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Screening Strategy for Gastrointestinal and Hepatopancreatobiliary Cancers in Cystic Fibrosis

Gastrointestinal Cancer Screening in Cystic Fibrosis

Abstract

Based on systematic review and meta-analysis, the risk for developing cancers in patients with cystic fibrosis is known to be significantly greater than in the general population, including site-specific cancers of the esophagus, small bowel, colon, liver, biliary tract, and pancreas. An even higher risk has been found in patients who have severe *CFTR* genotypes or who have undergone organ transplantation and are immunosuppressed. The risk continues to rise as life expectancies steadily climb due to advancements in medical care and treatment for CF. The colorectal cancer risk is at such a high level that CF has now been declared a hereditary colon cancer syndrome by the Cystic Fibrosis Foundation. The *CFTR* gene has been strongly-associated with the development of gastrointestinal cancers and mortality in the CF population. Even CF carriers have shown an increased rate of GI cancers compared to the general population. Several limitations exist with the reported guidelines for screening of GI and hepatopancreatobiliary cancers in the CF population, which are largely universal and are still emerging. There is a need for more precise screening based on specific risk factors, including *CFTR* mutation, medical co-morbidities (such as GERD, distal intestinal obstruction syndrome, and diabetes mellitus), familial risks for each cancer, gender, age, and other factors. In this review, we propose changes to the guidelines for gastrointestinal screening of patients with CF. With the development of *CFTR*

modulators, additional studies are necessary to elucidate if there is an effect on cancer risk.

Key Words: Colorectal cancer; CFTR gene; Cystic fibrosis; Gastrointestinal cancer; Hepatopancreatobiliary cancer; Screening

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Core Tip: Patients with cystic fibrosis are at a significantly elevated risk for gastrointestinal tract and hepatopancreatobiliary cancers when compared to the general population, especially in those with severe *CFTR* mutations or who have undergone organ transplantation. As life expectancies continue to increase with *CFTR* modulators and improved care, cancer screening will become increasingly important. Screening recommendations are largely universal and still emerging. Given the financial burden of universal screening, there is a need for more precise screening based on specific risk factors. In this review, we propose changes to the guidelines for gastrointestinal screening of patients with cystic fibrosis.

INTRODUCTION

As medical care and treatment for patients with cystic fibrosis (CF) continually improve over the decades, the life expectancies for these patients have steadily increased as well. Respiratory/cardiorespiratory failure remains the leading cause of mortality in this population; however, that percentage is shrinking, decreasing from 68.1% in 2013 to 62.9% in 2019 in the United States [1,2]. This corresponds with the median age of death increasing from 27.5 years to 32.4 years in the same period [1,2]. The median predicted survival age of a newborn born in 2019 was 48.4 years (95%CI: 45.9–51.5) [2]. With the approval of the drug Trikafta®, a cystic fibrosis transmembrane conductance regulator

(CFTR) gene modulator, in 2019 by the United States Food and Drug Administration, life expectancies are predicted to increase further in the CF population. However, because of the improvements in survival, cancer and other slowly progressing diseases are emerging as causes of mortality in this population.

In the CF population, the risk of developing cancer is known to be greater than in the general population, and the average age of cancer diagnosis is lower [34]. Of those cancers, gastrointestinal cancers are typically the most common malignancies faced by individuals with CF [3,5]. As such, physicians have increasingly considered screening their CF patients for these cancers in the hopes of improving the prognosis of these patients. In 2018, recommendations on colorectal cancer screening were published in *Gastroenterology* [6]. However, these recommendations were relatively arbitrary and recommendations on other gastrointestinal cancers, such as pancreatic cancer, are lacking. In this review, we discuss the epidemiology, options for screening, the benefits and risks of screening, as well as future directions of screening for the gastrointestinal cancers.

EPIDEMIOLOGY

Globally, over 72,000 individuals are estimated to be currently living with CF [7]. Overall, the incidence of cancer in the CF population is low; however, the risk of gastrointestinal cancers in particular are increased [3]. Of the gastrointestinal cancers, colon cancer has the greatest incidence rate of 39 per 100,000 CF individuals per year; however, small bowel cancer had the greatest increase in risk compared to the general population with a standardized incidence rate of 18.94 (95%CI: 9.37–38.27) [5]. In descending order, incidence rates per 100,000 CF individuals per year are 39 for colon cancer, 13 for small bowel cancer, 5.1 for biliary tract cancer, and 1–5.8 for pancreatic cancer [5,8]. Data on the incidence rates of rectal, gastric, and esophageal cancers are lacking. The standardized incidence ratios are 18.94 (95%CI: 9.37–38.27) for small bowel cancer, 17.87 (95%CI: 8.55–37.36) for biliary tract cancer, 10.91 (95%CI: 8.42–14.11) for colon cancer, 6.18 (95%CI: 1.31–29.27) for pancreatic cancer, 4.5 (95%CI: 1.2–12.3) for

