Leading Article

Gastrointestinal Cancers in Cystic Fibrosis

Megan W France[1] and Scott C Bell, MBBS, MD, FRACP[1,2,3]
[1]Adult Cystic Fibrosis Centre, Department of Thoracic Medicine, The Prince Charles Hospital; [2]Queensland Children's Medical Research Institute; [3]School of Medicine, University of Queensland, Brisbane, QLD, Australia

CML – Cystic Fibrosis 2014;4(1):1–14.

There are an estimated 70 000 people with cystic fibrosis (CF) globally, with the vast majority in Caucasian populations. Over the past 30 years, CF has been transformed from a predominantly fatal disease in children and young adults to one in which its greatest impact is borne in adult life [1,2]. In many countries, CF adults now outnumber CF children as a result of improved therapies in children and increased life expectancy of adults, resulting in the need to re-structure CF care systems and the development of adult specialist care centers [3,4].

The median survival of patients with CF in most parts of the world is close to 40 years of age, and even those patients with advanced airflow obstruction (percent predicted forced expiratory volume in 1 s <30%), which was previously thought to forebode a high risk of death within 2 years, now generally have prolonged survival [5]. For those patients with end-stage lung disease and their families, lung transplantation provides the opportunity and hope of enhanced survival [6]. Despite such developments, the vast majority of patients with CF will die as a result of progressive respiratory failure and the complications of suppurative lung disease [7].

Alongside enhanced life expectancy, a number of new complications in the management of patients with CF have emerged, and are now seen on a daily basis in adult CF clinics. These include CF-related diabetes, metabolic bone disease, chronic renal impairment, multiple drug allergies and intolerances, multi-drug resistant pulmonary infections, and complications of long-term vascular access devices including thrombosis of large vessels [8,9]. Consequently, the management of adults in CF specialist centers has become increasingly complex, further complicated by the rapidly growing adult CF population. Malignancy remains an uncommon event; however, it is yet another emerging complication in the CF adult population.

In the US in 2011, out of a total CF population of 27 213, there were 220 patients who underwent a lung transplant, seven a liver transplant, and seven a renal transplant [3]. In the UK, where the CF patient population was 9749 in 2011, 47 patients had lung transplants

(including four heart–lung transplants), two patients had liver transplants, and another two patients had renal transplants (one of whom also had a pancreas transplant) [4]. Survival after lung transplantation has improved significantly since the early 1990s, yet death from bronchiolitis obliterans syndrome (BOS) and related complications remains common [10,11]. There are a number of approaches to reduce the incidence and progression of BOS, including the use of higher levels of immunosuppression than are generally used in recipients of other solid organ transplants [12,13]. Complications of long-term immunosuppressive therapy include chronic renal insufficiency, enhanced risk of infection, and malignancy [9,11].

Gastrointestinal (GI) complications are protean in children and adults with CF. Detailed reviews of each of these are beyond the scope of this article but are extensively discussed elsewhere [14–17]. Importantly, pancreatic insufficiency is a complication in the vast majority of patients with CF, and is often associated with nutrient malabsorption and under-nutrition [17]. Effective exocrine pancreatic enzyme replacement has contributed to improved nutritional status of patients with CF over the past two to three decades. Recurrent distal intestinal obstruction syndrome (DIOS), chronic constipation, bacterial overgrowth, gastroesophageal reflux disease (GERD), and hepatobiliary complications (including biliary cirrhosis, cholelithiasis, and biliary stenosis) are also frequently encountered in CF. Patients who have at least one mild CF transmembrane regulator (CFTR) protein mutation (approximately 15% of most CF populations) often have pancreatic sufficiency, and this is usually associated with better nutritional status than pancreatic insufficiency but can lead to recurrent acute pancreatitis resulting from some preservation of pancreatic tissue. Acinar ductal obstruction can also result in recurrent acute pancreatitis [18,19].

Each of these GI complications of CF may not only enhance the risk of the development of both GI and hepatobiliary malignancies in the person with CF, but may also lead to delays in diagnosis of GI malignancy when chronic, and often life-long, GI symptoms co-exist [20–23].

Many CF patients (especially males) aged >30 years are overweight [4,24]. The combination of obesity, diabetes, and, in some patients, chronic renal insufficiency may in the future contribute to more lifestyle diseases (including malignancy) in the aging CF population.

In this article, we aim to review the literature relating to cancer in patients with CF, with a particular focus on GI malignancies, especially colon cancer, for which the evidence is greatest. We will discuss why GI malignancies might occur and examine the evidence for potential risk factors and the role of screening in "at-risk" populations – including older age groups and those being assessed for, or who have undergone, lung and/or liver transplants – within the CF population.

Terminology

Two large cohort studies based on data from the US-based CF Patient Registry (CFPR) have reported cancer risk using standardized incidence ratios (SIRs), a measure of relative risk defined as the ratio between the number of cancers observed to the number of cancers expected [25,26]. The expected numbers were determined from the Surveillance, Epidemiology, and End Results program of the US National Cancer Institute [26].

Rare cancers in a small population (e.g. in the CF population), in which risk of cancer can appear high (large SIR), may provide evidence for an increased risk but yet affect only a very small number of individuals (e.g. cholangiocarcinoma or small intestine cancers). One approach to mitigate this effect is to calculate absolute risk rates over 20 years, for example the ratio between the number of cancers observed in the cancer group between 1990 and 2009 and the number of patients with CF for whom data were available between 1990

and 2009. However, there are limitations to this approach, as the crude risk is likely to be an underestimate given that not all patients will have been followed for 20 years (i.e. some patients will have entered the cohort after 1990 and others may have left the cohort before 2009). As these details are not published, the use of the calculation of absolute risk from CFPR data is not practical [25,26]. It is important to recognize that reliable estimates of absolute rates of cancer would allow for a good estimate of the extent of the risk of very rare cancers.

Non-GI malignancy

The data to support the observation of an increased risk of non-GI cancers in patients with CF remain mixed. Early studies, including case series and cohort studies, suggested that there was an increased rate of malignancy in general, and specifically of leukemia, testicular cancer, and endocrine cancers including thyroid cancer [27,28]. Subsequently, Neglia et al., using a case–control study design involving more than 38 000 patients from two CF cohorts (one from Europe and one from North America), revealed similar risks of non-GI malignancy in CF patients when compared with the general population [29]. In a similar analysis of CFPR data, the numbers of cancers observed in transplanted and non-transplanted patients with CF were compared with the number expected from population-based cancer incidence data and, from 202 999 person-years of observation of non-transplanted patients with CF, 75 cancers were observed compared with the expected number of 70 cases (SIR 1.1, 95% confidence interval [CI] 0.8–1.4) [25]. In a more recent analysis, Maisonneuve and colleagues followed 41 188 patients in the US from 1990 to 2009 and compared the observed number of cancers in non-transplanted and transplanted patients with that expected in the general US population [26]. From 344 114 patient-years of observation of patients who had not undergone any organ transplants, the overall cancer risk in CF patients was similar to the background risk (SIR 1.1, 95% CI 1.0–1.3). However, the study demonstrated an increased risk of testicular cancer (SIR 1.7, 95% CI 1.0–2.7) and lymphoid leukemia (SIR 2.0, 95% CI 1.2–3.1), and, interestingly, a decreased risk of malignant melanoma (SIR 0.4, 95% CI 0.2–0.9) in CF patients compared with the general population.

