, often detected by colonoscopy, CT colonography (CTC), or other screening strategies [11,12]. Screening is advocated by the US Preventative Services Task Force to startat the age of 50 years [13], but earlier

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screening is recommended in the presence of genetic risk factors [4,12,14]. After colonoscopy irrespective of the type of indication, the risk for colon cancer has shown to be significantly reduced for up to 10 years [4,15]. Until recently, there were no recommendations for colon cancer screening in patients with CF [4]. Many studies on screening colonoscopy had exclusion criteria for CF patients with predicted FEV1<25, 40 or 50% [1,4,8]. However, these patients could be at higher risk for developing cancer because of the severity of their disease requiring organ transplantation [3].

The Minnesota Cystic Fibrosis centerhad recently recommended screening colonoscopy for their in-center CF patients starting at age 40, and they analyzed the data in 2 continuous studies [4,8]. Adenomas were found in half of their cases, with half of those being advanced adenomas. Three out of their 88 patients developed colon cancer. Surveillance of their study population revealed new adenomas in 47%, with more advanced adenomas in those previously detected. Findings suggested a high yield, even when screening was performed at 1 to 2 year intervals in these patients. This study also suggested that the adenoma progression to cancer is faster in CF. Furthermore, in additional 27 patients aged 30-39 who underwent diagnostic colonoscopy for various indications; 4 (15%) had adenomas, with one of them advanced. In this study, CF related diabetes and homozygous ΔF508 mutation were risk factors for polyp formation. Male gender, lung transplantation, and homozygous mutation were associated with advanced or multiple adenomas. This study supported early screening colonoscopybeginning at age 40 in clinically stable patients, and recommended annual surveillance colonoscopy if >3 polyps or advanced polyp were detected.

The first consensus recommendations for colorectal cancer screening in CF patients were developed in 2017 by a task-force convened by the CF foundation [16]. They recommend screening colonoscopy beginning at age 40 (30 in organ transplant recipients), with 5-year screening intervals and 3-year surveillance intervals, unless findings dictate shorter intervals. These guidelines are considered to be beneficial tomost CF patients above age 40. However, some studieshave reported colonic cancers in younger CF patients, for example, in the 3rd decade of life [17,18] and even cases of advanced cancer in 18- and 13-year olds reported by McKenna et al.[19]and Ibele et al.[20], respectively. We recently encountered a 36-year old CF patient who was found to have advanced sigmoid colonic cancer (figure coronal CT showing pancreas and sigmoid ca). Neglia et al. found many CF cases with cancer in their 3rd decade of life [2].

Newer colorectal cancer screening tests, including stool DNA testing and CT colonography (CTC), offer promise as less-invasive screening exams for CF patients [11,21]. These can be particularlymore useful for CF patientswith impaired respiratory reserve and/or with sedation or anesthesia risks preventing them from undergoing screening colonoscopy[11]. Plumb et al. studied CTCas part of national screening program in patients in whom colonoscopy was unfeasible or incomplete [11], and found it well tolerated and extremely safe. They concluded that CTC can be delivered across a national screening program. Devir et al. compared CTC to conventional colonoscopy [22], and they indicated that CTC is valuable alternative to colonoscopy with very high sensitivity and specificity for various pathologic colon findings. Some studies have reported 90-100% sensitivity of CTC in detecting colon cancer cases [23-25].

In contrast to a limited number of colonoscopy studies in patients with CF, there have been no studies evaluating use of CTC in CF patients. Thus, in our opinion, studies are needed to evaluate the utility of CTC in the younger CF population. Until then, a high index of suspicion for colorectal adenoma and cancer should be maintained in young symptomatic patients of CF. In summary, although new guidelines have recommended early screening colonoscopy for detection of colonic cancers or precancerous lesions in CF patients above age 40 years, many CF patients are unable to undergo such invasive procedures. This is particularly true for those that are considered to be at high risk forcolonoscopy and related procedure complications, and these cases are at the same time more prone to developing colonic cancers. Furthermore, many colon malignancies develop in CF patients who are younger than age 40. Therefore, more studies are needed to explore the utility of alternative screening methods like CTC and DNA stool testing with the potential of refining future screening recommendations for young CF population.

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