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RESEARCH ARTICLE

Clinical Characteristics and Specific Management Considerations in Children With Cystic Fibrosis and Childhood Cancer: Case Series and Review of the Literature

Jaques van Heerden[1] | Bénédicte Brichard[2] | Dries Ruttens[3] | Stijn Verhulst[4] | Katleen Balliauw[5] | Nicolette Moes[6] | Hilde Dotremont[7] | Anne Uyttebroeck[3] | Joris Verlooy[8] | Toon Van Genechten[8] | Liesbeth Vanheeswijck[8] | Kim Van Hoorenbeeck[4] | Machiel van den Akker[8]

[1]Department of Paediatric Haemato-Oncology, MIPRO Laboratory, Antwerp University Hospital, University of Antwerp, Antwerp, Belgium | [2]Department of Paediatric Oncology and Haematology, Cliniques Universitaires St Luc, Brussels, Belgium | [3]Department of Paediatric Haematology and Oncology, University Hospitals Leuven, Leuven, Belgium | [4]Lab of Experimental Medicine and Paediatrics, University of Antwerp and Department of Paediatric Pulmonology, Antwerp University Hospital, Antwerp, Belgium | [5]Pharmacy Department, Antwerp University Hospital, Antwerp, Belgium | [6]Department of Gastro-Enterology, Antwerp University Hospital, Antwerp, Belgium | [7]Department of Paediatric Endocrinology, Antwerp University Hospital, Antwerp, Belgium | [8]Department of Paediatric Haemato-Oncology, Antwerp University Hospital, Antwerp, Belgium

Correspondence: Jaques van Heerden (Jaques.vanheerden@uza.be)

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ABSTRACT

Background: Cystic fibrosis (CF) is an autosomal recessive inherited chronic disorder that predisposes adults to gastrointestinal malignancies. The latter has not been observed in children, perhaps due to the limited documentation of the copresentation of childhood cancer in CF. The following review will provide a comprehensive overview of the relevant literature on this subject.

Methodology: The objective of this study was to identify cases in Belgium over a 25-year period and to review the literature for similar cases. Our secondary objective was to identify areas of attention during oncological management based on the clinical cases and extant literature.

Results: Four cases were diagnosed in Belgium and a further 10 cases were identified in the literature. These fourteen cases exhibited a 1:1 male-to-female ratio. Four cases were hematological malignancies, and 10 cases were solid tumors, predominantly neuroblastomas and osteosarcomas. No specific age group predominated at the time of diagnosis of the malignancy. As the literature indicated that organs were at risk in all systems, at increased risk for treatment toxicities, and a need for increased nutritional and antimicrobial support. The threshold for intervention with supportive care should be substantially lower than in non-CF patients. These patients are predisposed to an increased risk for premature morbidity and mortality.

Conclusion: Short and long-term CF-specific survivorship care plans should be developed based on both disease entities in anticipation of compounded risks for early cardio-respiratory disease and an increased awareness of secondary cancer screening. Research into the copresentation of these diseases should be promoted.

Abbreviations: B-ALL, B-cell acute lymphoblastic leukemia; CF, cystic fibrosis; CFLD, cystic fibrosis-related liver disease; CFTR, cystic fibrosis transmembrane conductance regulator; CFRD, cystic fibrosis-related diabetes; DIOS, distal intestinal obstruction syndrome; DKA, diabetic ketoacidosis; GI, gastrointestinal; PERT, pancreatic enzyme replacement therapy; PTLD, posttransplant lymphoproliferative disease; PwCF, persons with cystic fibrosis.

Kim Van Hoorenbeeck and Machiel van den Akker contributed equally as the last authors.

1 | Introduction

Cystic fibrosis (CF) is an autosomal recessive inherited disorder affecting the CF transmembrane conductance regulator (CFTR) protein, causing a chronic, life-limiting damage to the lungs, pancreas, and other gastrointestinal and endocrine organs [1]. Impairment of the transport over the *CFTR*-channel leads to dysregulated hydration and pH levels in the mucosal surfaces and epithelial secretions [1]. Complications include impaired mucus clearance from the lungs, facilitating pulmonary colonization and bacterial infection [1]. The incidence of CF is one in 2500 to 3500 in Caucasian groups, one in 17,000 in black ethnic groups, and one in 31,000 in Asiatic groups [2, 3].