The two studies by Maisonneuve and colleagues demonstrated increased rates of cancer in patients with CF who had undergone transplantation compared with those who had not [25,26]. The earlier study, published in 2003, reported that 26 tumors were observed compared with the expected 9.6 (SIR 2.7, 95% CI 1.8–3.9) from 8235 patient-years of observation [25]. Similarly, in the more recent analysis published in 2013, 13 cancers were observed compared with the expected 2.1 (SIR 6.3, 95% CI 3.4–10.8) from 2725 person-years in 1063 transplanted patients [25,26]. In the absence of accurate estimates of absolute risk of cancer in post-transplant CF patients, it is not possible to estimate the extent of increased risk post-transplant compared with CF patients who have not undergone an organ transplant.

Screening of skin for malignant and pre-malignant lesions during transplant assessment is recommended, especially in climates where skin cancers are prevalent [30–32]. Urogynecological malignancy requires careful screening and monitoring in females, both at assessment for transplant and following transplantation [33]. In a large cohort of 166 females from Sydney, NSW, Australia, who had undergone lung transplantation in 1989–2001, there were significant increases in the incidences of cervical intraepithelium neoplasia (CIN) I and pre-cancerous cervical epithelial changes (CIN III; 42.2 per 1000 and 30.0 per 1000, respectively) compared with a large reference population (8.3 per 1000 and 6.2 per 1000, respectively) [34]. Human papillomavirus vaccination is advocated (and funded) for adolescents in many healthcare settings globally to reduce the risk of cervical and uro-gynecological cancers.

Post-transplant lymphoproliferative disorder

The immunosuppressive therapy setting increases the general risk of malignancy [31,35]. Additionally, patients who have not been exposed to Epstein–Barr virus (EBV) infection and who receive EBV-positive organs have a significantly increased risk of developing post-transplant lymphoproliferative disease (PTLD) following a seroconversion illness [32]. PTLD is the most common post-transplant malignancy in children and the second most common, after skin cancer, in adults [36]. T cell suppression causes increased proliferation of viruses such as EBV and cytomegalovirus, resulting in B cell proliferation and malignancy [37].

PTLD is further increased in the lung transplantation setting because of higher levels of immunosuppression compared with other organ transplants [36]. A review of 705 post-lung transplantation patients in the US from 1991 to 2001 revealed 34 (4.8%) cases with PTLD [37]. The median time from transplant to diagnosis of PTLD was 11 months (range 11 days to 15 years). Symptoms at presentation were non-specific but included fatigue, pain, loss of body weight, anemia, raised creatinine levels, and abnormal liver function tests. PTLD involving the GI tract was most common in patients aged >11 months post-transplant. Eight patients developed PTLD of the GI tract with six of these presenting with GI symptoms such as diarrhea, nausea, dysphagia, or GI bleeding [37]. Sites of involvement included the small intestine (n=4), colon (n=2), stomach (n=1), and esophagus (n=1). Thus, any new GI symptoms in a post-transplant patient should be investigated by a clinician and PTLD considered as the cause.

GI malignancy

In a study based on CFPR data from 1990 to 1999, non-transplant patients with CF had a significantly increased risk of cancers of the GI tract (SIR 5.1, 95% CI 3.2–7.6) [25]. The mean age at diagnosis was 39 years, with one patient diagnosed before the age of 20 years. An excess absolute risk of 153 per 100 000 patients per year for patients aged 40–49 years, and 401 per 100 000 patients per year for those aged >50 years, highlights the risk of GI cancer in aging patients with CF. Previously, GI disorders were not associated with an increased risk of GI cancer in CF.

In their follow-up analysis, Maisonneuve et al. reported an elevated risk of digestive tract cancer in patients with CF (SIR 3.5, 95% CI 2.6–4.7) [26]. Similarly, the risk of digestive tract cancers was particularly high in CF patients who underwent a transplant (SIR 17.3, 95% CI 10.7–26.5), with most cases arising in the colon [25].

Luminal GI malignancy

Esophageal and gastric malignancy

There is an increased risk of esophageal and gastric malignancies in CF; however, there are no detailed case reports in the literature. Maisonneuve et al. described five esophago-gastric malignancies (two esophageal and three gastric) over 20 years and across 344 114 patient-years of observation in CF patients who had not undergone a transplant, giving an SIR of 3.1 (95% CI 1.1–6.8) [26].

It is likely that GERD has a significant role in the etiology of gastroesophageal cancers. This is supported by recent reports of the anatomical location of these malignancies. Three cases of gastric cancer were described that were located at the gastroesophageal junction, and the esophageal malignancies were associated with Barrett's esophagus and also located at the gastroesophageal junction [26]. GERD is a well-recognized and frequent complication of CF owing to cough and therapies such as prednisolone. GERD may contribute to the increased occurrence of esophageal malignancy. Barrett's esophagus is considered to be a pre-malignant lesion, with an estimated annual transition rate of 0.12–0.5% [38].

The diagnosis of gastric and esophageal malignancies can be challenging in light of the frequency of GERD symptoms. Epigastric pain, nausea, vomiting, and

difficulty with maintaining body weight are common issues in patients with CF, and overlap with the presenting symptoms of these malignancies. Clinicians should consider upper GI endoscopies if symptoms are persistent or poorly responsive to therapy, or if alarm symptoms, such as persistent dysphagia and unexplained weight loss, are present.

Surgical resection may be hazardous in patients with even moderate lung disease, and many tumors will not be amenable to surgery. Chemotherapy presents substantial challenges by increasing the frequency and severity of infective exacerbations. Radiotherapy is likely to be similarly challenging from a pulmonary and nutritional perspective.

The increased incidence of esophageal and gastric malignancy in CF patients post-transplantation is likely multifactorial. There is a very high incidence of GERD in CF patients post-transplantation, and this is one likely explanation for the greatly increased incidence of gastroesophageal malignancies seen post-transplantation by Maisonneuve et al. [26]. In the post-transplant setting, high doses of prednisolone and other agents, such as tacrolimus, contribute to the greatly increased incidence of GERD in patients with CF, which is increasingly being managed by fundoplication. Additionally, immunosuppression itself contributes to the increased risk of malignancy [31]. The SIR for gastroesophageal cancers is 13.2 (95% CI 2.2–43.8) and the SIR specifically for esophageal cancers is 35.8 (95% CI 6.0–118.0) [26]. Vigilance is required when investigating any persistent upper GI symptoms in CF patients post-transplant.

Small intestine malignancy

Small intestine malignancy represents only 1% of digestive organ cancers in the general population [39]. There is a significant increase in the risk of adenocarcinoma of the ileum in CF [26]. Five cases of small intestine malignancy were described between 1982 and 1995 [39–43], and these findings were supported by the more recent data from Maisonneuve et al., who determined an SIR of 11.5 (95% CI 4.2–25.4) for carcinoma of the small intestine [26].