gastric cancer, 2.8 (95%CI: 0.1–13.8) for esophageal cancer, and 0.5 (95%CI: 0.0–2.6) for rectal cancer [3,5]. The insignificant difference in esophageal cancer and rectal cancer risk in the CF population is potentially due to the low number of cases reported, only one each in Maisonneuve *et al* [3]. Pancreatic cancer is uncommon in the general population as well as in the CF population. By 2018, only 12 cases of pancreatic cancer in individuals with CF have been published in the literature [8]. The incidence rates and risks of gastrointestinal cancers in CF are summarized in Table 1.

The overall frequency of cancer typically increases with age in the general population, and this remains true in the CF population. However, in a study by Maisonneuve *et al*, the difference in cancer risk of the colon and small bowel between the CF and general population appears to decrease with age from standardized incidence ratio of 23.3 in the 0–19 age group to 5.6 in the 50+ age group [3]. Still, cancer risk in the CF population remains greater than in the general population in every age group and every other demographic [3]. There is increased risk of developing cancer of the colon and small bowel in males compared to females. Additionally, individuals with severe CF genotypes (i.e., one or more class I, class II, or class III mutation in the *CFTR* gene) are at increased risk of developing colon and small bowel cancer as well [3]. In CF patients who receive solid organ transplant, predominately lung in studies, the risk of cancer in general is increased, particularly gastrointestinal cancers [3,9].

NATURAL HISTORY

The natural history of cancer in individuals with CF is unique to each type of cancer, but there are many similarities. Exposure begins at conception with either the inheritance or spontaneous formation of defective cystic fibrosis transmembrane conductance regulator (*CFTR*) genes. Individuals with either homozygous or even heterozygous defective *CFTR* genes are at increased risk of cancer [10]. While the most severe complications of CF occur in the lungs, *CFTR* is expressed in a variety of extra-pulmonary regions including the gastrointestinal tract and the accessory organs of digestion [11–13]. *CFTR* controls the movement of chloride ions, and thus, the movement

of water. In the lungs, defects in *CFTR* result in increased viscosity of mucosal secretions, leading to the classic lung-related complications of CF. In the gastrointestinal tract, a similar mechanism results in increased viscosity of the luminal secretions, causing mucosal obstruction and inflammation of the epithelium due to bacterial contact [14,15]. The resulting chronic inflammation leads to damage of epithelial cells and bacterial dysbiosis which further increases inflammation, causing cell turnover to increase which in turn increases the risk of cancer cell formation [16]. This chronic inflammation has been confirmed in both humans and mice models [17,18]. Chronic increased gastrointestinal epithelial cell turnover has been reported in individuals with CF, beginning in infancy and early childhood, potentially explaining the relatively early occurrence of cancer in the CF population [19,20].

RATIONALE FOR SCREENING OF GASTROINTESTINAL AND HEPATOPANCREATOBILIARY CANCERS

Gastrointestinal Tract

Colorectal cancer (CRC) is a major site of malignancy in the gastrointestinal tract and is associated with significant morbidity and mortality. An estimated 1.8 million new cases of CRC occur worldwide each year with about 900,000 associated deaths [21]. The annual incidence of CRC in the United States was predicted to be nearly 150,000 cases with more than 50,000 deaths in 2020 [22]. When compared to the general population, adults with CF have a 5–10 times greater risk for CRC, which further rises to a 25–30 times greater risk after solid organ transplantation [6]. Endoscopic studies have revealed that up to 50% of patients with CF will develop adenomas by age forty with 25% developing advanced and aggressive adenomas [23]. Early detection and removal of adenomatous polyps is known to reduce mortality from CRC, making surveillance of dire importance. While a broad consensus exists for colonoscopy screening of the general population based on risk factors, specific recommendations for patients with CF are not as robust and are still emerging [24].