The dysregulation of the *CFTR*-gene and, consequently the transcellular transportation of substances, increases the predisposition to cancerous transformation of colorectal, pancreatic, and respiratory malignancies [4]. Furthermore, the chronic inflammation and the dysregulated immune response create a pro-oncogenic environment [4]. Mutations in the *CFTR* gene have been linked to an increased risk of various cancers, because *CFTR* gene functions as a tumor suppressor, and its dysfunction can lead to carcinogenesis through several mechanisms, including epigenetic silencing and dysregulation of signaling pathways [5]. This connection is present in both persons with CF (PwCF) and heterozygous carriers of *CFTR* mutations [6].

In general, the incidence of malignancies in PwCF is similar to that in the general population and the risk is even lower for malignant melanoma [7, 8]. The malignancies associated with CF that have a higher incidence, such as breast cancer, colorectal cancer, and pancreatic tumors, are primarily found in adults [8]. Historical data suggest that PwCF do not have an elevated overall cancer risk, but adult PwCF do demonstrate a threefold to sixfold increased risk of developing malignancies of the gastrointestinal tract [9, 10]. This risk significantly increases when receiving a lung transplant due to the need for immunosuppressive medication [9, 10].

Childhood cancer is a heterogeneous group of malignancies [11]. Unlike adult tumors, childhood malignancies often originate from primordial or embryonic cells and may involve somatic or germline mutations, often being associated with syndromes [11]. The global age-standardized incidence rate of childhood cancer is 10.5 per 100,000 children under 18 years, or one in 9524 children [12]. The incidence of childhood cancer in children living with CF is not documented. The calculated synchronous cumulative incidence of CF and childhood cancer is one in 23,810,000 for Caucasian children, one in 161,908,000 for black children, and one in 295,244,000 for Asian children. A case series from Austria identified 11 cases of malignancy in 229 patients followed at a CF center over a 24-year period, of whom three were below the age of 18 years [13]. A study conducted in the United Kingdom reported that 5% of PwCF who develop cancer are children [14].

When a child is diagnosed with cancer and has a comorbidity, careful assessment of their overall health and organ function is a crucial consideration during cancer treatment. Medication interactions, polypharmacy, and increased toxicity risks must be monitored, and multidisciplinary coordination should ensure balanced management of both the malignancy and any coexisting conditions [15]. Due the low incidence of malignancies in PwCF, especially in children, there is little known regarding the effect of CF, oncological diagnoses, and the management of both disease entities on each other [15] as well as the prevention of further deterioration of CF during management to prevent death [16].

The aim of this descriptive case series was to evaluate the characteristics of children with CF developing pediatric malignancies in Belgium and in the literature and to provide practical overview in the diagnosis, treatment, and follow-up of these children.

2 | Methodology

All Belgian pediatric oncology units were invited to include PwCF under the age of 18 years diagnosed with pediatric tumors between 2000 and 2024. Data on both the CF and oncological management were sourced. Individual consent was granted to use patient data.

A comprehensive literature search was conducted via PubMed, Google Scholar, Web of Science, and Researchgate as well as gray literature and reference screening of identified articles (Figure 1). There were no restrictions on language or publication date. The search used the keywords "cystic fibrosis" AND "childhood cancer" or "tumor"; "cystic fibrosis" AND "cancer" AND "child"; and/or "adolescent" and/or "infant" (Table S1). Inclusion criteria included case reports, case series, reviews, and research studies that included cases or discussions of synchronous childhood cancer and CF topics. Records were excluded if the articles only discussed synchronous adult cancer and CF topics and cases. Additional cases were identified by consulting cited references of the identified articles. Since the incidence of synchronous childhood cancer and CF is low, the decision was taken to select all articles containing at least one pediatric case based on the title and abstract. From a total of 122,632 records identified, 13 records containing one or more pediatric CF synchronous cancer case were included.