The rarity of small intestine malignancy in the general population has been postulated to be related to the rapid transit times of gut material leading to short contact time for potential carcinogens with the mucosa [39]. There are also effective local immune defenses and an alkaline pH, which may retard carcinogenesis, alongside mucosal enzymes that destroy some carcinogens [39]. Some theories also cite the lack of bacteria in the small intestine as potentially reducing the production of carcinogens from gut material. In CF, it has been postulated that slower small intestinal transit times, altered bowel flora, and raised fecal bile acid concentrations may contribute to an increased risk of malignancy [39,41]. Furthermore, patients with malabsorption from other causes are known to be predisposed to small intestine malignancy [39].

Presenting symptoms are often non-specific but may include abdominal pain and nausea with vomiting [44]. This often leads to delayed diagnosis and the presence of late-stage disease when diagnosis is confirmed.

The management of small intestine malignancy is surgical, with minimal evidence to support adjuvant therapy, including chemotherapy or radiotherapy [44]. When chemotherapy is considered, the regimens are usually based upon those used for colon carcinoma.

A significant increase in the incidence of small intestine tumors is seen in CF patients post-transplantation – Maisonneuve et al. report an SIR of 52.5 (95% CI 8.8–175) [26]. Again, abdominal symptoms in a post-transplant patient with CF should be investigated carefully.

Large intestine malignancy

Numerous case reports suggest there are increased rates of colonic malignancy in patients with CF. Neglia and colleagues reported increased rates of colonic malignancy in two cohorts, one from Europe (CF patients registered in 1992) and one from North America (CF patients registered

Figure 1. A 52-year-old woman with cystic fibrosis who had a colonic adenocarcinoma diagnosed after a routine colonoscopy during an assessment for transplantation. Computed tomography shows a semi-annular infiltrative mass at the splenic flexure (black arrow) and multiple hepatic metastases (gray arrow).

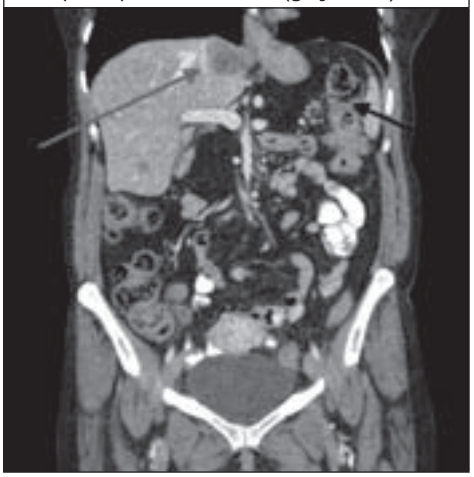
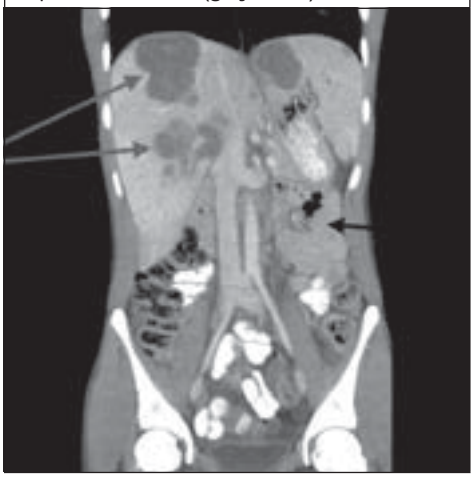


Figure 2. A 26-year-old man with cystic fibrosis who presented with several months of loss of body weight and anorexia. Thickening of the descending and sigmoid colon is noted (black arrow) on computed tomography with large hepatic metastases (gray arrow).



between 1985 and 1992) [29]. The European cohort demonstrated an increased odds ratio for colon cancer of 9.3 (95% CI 3.5–25.0). In a large follow-up study, the SIR for colon cancer was 7.4 (95% CI 3.7–13.2) [25]. This study also examined those patients who had undergone transplantation and the SIR for these patients was estimated to be 30.3 (95% CI 3.7–109.0). The wide confidence intervals reflect a smaller number of cases and the historical nature of data from the 1990s, as noted for many of the cancers discussed earlier in this review.

The more recent registry analysis provides further data to support the earlier studies, using a larger observation set over 20 years. Between 1990 and 2009, the risk of colon cancer in CF increased (SIR 6.2, 95% CI 4.2–9.0) but the risk of rectal cancer did not (SIR 0.7, 95% CI 0.1–2.3) [26]. Two interesting additional findings were reported for colon cancer risk. Firstly, there were higher SIR estimates in males with CF (SIR 8.4, 95% CI 5.4–12.4) compared with females with CF (SIR 4.6, 95% CI 2.2–8.3). Secondly, the increase in SIR was clearly seen in the CF population aged ≥30 years but was not significantly greater than the general population for the 20–29-years age group. While the SIR was highest in the <20-years age group, the number of cases in this age group was very small. This study also updated estimates of the risks post-transplantation of developing bowel cancer (SIR 30.1, 95% CI 15.8–52.2) [26].

How does this compare with other scenarios in which increased risks of bowel cancer would be expected and have been reported? The reported SIRs for the risks of bowel cancer for patients with ulcerative colitis (UC) is 4.1 (95% CI 2.7–5.8), for patients with Crohn's disease is 2.5 (95% CI 1.7–3.5), and for patients with celiac disease is 1.6 (95% CI 0.7–3.0) [45–47]. Furthermore, this compares with an SIR of 2.2 (95% CI 2.1–2.4) for an individual with any first degree family history of colon cancer, and an SIR of 2.0 (95% CI 1.8–2.3) for an individual with a sibling with colon cancer [48].

The increased risk of common cancers in CF patients with lung transplants has also been reported for other solid-organ transplant (including liver and kidney) CF recipients. The SIRs are lower than those reported above, suggesting that the

Figure 3. Hematoxylin and eosin stain at ×100 magnification shows invasive tumor (black arrow) and luminal necrosis within malignant glands (gray arrow). Luminal necrosis is a characteristic feature of colonic adenocarcinoma.

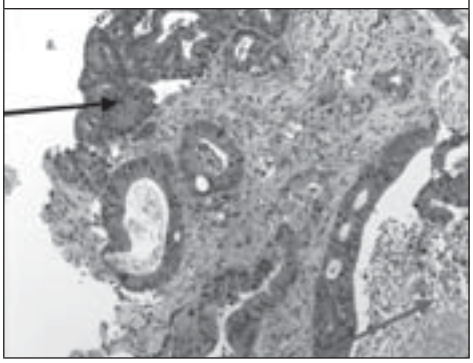
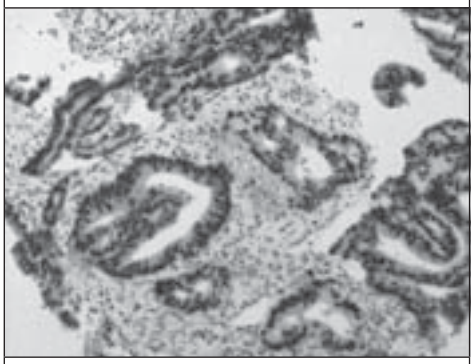


Figure 4. Immunohistochemical stain of colonic biopsy for MSH6 MMR protein, which shows positivity in the tumor nuclei (i.e. no loss of staining); therefore, the MMR proteins are expressed and probably functioning, and not, or very unlikely to be, indicative of an MSI-H tumor status.