Genetic susceptibility and inheritance are known to play a role in the development of CRC with at least one third to one half of cases involving some form of familial susceptibility. Many well-known CRC hereditary syndromes exist, such as familial adenomatous polyposis and Lynch syndrome, which are associated with CRC in up to 5–10% of cases [15,25,26]. Importantly, the full extent of the genes involved in CRC and the precise mechanisms of action are not yet fully understood. An association between CF and a familial CRC syndrome was recently found, in which high susceptibility to early and aggressive CRC was discovered in patients with homozygous inactivating mutations in the *CFTR* gene [24]. Findings like these led to CF being considered a CRC hereditary syndrome by the Cystic Fibrosis Foundation [6].

CFTR's relation to gastrointestinal cancer development is likely due to the key role throughout the entirety of the GI tract, where disruption of *CFTR* leads to alterations in the composition of gut microbiota, maintenance of the barriers that protect the epithelium, and homeostasis of both the adaptive and innate immune responses [15]. Studies have also identified *CFTR* as a tumor suppressor gene in the GI tract with deficiency of *CFTR* resulting in intestinal tumors in >60% of mice after 1 year [18]. Additionally, *CFTR* silencing has been shown to promote growth of tumors and invasion of cancer cells in mice [27]. In another study, stem cell proliferation was seen in *CFTR* knockout mice [28]. In humans with CRC, loss of *CFTR* expression has been associated with poor disease-free survival rates [18].

While the colorectal region is the most common site for GI tract malignancy with CF, all areas of the GI tract may be affected. Gastroesophageal junction and esophageal adenocarcinoma (EAC) are more prevalent among patients with CF. The exact mechanisms are not fully understood, though gastroesophageal reflux disease (GERD) is quite common with CF and is known to be the strongest modifiable risk factor for EAC. In fact, GERD is reported in up to 80% of CF patients, who are noted to have a greater degree of proximal esophageal reflux [29]. Furthermore, patients with CF have higher rates of delayed gastric emptying (up to 33%) and increased duodenogastro-esophageal reflux, which may contribute to more severe GERD [30]. Prolonged exposure

of the esophageal mucosa to both stomach acid and bile acid may result in a premalignant lesion to EAC, known as Barrett's esophagus (BE) [29,31,32]. Multiple studies have shown an increased risk for BE with CF [33], especially after liver transplantation [29,34]. One study demonstrated a 3-fold increased risk for BE and related neoplasia in adults with CF, which developed at earlier ages than the general population [29]. Development of BE has additionally been seen in children with CF [33]. The *CFTR* gene itself has been strongly linked with BE and EAC in several studies [27,29,35], including a meta-analysis of all genome-wide association studies of BE and EAC [36]. This meta-analysis identified a significantly associated risk variant in the *CFTR* gene with data suggesting a pathophysiological connection between CF, GERD, BE, and EAC [36]. At this time, recommendations for BE and EAC screening in the CF population are lacking.

Hepatopancreatobiliary System

The relation of *CFTR* and development of other GI cancers, including the hepatopancreatobiliary system, has been elucidated as well. CF liver disease (CFLD) has a prevalence around 23% with a range from 2–62%, increasing linearly with age from 3.7% at age 5 to 32.2% at age 30 [37,38]. A significant proportion of CF patients develop cirrhosis by the second decade of life, meaning that by the time a patient has reached their third or fourth decade of life, they could have developed cirrhosis for 20–30 years. CFLD has become an increasingly important finding as patients with CF are living longer due to excellent pulmonary care, antimicrobial regimens, improved nutrition, and the clinical use of *CFTR* modulators [37,38]. The pathogenesis of CFLD involves expression of abnormal *CFTR* on the biliary epithelium, leading to thicker and less alkaline bile that accumulates in the biliary system. This further leads to fibrosis and subsequent cirrhosis, occurring over a period of years. Longstanding cirrhosis is a risk factor for development of hepatocellular carcinoma (HCC) [39,40] one of the most common malignancies worldwide with an incidence of up to 600,000 yearly cases [41]. Chronic hepatitis B and C infections account for up to 80% of HCC cases [39].

Statistically, HCC in CFLD is a relatively uncommon finding, but has been described in some case reports with a poor prognosis [39,40,42,43].

Early detection and diagnosis of HCC is primarily completed with use of imaging. Ultrasonography remains the first-line screening tool for HCC with recommendations for bi-annual liver ultrasounds from both the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Disease (AASLD).