According to institutional policies, ethical approval was not required for this retrospective case series. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent for publication of clinical details was obtained from the patients and/or their legal guardians. All identifying information has been anonymized.

3 | Results

3.1 | Case Presentations in Belgium

In the 24-year period under consideration, only four Belgian children under medical care for CF developed a childhood malignancy. Table 1 shows the characteristics of all four cases.

In 2009, an 11-month-old male was diagnosed with embryonal hepatoblastoma with pulmonary metastasis. The patient was identified as a PwCF through neonatal screening and confirmed with genetics at 1 month. In 2019, a 16-year-old male was diagnosed with embryonal carcinoma of his right testis. The patient was diagnosed with CF at the age of four after developing

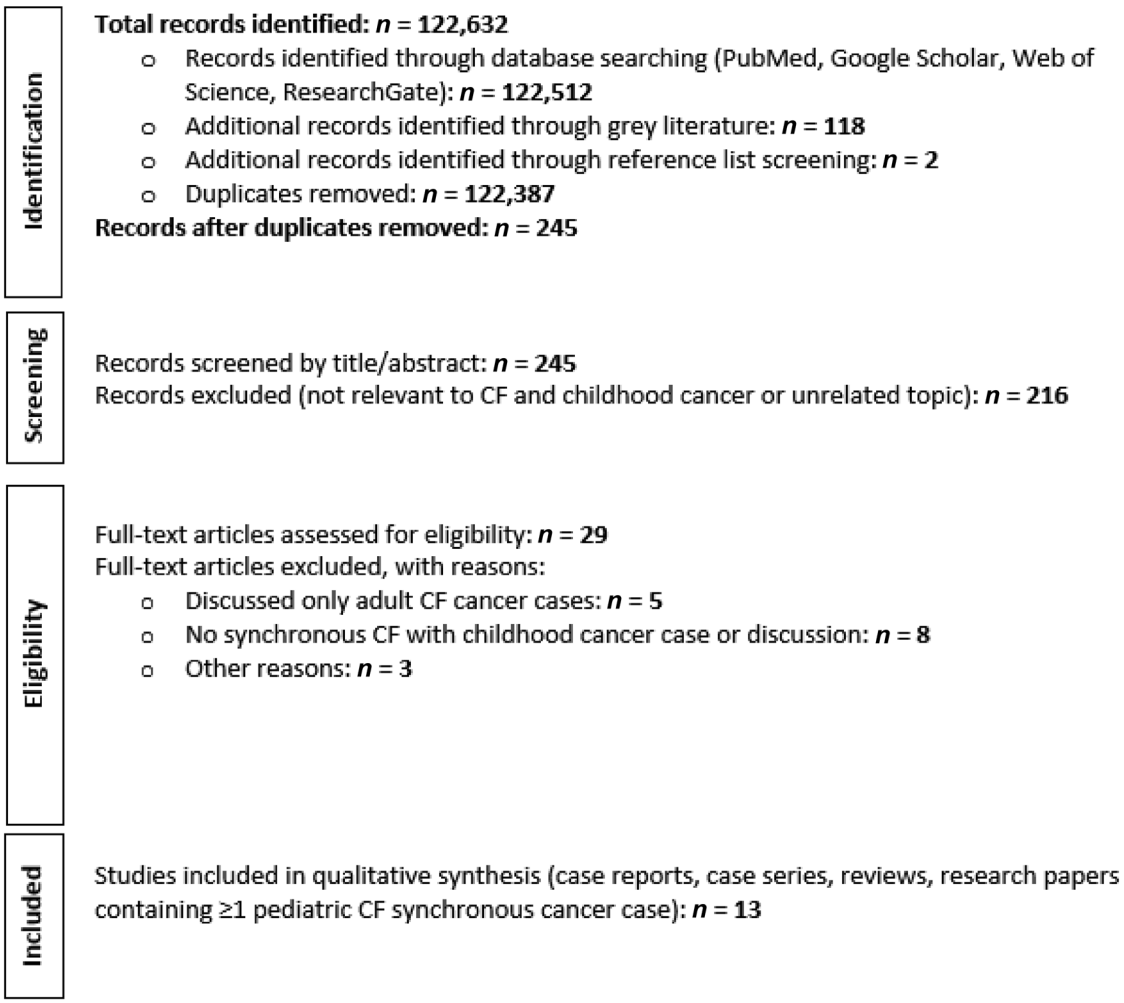

FIGURE 1 | PRISMA flow diagram

a chronic lung disease. In 2021, a 12-year-old male was diagnosed with B-cell acute lymphoblastic leukemia (B-ALL) after the patient was identified as PwCF through neonatal screening and confirmed with genetics at 1 month. The fourth patient is a 4-year-old female who was diagnosed in 2024 with B-ALL after the patient was identified as PwCF through neonatal screening and confirmed with genetics at 1 month. Three of the four patients are in remission with the fourth in remission and currently receiving her maintenance treatment for B-ALL.

3.2 | Case Studies From International Literature

A review of the literature revealed eight cases of childhood cancer diagnosed in children with CF between 1983 and 2025. From an Austrian case series of 11 PwCF that developed malignancies, three patients were children [13]: a 9-month-old girl with neuroblastoma, and a 14-year-old and 17-year-old girl with B-ALL. The two patients with B-ALL succumbed to treatment-related-toxicity, a development that was not related to their CF diagnosis, while the patient with neuroblastoma died of disease progression after relapse. The remaining seven cases are briefly summarized in Table 2. These cases included a male neonate and a 1-year-old male diagnosed with neuroblastoma [17], a 5-year-old male [18] and a 13-year-old male with colonic adenocarcinoma [19], a 16-year-old male diagnosed with osteosarcoma [20], a 9-year-old female with an Askin tumor [21], and a 3-year-old girl with bilateral Wilms tumor [22].