MMR: mismatch repair; MSH6: MutS homolog 6 *(Escherichia coli)*; MSI-H: microsatellite instability-high.

combination of pre-existing risk (underlying CF-related disease) within the setting of long-term high-level immunosuppression may account for the increased risk [26,31,35,49–51].

While several potential factors have been suggested, the pathogenic mechanisms underlying the increased risk colon cancer in CF is unknown. Colon cancer is more common in patients with CF who are homozygous for the ΔF508 mutation, while those who are heterozygous for the ΔF508 mutation have an intermediate risk, and those who do not have the ΔF508 mutation have the lowest risk [25]. This was not as clearly demonstrated in the follow-up study by Maisonneuve et al.; while SIR rates were reported, the rates for non-ΔF508 patients were similar to those for ΔF508-homozygous patients [26].

An association between mucin (*MUC*) genes and the development of GI malignancies has been postulated [52]. Mucin glycoprotein production is influenced by *MUC* gene expression and it is postulated that mucins may play a role in CF [53–55]. Linkage analyses have demonstrated that the *CFTR* gene is found in the chromosome band adjacent to the *MUC3*, *MUC11*, and *MUC12* genes [25]. It has been suggested that decreased expression of these three *MUC* genes may explain the increased risk of colon cancers and other GI malignancies in patients with CF.

Persistent GI epithelial inflammation in UC is thought to be a contributing factor to increased rates of GI cancer, especially cancer of the colon. GI tract inflammation occurs in patients with CF and may also be a factor in the development of GI malignant disease [56]. The consequences of the accumulation of toxic bile salts and the administration of pancreatic enzymes may also be factors, though these potential mechanisms are speculative [57]. Similarly, the presence of an abnormal GI microbiome, which may include ingested airway bacteria and altered bowel flora under intense antimicrobial pressure, requires further study [58].

A diagnosis of colon cancer can be delayed in the person with CF for a number of reasons including the low index of suspicion because of the relatively young age of the patient and the overlap of symptoms with previous GI diagnoses (e.g. recurrent DIOS or severe constipation); these may distract the clinician from considering a new and more sinister diagnosis (**Figures 1– 4**) [21,23].

Once a diagnosis of colon cancer is made, careful consideration of the appropriate management, including standard screening,

should be undertaken in order to stage the tumor and then plan treatment. Surgery is the treatment of choice to attempt cure (and to perform surgical staging) although incurable disease has commonly been reported. Prevention of bowel obstruction by the tumor should be considered in a standard manner. However, the co-existence of chronic pulmonary infection is likely to influence the course of recovery if chemotherapy is required for treatment of the cancer. Chemotherapy for consolidation and for palliation should be considered although complications of chemotherapy are common, especially their impact on lung infections.

There are currently limited reports detailing survival rates for colon cancer in patients with CF. Five-year survival rates for large intestine malignancies are dramatically lower in solid-organ transplant recipients suggesting that, in this setting, tumors are biologically more aggressive than in the general population [59]. This analysis, based on the Israel Penn International Transplant Tumor Registry, indicates that for several common cancers (including colon, non-small-cell lung cancer, breast cancer, prostate cancer, bladder and kidney cancers, and melanoma), transplant patients have worse cancer-specific survival rates than the general population. This study demonstrated that transplantation and tumor stage at diagnosis had the most significant negative impacts on survival. The extent to which immunosuppression and other pre-existing comorbidities (such as the indication that leads to organ transplant) contribute to the worse outcome is not known. Decreasing the level of immunosuppression cautiously is standard management in patients in whom the allograft function is stable.

Hepatobiliary malignancy

Hepatocellular carcinoma

Three detailed case reports of hepatocellular carcinoma (HCC) in CF patients have been documented, with the first case published in 2004 [60]. All occurred in young patients (aged 18 years, 32 years, and 34 years, respectively) with co-existent macronodular cirrhosis, and all were found to have new hepatic lesions detected on ultrasound computed tomography (CT) scans of the abdomen [60–62]. Two of the patients had the lesions discovered after routine scanning of their livers, and the other patient's lesion was found during an investigation for fatigue, abdominal pain, and substantial loss of body weight. Maisonneuve et al. reported a small increase in the risk of HCC in patients with CF (SIR 1.5, 95% CI 0.3–5.1) [26].

Chronic liver disease and cirrhosis are known risk factors for HCC in the general population, suggesting that patients with CF who have macronodular cirrhosis are at an increased risk of HCC. CF-associated liver disease (CFLD) is characterized by macronodular cirrhosis and portal hypertension, occurs in 5–10% of patients with CF, and typically peaks in adolescence and progresses slowly in adult life [15].

There are some potential diagnostic challenges for HCC in the setting of CF given the frequent occurrence of non-specific abdominal symptoms. A new lesion, or growth of an existing lesion within the cirrhotic liver, should prompt further investigation by modalities such as contrast-enhanced CT or magnetic resonance imaging (MRI). Consultation with a hepatologist is indicated, a tissue biopsy should be obtained, and a discussion with the local liver transplantation service should be considered.

Management of an HCC in a CF patient can be challenging. Single lesions <3 cm in diameter may be considered for surgical resection, although this may not be practical for patients in whom there is evidence of portal hypertension and severe lung disease [63]. Liver transplantation may be considered, although the severity of lung disease may well preclude this in many patients with CF. Image-guided tumor ablation may be considered for early-stage HCC. Patients with large lesions or multifocal lesions may be considered for trans-catheter tumor treatment with chemotherapeutic agents, embolic particles, or radioactive materials.

For advanced HCC, an orally administered multikinase inhibitor (sorafenib) with antiproliferative and antiangiogenic activity may slow disease progression [63]. One case report of CF and HCC details therapy with sorafenib that was well-tolerated, with only a marginal increase in size at 21 months after diagnosis [62].

Surveillance for HCC needs to be heightened as the risk of liver malignancy has been documented to be raised above expected levels in post-transplant CF patients [26]. In the review by Maisonneuve et al. of malignancy in post-transplant patients with CF in the US over 20 years, two liver tumors were seen post-transplant, giving an SIR of 11.3 (95% CI 0.6–55.4).

Cholangiocarcinoma

Although cholangiocarcinomas are rare in the general population, their incidence is significantly increased in the CF population. There are three case reports of cholangiocarcinoma in CF in the literature, with right upper quadrant pain, weight loss, and abnormal liver function tests identified as common presenting features [40,63,64]. Maisonneuve et al. calculated an SIR of 11.4 (95% CI 3.6–27.4) for gallbladder malignancy and cholangiocarcinoma [26].