Ultrasound is cost-effective and easy to perform; however, studies have revealed around 60% sensitivity, 90% specificity, and a positive predictive value of 70% [40,44]. Bi-annual monitoring of serum alpha-fetoprotein (AFP) levels have also been suggested in patients with CF [39,40], though official statements do not exist regarding this recommendation. Serum AFP is a widely used biomarker for prognostication of HCC and has even been shown to be a strong predictor of mortality in patients with cirrhosis and HCC. In patients with cirrhosis, systematic reviews have demonstrated sensitivities and specificities ranging from 41–66% and 80–94%, respectively. This indicates that the monitoring with serum AFP alone may not be sufficient for HCC screening; however, it is likely beneficial when combined with ultrasonography [45].

Pancreatic cancer is considered one of the most lethal and difficult to treat malignancies with a poor prognosis [46]. While the risk of pancreatic cancer remains low, this risk is increased 6-fold in patients with CF compared to the general population. Still, only 12 cases of pancreatic cancer in CF patients have been published in the literature as of 2018 [8,46–53]. The majority of pancreatic cancers are thought to be sporadic, though up to 10% may be attributed to genetic factors. Chronic pancreatitis has a clear association with neoplastic transformation related to long-standing inflammation. Absence of the *CFTR* protein results in impaired secretion of bicarbonate and chloride. Mutation in the *CFTR* gene is a strong risk factor for development of chronic pancreatitis, increasing the risk for pancreatic adenocarcinoma [46].

Screening for malignancies of the biliary tree and pancreas may be difficult in patients with CF. Fortunately, cholangiocarcinoma and pancreatic cancer are rare with about 5.1 cases and 1–5.8 cases per 100,000 CF cases, respectively [5,8]. Carbohydrate-19-9 antigen

(CA-19-9) is generally considered a sensitive marker for several GI malignancies, including cholangiocarcinoma and pancreatic cancer [54]. Some CF recommendations advocate for hepatopancreatobiliary cancer screening every 1–3 years after 40 years of age depending on if organ transplantation has been completed. Screening may include laboratory testing (serum CA-19-9) or imaging studies (abdominal or endoscopic ultrasound and magnetic resonance cholangiopancreatography (MRCP) [5]. Patients with CF have shown to experience non-specific elevations in serum CA-19-9 Levels, with volumes up to 500 U/mL (reference range 0–37 U/mL) [55–58]. Some sources have linked increased serum CA-19-9 Levels with active CF-related liver disease [54] and pulmonary exacerbation [57,59–61]. CA-19-9 has a 20% false-positive rate as a screening test and the serum level may also be elevated with other conditions, including an increased production of sputum, diabetes, chronic kidney failure, and infections. For these reasons, an elevated CA-19-9 Level alone may not be enough to justify additional expensive and unnecessary investigations [56]. The false-positivity rate, financial burden of testing, and unknown age to begin the screening has made the surveillance for pancreaticobiliary malignancies more difficult in the CF population.

CFTR Carriers

Approximately 3–4% of the US population (10 million people) are heterozygous carriers of *CFTR* gene mutations. Though these patients do not have CF, they see somewhat similar changes with an increased risk for malignancies and other CF-related conditions [15]. One study found that the prevalence of GI cancers in CF carriers was increased by 44% when compared to the general population, including cancer of the stomach, GI tract, pancreas, and other GI organs [10,15]. These findings indicate that deficiency in *CFTR* likely has a large impact on malignancies and may affect first-degree relatives who are heterozygous carriers. Additional studies are required to further elucidate the association between *CFTR* and malignancy, in addition to the effect of *CFTR* modulators on this risk.

GUIDELINES FOR SCREENING OF GASTROINTESTINAL CANCERS

The reported guidelines for gastrointestinal cancer screening in the CF population mostly stem from a ³ 20-year-long epidemiological study using the US CF Registry data. The risk of all types of gastrointestinal cancers was increased, including a 6-fold increase in CRC compared with the predicted age-adjusted risk in the general population ^[3]. A more recent systematic review and meta-analysis study from 2018 demonstrated even higher standardized incidence ratios ⁵ for these cancers and found that those with CF who had received a solid organ transplantation had a 2–5 times increased risk of gastrointestinal cancer development compared to those who did not ^[5]. Furthermore, larger and more aggressive colonic polyps were found in individuals with CF ^[5]. The risk is also increased for cancers of the gastroesophageal junction, biliary tract, and small intestine. Table 2 highlights the current strategy for screening the gastrointestinal system for cancer in patients with CF. The age at the time of cancer diagnosis was often not known in these CF cases, making implementation of the data for screening more challenging. Above all, these studies were performed before use of CFTR modulators was initiated.