Risk factors for cholangiocarcinoma in the general population include primary biliary sclerosis, hepatolithiasis, gallbladder polyps, obesity, infectious liver diseases, non-infectious chronic liver disease such as cirrhosis, calcification of the gallbladder wall, and congenital abnormalities of the biliary tree [66]. There is a strong link between hepatolithiasis and cholangiocarcinoma [67]. It is thought that recurrent damage to the epithelium of the ductal structures predisposes individuals to cholangiocarcinoma.

CFTR is highly expressed in the biliary tree, and important for alkalinizing bile and maintaining the solubility of bile components. A case series of five CF patients with hepatolithiasis, a complication of cholangiocarcinoma, was reported [65]. The authors postulated that protein malnutrition may produce a decrease in bile glucaro-1:4-lactone, an inhibitor of bacterial β-glucuronidase. An increase in activity of this enzyme leads to increased deconjugation of bilirubin and results in lithogenesis. Only 14 cases of hepatolithiasis in CF had been reported prior to this series.

MR cholangiopancreatography (MRCP) may be required if a high clinical suspicion of cholangiocarcinoma exists, as some of the patients described in the case reports presented with normal liver function tests and an unremarkable appearance of the biliary tree on ultrasound scan [66]. Treatment options, including surgical resection and radiation, are usually limited by the frequently advanced nature of this malignancy at diagnosis. Treatment in the setting of CF is likely to be determined by co-existent liver and pulmonary disease.

A case report was published in 2008 describing a patient with CF and post-transplant cholangiocarcinoma [66]. Maisonneuve et al. demonstrated a particularly high incidence of gallbladder malignancy and cholangiocarcinoma post-transplantation, with an SIR of 31.9 (95% CI 1.6–159) [26].

Pancreatic cancer

Several cases of pancreatic adenocarcinoma in patients with CF have been reported [68–71]. Most of the patients presented with epigastric or right upper quadrant pain [72]. Importantly, not all of the patients had abnormal liver function tests at the time of diagnosis. In most of the cases, an ultrasound scan of the abdomen revealed a mass within the pancreas. A case of mucinous cystadenocarcinoma in a long-standing pancreatic cyst in a young woman has also been reported [73]. Interestingly, Maisonneuve et al. identified no substantially increased risk of pancreatic cancer in their non-transplanted cohort (SIR 0.8, 95% CI 0.0–4.2] [26].

Chronic pancreatitis has been reported as a risk factor for pancreatic adenocarcinoma [74]. *CFTR* mutations (a

CF carrier state) have also been described as increasing the risk of pancreatic adenocarcinoma [75].

The presenting symptoms of pancreatic cancer often overlap with many of the abdominal symptoms that are frequently seen in patients with CF. Loss of body weight, epigastric pain, nausea, vomiting, and lethargy are frequently seen at presentation. Ultrasound scans will often reveal a mass, although MRI or MRCP may be the investigations of choice.

Management of pancreatic cancer is challenging, with many tumors diagnosed at an advanced stage and only a minority amenable to surgical resection. The suitability of radiotherapy or chemoradiotherapy is dependent upon the severity of co-existent lung disease.

One case report of an 18-year-old CF female with pancreatic adenocarcinoma post-lung transplantation has been documented [76]. At 6 years post-transplant, recurrent episodes of cholestasis were noted and a CT scan of the abdomen showed an enlarged pancreatic head. A Whipple's procedure was performed and the patient survived for an 8-month period postoperatively before succumbing to metastatic disease. Recently, a similar case was seen in our CF center (The Prince Charles Hospital, Brisbane, QLD, Australia).

Screening for GI malignancy

Large intestine screening

The strongest evidence base to support screening for GI malignancy exists for large intestine malignancy. Screening for bowel cancers in the general population reduces the incidence and mortality of colorectal cancer. Various tests are available to identify and allow for the removal of pre-cancerous lesions (polyps) and early occult cancers. Early bowel cancer detection generally relies on stool-based tests such as the fecal occult blood test (FOBT), fecal immunochemical tests, and stool DNA testing. The guaiac FOBT (guaiac refers to the coating of α-guaiaconic acid on the FOBT cards) reduce mortality by 15–33% in randomized controlled trials and may reduce incidence if polyps are detected and subsequently removed [77–79].

The sensitivity of the FOBT is increased by repeat testing, and a positive test should lead to a colonoscopy being performed, but concerns about adherence to both follow-up FOBT and colonoscopy remain. Other stool tests have unresolved issues that prevent their routine clinical use, including the required number of stool samples per patient, the sample processing methods, which of the commercially available tests is superior, and cost-effectiveness [79].

Structural examinations by direct visualization with colonoscopy or sigmoidoscopy, or by imaging with barium enemas or CT colonography, have been shown to be effective for the detection of adenomas and have the potential to result in cancer prevention. Their disadvantages include high upfront costs, and the need for bowel preparation and hospital attendance for the examination. The US Preventive Services Task Force (USPSTF) recently made extensive recommendations for screening for colorectal cancer [80]. The USPSTF recommends screening using FOBT, sigmoidoscopy, or colonoscopy, beginning at 50 years of age and continuing until 75 years of age [80]. A comprehensive description of the risks and benefits are provided in the Task Force recommendations. The USPSTF concludes that there is insufficient evidence at present to assess the role of CT colonoscopy or fecal DNA testing as screening tools [80]. Areas of uncertainty, in addition to the optimum screening investigation, include the age at which to start screening, particularly when considering sex and race differences, the age at which to stop screening, and the approach needed for detection of "flat adenomas" [77].

A beneficial role of screening for colorectal cancer in CF is unproven, and false-positive FOBTs can be anticipated in many patients because of small sample volumes and even occult hemoptysis. A beneficial role of colonoscopy screening is also unproven although, in some centers, all patients

aged >40 years are offered this procedure. The age and indication for screening of patients being assessed for, and following, lung transplantation are unclear; however, colonoscopy is increasingly becoming part of the transplantation assessment process. This is likely to become a more important issue as the age of patients undergoing transplantation increases [9]. Reporting on a single-center series, Meyer and colleagues noted that four patients developed bowel cancer in the CF post-transplant cohort (n=70), all presenting with advanced disease, compared with just one of 287 transplant recipients with indications other than CF [21]. They reported that of 20 patients with CF who underwent screening colonoscopies, 35% had colonic polyps, highlighting the need to consider surveillance of this high-risk cohort following transplantation, and for further multicenter studies to confirm these findings. Our experience suggests that standard bowel preparation is frequently inadequate because of retention of stool adherence to the bowel mucosa limits vision during colonoscopy, and so more intense preparation of the bowel is now a routine in order to reduce the need for repeat procedures. The beneficial role of CT colonography is also unproven in patients with CF; it requires an adequate level of colon preparation and delivers a large dose of radiation.

In their latest report, Maisonneuve et al. recommend a targeted approach to screening for bowel cancer in CF patients pre-transplant as the background absolute risk is low, but they suggest screening for higher-risk groups, including those CF patients with inflammatory bowel disease and those who have undergone lung transplantation [26]. If there is a strong family history of bowel cancer, consideration for an earlier procedure could also be made. Of the 425 adults with CF managed at our center since January 2001, we have diagnosed six bowel cancers in five patients and we advocate considering a colonoscopy as the primary screening investigation for polyp and colorectal cancer detection in patients with CF >40 years of age or those preparing for a transplantation listing at an earlier age. We also advocate a low threshold for patients with persistent and /or atypical GI symptoms.

Screening for other GI cancers

Given the frequency of upper GI symptoms in patients with CF and the low incidence rates of esophageal and gastric malignancies, it is difficult to make recommendations regarding screening for these cancers in the general CF population. Patients with persistent and unexplained upper GI symptoms, including GERD, should be investigated with upper GI endoscopy. Any patient with Barrett's esophagus should be screened for esophageal adenocarcinoma according to local gastroenterologist advice. Surveillance for Barrett's esophagus in the general population is dependent upon histopathology and is reviewed elsewhere [81].

Regular examination of the abdomen is advised in adults with CFLD [82]. Annual liver function tests and coagulation profiles are recommended in patients with CF [15]. An annual ultrasound scan and α-fetoprotein test is also recommended in patients with cirrhosis in order to screen for HCC. There is no evidence to support CT or MRI in screening programs for the general population (or for patients with CF) with cirrhosis [83].

There is little evidence to support screening for pancreatic cancer in the general population because of the low incidence of the tumor, the difficulties in successfully treating the malignancy, and the lack of a low-cost, high-sensitivity, and high-specificity screening test [84]. Endoscopic ultrasound and MRI are suggested if clinical suspicion of pancreatic cancer is high.

The paucity of literature and relative rarity makes recommendations for screening for small intestine malignancy and biliary malignancy difficult. Persistent symptoms should be assessed on an individual basis.

Potential risk of cancer due to lifetime radiation exposure

Increased lifespan, and more aggressive treatments and investigations has inevitably

increased lifetime exposure to radiation for patients with CF. The mean cumulative effective radiation dose per patient in a CF center in Ireland increased over 17 years from 0.39 mSv in the early- to mid-1990s to 1.67 mSv in the mid- to late-2000s [85]. This was associated with an almost six-fold increase in the number of CT scans performed per patient (predominantly thoracic and abdominal). This is an important consideration as median survival rates rise, and imaging is being performed earlier, in young children with CF (albeit now using lower radiation protocols) [86].

CFTR carrier status and malignancy

The association between *CFTR* mutant carrier status and disease has been reported for recurrent acute pancreatitis, male infertility, chronic rhinosinusitis, and idiopathic bronchiectasis [87–91]. Several studies have suggested that being a *CFTR* mutant gene carrier may increase, or even decrease, the rates of certain cancers [74, 91–94]. The role of *CFTR* mutant carrier status in pancreatic cancer has been reported to vary from an increased risk to no impact. In the 1990s, after the initial description of a possible link between leukemia and CF, a study by Padua et al. failed to confirm any link between *CFTR* mutant gene carriage and leukemia [92]. Unconfirmed and sometimes contradictory results have been reported regarding the association between *CFTR* mutant carrier status and lung cancer, breast cancer, pancreatic cancer, thyroid cancer, and malignant melanoma [74,91–94]. Similar to many association studies, interpretation is influenced by the size of the population studied and the lack of replicated and confirmatory studies.

Owing to a lack of evidence, there appears to be little role for screening for common cancers in people who are known to be *CFTR* mutant gene carriers. Similarly, there is no role for screening of patients with these cancers for evidence of a *CFTR* gene mutation.

Conclusion

There is an increased risk of GI malignancies in people with CF, and this is especially high for some types of GI malignancy, including tumors of the esophago-gastric region, small intestine, colon, and biliary tree. Clinicians need to consider these risks as the median age of people living with CF continues to increase. Immunosuppression further increases the risk of malignancy and, hence, transplant physicians need to be especially vigilant in managing CF patients with persistent GI symptoms following transplantation.

Acknowledgments: We are grateful to Dr Kayla Tran for the provision of the histology images of colon cancer in one of our patients. We are also grateful to Dr Rob Ware, Queensland Children's Medical Research Institute, for support with statistical advice, and to all members of the multi-disciplinary team at The Prince Charles Hospital who provide excellence in clinical care to our patients. Family consent (next of kin) has been provided to utilize imaging and histology photographs.

Disclosures: The authors have no relevant financial interests to disclose.

Address for correspondence: MW France, Adult Cystic Fibrosis Centre, Department of Thoracic Medicine, The Prince Charles Hospital, Rode Road, Chermside, 4032, Brisbane, QLD, Australia. Email: megan_france@health.qld.gov.au

References

1. Buzzetti R, Salvatore D, Baldo E et al. An overview of international literature from cystic fibrosis registries: 1. Mortality and survival studies in cystic fibrosis. *J Cyst Fibros* 2009;8:229–37.
2. Dodge JA, Lewis PA, Stanton M et al. Cystic fibrosis mortality and survival in the UK: 1947–2003. *Eur Respir J* 2007;29:522–6.
3. Cystic Fibrosis Foundation. *Patient Registry 2011 Annual Data Report*. Bethesda, MD: Cystic Fibrosis Foundation, 2012.
4. Cystic Fibrosis Trust. *UK CF Registry Annual Data Report 2011*. Bromley, UK: Cystic Fibrosis Trust, 2013.
5. George PM, Banya W, Pareek N et al. Improved survival at low lung function in cystic fibrosis: cohort study from 1990 to 2007. *BMJ* 2011;342:d1008.
6. Meachery G, De Soyza A, Nicholson A et al. Outcomes of lung transplantation for cystic fibrosis in a large UK cohort. *Thorax* 2008;63:725–31.
7. O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet* 2009;373:1891–904.
8. Simmonds NJ, Cullinan P, Hodson ME. Growing old with cystic fibrosis – the characteristics of long-term survivors of cystic fibrosis. *Respir Med* 2009;103:629–35.
9. Plant BJ, Goss CH, Plant WD et al. Management of co-morbidities in older patients with cystic fibrosis. *Lancet Respir Med* 2013;1:164–74.
10. Inci I, Stanimirov O, Benden C et al. Lung transplantation for cystic fibrosis: a single center experience of 100 consecutive cases. *Eur J Cardiothorac Surg* 2012;41:435–40.
11. Thabut G, Christie JD, Mal H et al. Survival benefit of lung transplant for cystic fibrosis since lung allocation score implementation. *Am J Respir Crit Care Med* 2013;187:1335–40.
12. Neuringer IP, Noone P, Cicale RK et al. Managing complications following lung transplantation. *Expert Rev Respir Med* 2009;3:403–23.