GASTROINTESTINAL CANCER SCREENING

The majority of epidemiologic studies reported the incidence of cancer in the colon more than any other gastrointestinal site. Early colon screening in adult individuals with CF demonstrated that, by their fourth decade, approximately 50% had developed adenomas, half of which were already aggressive and advanced ^[23,24]. In fact, adenocarcinoma of the colon was present in 3% of the study population. The risk is even greater in the CF population who have undergone solid organ transplantation. In non-transplanted CF cases, the risk for small intestinal and colon cancer ¹ was particularly elevated in patients reported to have previously had distal intestinal obstruction syndrome (9 observed *vs* 0.8 expected; SIR = 11.2, 95% CI = 5.5 to 20.5). The diagnosis of distal intestinal obstruction syndrome preceded that of bowel cancer on average by 9 years ^[3]. For other prior gastrointestinal conditions or CF complications,

including GERD, gallbladder disease, liver disease, CF-related diabetes, or nasal polyps, the risk of developing intestinal cancers was not higher. The risk of bowel cancer following transplantation was higher in CF patients, particularly those with a homozygous F508del mutation and those with more severe *CFTR* genotypes. The transplantation data was analyzed for two separate time periods because more post-transplant cancers were reported during the period from 2000 to 2009 than during the period from 1990 to 1999. When comparing these two time periods, no difference in standardized incidence ratios was reported.

Colonoscopy is currently the preferred CRC screening method compared to imaging studies, such as virtual colonoscopy, or fecal occult blood testing. In addition, tumors were more frequently detected in the right colon in both non-transplanted and transplanted CF cases than in the general population. Therefore, flexible sigmoidoscopy is an inappropriate method for screening. Colonoscopy should be recommended in all patients with CF by age 40 with 5-year screening and 3-year surveillance intervals (unless a shorter interval is indicated by individual findings). In immunocompromised or transplanted patients, CRC screening should be initiated by age 30^[3,6], within 2 years of transplantation, given the additional risk for CRC associated with immunosuppression^[6].

HEPATOPANCREATOBILIARY CANCER SCREENING

The risks of biliary tract and pancreatic cancers were reported to be slightly increased in CF cases compared with the general population. For example, there was an increase in biliary tract cancer (4 observed *vs* 0.4 expected; SIR = 11.4, 95% CI = 3.6 to 27.4)^[3]. A screening strategy for pancreatobiliary cancer would include magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound, or abdominal ultrasound and measurement of a tumor marker level (CA-19-9) (Table 2). This screening method has been applied from the experience of screening cholangiocarcinoma in patients with primary sclerosing cholangitis and pancreatic cancer in individuals with a history of hereditary pancreatic cancer.

The recommendation for screening is suggested to start at age 40 with 2–3 year screening intervals (Table 2). The cost-effectiveness of these approaches needs further investigation before implementation [6,14]. Due to the increased risk for biliary tract and pancreatic cancers following transplantation, screening of these organs should be initiated. Further assessment is needed to determine whether or not to begin screening CF cases who are on immunosuppression following transplantation at a younger age (i.e., 30 years), like with CRC screening. However, since decreased immune surveillance may increase cancer risk, ² the Cystic Fibrosis Foundation Task Force specifies that screening for colorectal cancer should begin within 2 years of transplant or even before transplant to ensure that additional surgical comorbidities exist. The pathogenesis of pancreatobiliary cancer in patients with CF cases remains unclear, but multiple hypotheses exist, including gut dysbiosis. Other risks to consider include medical history of inflammatory bowel disease or primary sclerosing cholangitis, family history of pancreatic cancers (hereditary pancreatitis), and frequent exposure to radiation (i.e., x-rays and CT scans).

CONCLUSION

Increased risks of digestive tract cancer are site-specific and variable with pre-existing history or risk factors. The risk is specifically greater in individuals with severe *CFTR* genotypes and in those with immunosuppression following organ transplantation. Although many case reports of cancers in children and young adults exist, there is currently no evidence for screening of gastrointestinal cancers in children with CF or before their fourth decade of life without definite risk factors. The role of precision screening may be reasonable, considering the financial burden of universal screening. The development of *CFTR* modulators, mainly to treat CF pulmonary disease, has also shown beneficial effects on other organs affected by dysfunction of *CFTR* protein and perhaps may reduce gastrointestinal cancer risks. The impact of the longer life expectancy and *CFTR* modulator usage needs further collaborative research studies to develop strategic cancer screening in the CF population.

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