13. Braun AT, Merlo CA. Cystic fibrosis lung transplantation. *Curr Opin Pulm Med* 2011;17:467–72.
14. Rowland M, Bourke B. Liver disease in cystic fibrosis. *Curr Opin Pulm Med* 2011;17:461–6.
15. Debray D, Kelly D, Houwen R et al. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. *J Cyst Fibros* 2011;10(Suppl. 2):S29–36.
16. Colombo C, Ellemunter H, Houwen R et al. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. *J Cyst Fibros* 2011;10(Suppl. 2):S24–8.
17. Gelfond D, Borowitz D. Gastrointestinal complications of cystic fibrosis. *Clin Gastroenterol Hepatol* 2013;11:333–42; quiz e30–1.
18. Gilljam M, Ellis L, Corey M et al. Clinical manifestations of cystic fibrosis among patients with diagnosis in adulthood. *Chest* 2004;126:1215–24.
19. Ooi CY, Durie PR. Cystic fibrosis transmembrane conductance regulator (*CFTR*) gene mutations in pancreatitis. *J Cyst Fibros* 2012;11:355–62.
20. Hernandez-Jimenez I, Fischman D, Cheriyath P. Colon cancer in cystic fibrosis patients: is this a growing problem? *J Cyst Fibros* 2008;7:343–6.
21. Meyer KC, Francois ML, Thomas HK et al. Colon cancer in lung transplant recipients with CF: increased risk and results of screening. *J Cyst Fibros* 2011;10:366–9.
22. Brown JA, Chaun H, Mason AC. Delayed diagnosis of colon carcinoma in cystic fibrosis. *Clin Radiol* 2000;55:240–2.
23. Chaun H, Paty B, Nakielna EM et al. Colonic carcinoma in two adult cystic fibrosis patients. *Can J Gastroenterol* 1996;10:440–2.
24. Cystic Fibrosis Australia. Cystic Fibrosis in Australia 2011. *14th Annual Report from the Australian Cystic Fibrosis Data Registry.* Baulkham Hills, NSW: Cystic Fibrosis Australia, 2012.
25. Maisonneuve P, FitzSimmons SC, Neglia JP et al. Cancer risk in nontransplanted and transplanted cystic fibrosis patients: a 10-year study. *J Natl Cancer Inst* 2003;95:381–7.
26. Maisonneuve P, Marshall BC, Knapp EA et al. Cancer risk in cystic fibrosis: a 20-year nationwide study from the United States. *J Natl Cancer Inst* 2013;105:122–9.
27. Sheldon CD, Hodson ME, Carpenter LM et al. A cohort study of cystic fibrosis and malignancy. *Br J Cancer* 1993;68:1025–8.
28. Neglia JP, Wielinski CL, Warwick WJ. Cancer risk among patients with cystic fibrosis. *J Pediatr* 1991;119:764–6.
29. Neglia JP, FitzSimmons SC, Maisonneuve P et al. The risk of cancer among patients with cystic fibrosis. Cystic Fibrosis and Cancer Study Group. *N Engl J Med* 1995;332:494–9.
30. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. Management of skin cancer in solid organ transplant recipients. *J Am Acad Dermatol* 2011;65:263–79; quiz 80.
31. Hall EC, Pfeiffer RM, Segev DL et al. Cumulative incidence of cancer after solid organ transplantation. *Cancer* 2013;119:2300–8.
32. Robbins HY, Arcasoy SM. Malignancies following lung transplantation. *Clin Chest Med* 2011;32:343–55.
33. Dugue PA, Rebolj M, Garred P et al. Immunosuppression and risk of cervical cancer. *Expert Rev Anticancer Ther* 2013;13:29–42.
34. Malouf MA, Hopkins PM, Singleton L et al. Sexual health issues after lung transplantation: importance of cervical screening. *J Heart Lung Transplant* 2004;23:894–7.
35. Kasiske BL, Snyder JJ, Gilbertson DT et al. Cancer after kidney transplantation in the United States. *Am J Transplant* 2004;4:905–13.
36. Parker A, Bowles K, Bradley JA et al. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients – BCSH and BTS guidelines. *Br J Haematol* 2010;149:675–92.
37. Kremer BE, Reshef R, Misleh JG et al. Post-transplant lymphoproliferative disorder after lung transplantation: a review of 35 cases. *J Heart Lung Transplant* 2012;31:296–304.
38. Pohl H, Wrobel K, Bojarski C et al. Risk factors in the development of esophageal adenocarcinoma. *Am J Gastroenterol* 2013;108:200–7.
39. Samuels LE, Amrom G, Kerstein MD. Adenocarcinoma of the ileum in a patient with cystic fibrosis. *Dig Dis Sci* 1995;40:107–8.
40. Abdul-Karim FW, King TA, Dahms BB et al. Carcinoma of extrahepatic biliary system in an adult with cystic fibrosis. *Gastroenterology* 1982;82:758–62.
41. Redington AN, Spring R, Batten JC. Adenocarcinoma of the ileum presenting as non-traumatic clostridial myonecrosis in cystic fibrosis. *Br Med J (Clin Res Ed)* 1985;290:1871–2.
42. Roberts JA, Tullett WM, Thomas JS et al. Bowel adenocarcinoma in a patient with cystic fibrosis. *Scott Med J* 1986;31:109.
43. Siraganian PA, Miller RW, Swender PT. Cystic fibrosis and ileal carcinoma. *Lancet* 1987;2:1158.
44. Halfdanarson TR, McWilliams RR, Donohue JH et al. A single-institution experience with 491 cases of small bowel adenocarcinoma. *Am J Surg* 2010;199:797–803.
45. Karlen P, Lofberg R, Brostrom O et al. Increased risk of cancer in ulcerative colitis: a population-based cohort study. *Am J Gastroenterol* 1999;94:1047–52.
46. Jess T, Gamborg M, Matzen P et al. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. *Am J Gastroenterol* 2005;100:2724–9.
47. Card TR, West J, Holmes GK. Risk of malignancy in diagnosed coeliac disease: a 24-year prospective, population-based, cohort study. *Aliment Pharmacol Ther* 2004;20:769–75.
48. Butterworth AS, Higgins JP, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. *Eur J Cancer* 2006;42:216–27.
49. Nishihori T, Strazzabosco M, Saif MW. Incidence and management of colorectal cancer in liver transplant recipients. *Clin Colorectal Cancer* 2008;7:260–6.
50. Parnaby CN, Barrow EJ, Edirimanne SB et al. Colorectal complications of end-stage renal failure and renal transplantation: a review. *Colorectal Dis* 2012;14:403–15.
51. Sint Nicolaas J, de Jonge V, Steyerberg EW et al. Risk of colorectal carcinoma in post-liver transplant patients: a systematic review and meta-analysis. *Am J Transplant* 2010;10:868–76.
52. Byrd JC, Bresalier RS. Mucins and mucin binding proteins in colorectal cancer. *Cancer Metastasis Rev* 2004;23:77–99.
53. Harris A, Reid C. Cystic fibrosis and mucins. *J Med Genet* 1998;35:82–3.
54. Kim YS, Ho SB. Intestinal goblet cells and mucins in health and disease: recent insights and progress. *Curr Gastroenterol Rep* 2010;12:319–30.
55. Johansson ME, Sjövall H, Hansson GC. The gastrointestinal mucus system in health and disease. *Nat Rev Gastroenterol Hepatol* 2013;10:352–61.
56. Werlin SL, Benuri-Silbiger I, Kerem E et al. Evidence of intestinal inflammation in patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2010;51:304–8.
57. Degirolamo C, Modica S, Palasciano G et al. Bile acids and colon cancer: solving the puzzle with nuclear receptors. *Trends Mol Med* 2011;17:564–72.
58. Zhu Q, Gao R, Wu W et al. The role of gut microbiota in the pathogenesis of colorectal cancer. *Tumour Biol* 2013;34:1285–300.
59. Miao Y, Everly JJ, Gross TG et al. *De novo* cancers arising in organ transplant recipients are associated with adverse outcomes compared with the general population. *Transplantation* 2009;87:1347–59.
60. McKeon D, Day A, Parmar J et al. Hepatocellular carcinoma in association with cirrhosis in a patient with cystic fibrosis. *J Cyst Fibros* 2004;3:193–5.
61. Kelleher T, Staunton M, O'Mahony S et al. Advanced hepatocellular carcinoma associated with cystic fibrosis. *Eur J Gastroenterol Hepatol* 2005;17:1123–4.
62. O'Donnell DH, Ryan R, Hayes B et al. Hepatocellular carcinoma complicating cystic fibrosis related liver disease. *J Cyst Fibros* 2009;8:288–90.
63. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012;379:1245–55.

64. Tesluk H, McCauley K, Kurland G et al. Cholangiocarcinoma in an adult with cystic fibrosis. *J Clin Gastroenterol* 1991;13:485–7.
65. Perdue DG, Cass OW, Milla C et al. Hepatolithiasis and cholangiocarcinoma in cystic fibrosis: a case series and review of the literature. *Dig Dis Sci* 2007;52:2638–42.
66. Naderi AS, Farsian FN, Lee WM. Cholangiocarcinoma after lung transplantation in a patient with cystic fibrosis. *Eur J Gastroenterol Hepatol* 2008;20:1115–7.
67. Lee CC, Wu CY, Chen GH. What is the impact of coexistence of hepatolithiasis on cholangiocarcinoma? *J Gastroenterol Hepatol* 2002;17:1015–20.
68. Davis TM, Sawicka EH. Adenocarcinoma in cystic fibrosis. *Thorax* 1985;40:199–200.
69. Tedesco FJ, Brown R, Schuman BM. Pancreatic carcinoma in a patient with cystic fibrosis. *Gastrointest Endosc* 1986;32:25–6.
70. McIntosh JC, Schoumacher RA, Tiller RE. Pancreatic adenocarcinoma in a patient with cystic fibrosis. *Am J Med* 1988;85:592.
71. Tsongalis GJ, Faber G, Dalldorf FG et al. Association of pancreatic adenocarcinoma, mild lung disease, and ΔF508 mutation in a cystic fibrosis patient. *Clin Chem* 1994;40:1972–4.
72. Rittenhouse DW, Talbott VA, Anklesaria Z et al. Subject review: pancreatic ductal adenocarcinoma in the setting of mutations in the cystic fibrosis transmembrane conductance regulator gene: case report and review of the literature. *J Gastrointest Surg* 2011;15:2284–90.
73. Oermann CM, Al-Salmi Q, Seilheimer DK et al. Mucinous cystadenocarcinoma of the pancreas in an adolescent with cystic fibrosis. *Pediatr Dev Pathol* 2005;8:391–6.
74. Lowenfels AB, Maisonneuve P, Cavallini G et al.; International Pancreatitis Study Group. Pancreatitis and the risk of pancreatic cancer. *N Engl J Med* 1993;328:1433–7.
75. McWilliams RR, Petersen GM, Rabe KG et al. Cystic fibrosis transmembrane conductance regulator (*CFTR*) gene mutations and risk for pancreatic adenocarcinoma. *Cancer* 2010;116:203–9.
76. Petrowsky H, Schuster H, Irani S et al. Pancreatic cancer in cystic fibrosis after bilateral lung transplantation. *Pancreas* 2006;33:430–2.
77. Lieberman D. Colon cancer screening and surveillance controversies. *Curr Opin Gastroenterol* 2009;25:422–7.
78. Whitlock EP, Lin JS, Liles E et al. Screening for colorectal cancer: a targeted, updated systematic review for the US Preventive Services Task Force. *Ann Intern Med* 2008;149:638–58.
79. Levin B, Lieberman DA, McFarland B et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008;134:1570–95.
80. Whitlock EP, Lin J, Liles E et al. Screening for colorectal cancer: an updated systematic review. Rockville (MD): Agency for Healthcare Research and Quality; 2008 Oct. Report No.: 08-05-05124-EF-1.
81. Evans JA, Early DS, Fukami N et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. *Gastrointest Endosc* 2012;76:1087–94.
82. Sokol RJ, Durie PR; Cystic Fibrosis Foundation Hepatobiliary Disease Consensus Group. Recommendations for management of liver and biliary tract disease in cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1999;28(Suppl. 1):S1–13.
83. Verslype C, Rosmorduc O, Rougier P. Hepatocellular carcinoma: ESMO–ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;23(Suppl .7):vii41–8.
84. Seufferlein T, Bachet JB, Van Cutsem E et al. Pancreatic adenocarcinoma: ESMO–ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;23(Suppl. 7):vii33–40.
85. O'Connell OJ, McWilliams S, McGarrigle A et al. Radiologic imaging in cystic fibrosis: cumulative effective dose and changing trends over 2 decades. *Chest* 2012;141:1575–83.
86. Tiddens HA, Stick SM, Davis S. Multi-modality monitoring of cystic fibrosis lung disease: the role of chest computed tomography. *Paediatr Respir Rev* 2013 Jul 2; Epub ahead of print.
87. Yu J, Chen Z, Ni Y et al. *CFTR* mutations in men with congenital bilateral absence of the vas deferens (CBAVD): a systemic review and meta-analysis. *Hum Reprod* 2012;27:25–35.
88. Gonska T, Choi P, Stephenson A et al. Role of cystic fibrosis transmembrane conductance regulator in patients with chronic sinopulmonary disease. *Chest* 2012;142:996–1004.
89. Bombieri C, Claustres M, De Boeck K et al. Recommendations for the classification of diseases as CFTR-related disorders. *J Cyst Fibros* 2011;10(Suppl. 2):S86–102.
90. Cohn JA, Neoptolemos JP, Feng J et al. Increased risk of idiopathic chronic pancreatitis in cystic fibrosis carriers. *Hum Mutat* 2005;26:303–7.
91. Feuillet-Fieux MN, Lenoir G, Sermet I et al. Nasal polyposis and cystic fibrosis (CF): review of the literature. *Rhinology* 2011;49:347–55.
92. Padua RA, Warren N, Grimshaw D et al. The cystic fibrosis ΔF508 gene mutation and cancer. *Hum Mutat* 1997;10:45–8.
93. Oh IH, Oh C, Yoon TY et al. Association of *CFTR* gene polymorphisms with papillary thyroid cancer. *Oncol Lett* 2012;3:455–61.
94. Southey MC, Batten L, Andersen CR et al. CFTR ΔF508 carrier status, risk of breast cancer before the age of 40 and histological grading in a population-based case–control study. *Int J Cancer* 1998;79:487–9.
95. Son JW, Kim YJ, Cho HM et al. Promoter hypermethylation of the *CFTR* gene and clinical/pathological features associated with non-small cell lung cancer. *Respirology* 2011;16:1203–9.