In summary, these 10 cases exhibited a 1:1 male-to-female ratio. Of the cases examined, only two were hematological malignancies, with the remaining eight cases consisting of solid tumors, predominantly neuroblastomas and osteosarcomas. The analysis revealed that no specific age group predominated at the time of diagnosis of the malignancies. None of the cases were posttransplant patients.

3.3 | Literature Review and Discussion

Despite the absence of documented disparities in the prevalence of childhood cancer among children with CF, the underlying pathophysiology of CF may nevertheless warrant additional attention when evaluating cancer-related symptoms. The challenge lies in the fact that the spectrum of CF disease can result in a delayed diagnosis of malignancies due to presence of overlapping symptoms, such as chronic cough, weight loss, and fatigue. The base line inflammation and chronic infections in CF

TABLE 1 | Belgian patients with cystic fibrosis diagnosed with childhood cancer between 2000 and 2024.

Oncological information				
Age of diagnosis and sex (year of diagnosis)	11 months male (2009)	16 years male (2019)	12 years male (2021)	4 years female (2024)
Tumor diagnosis	Embryonal hepatoblastoma with pulmonary metastasis in liver	Embryonal carcinoma Right testis	B-cell ALL CNS1 EBF1 deletion, CDKN2A/B deletion, IKZF1 deletion	B-cell ALL CNS1 PAR1 deletion (P2RY8 CRLF2 fusion)
Presenting symptoms	Unexplained weight loss	Firm mass of right testis	Pancytopenia	Pancytopenia with blasts during CF appointment
Stage and site of metastases	Stage 4, lung metastases	Stage 1	CNS 1	CNS 1
Treatment protocol	SIOPEL 4	Cisplatin/etoposide Ochidectomy	ALLTogether, IR-high risk	ALLTogether, IR-high risk
Significant events during treatment course	Hypomagnesemia Invasive *Pseudomonas aeruginosa* infection successfully treated with intravenous antibiotics	None	Thrombosis vena axillaris and subsegmental peripheral lung emboli Pulmonary aspergillosis	Pancreatitis
Comorbidities independent from cystic fibrosis	None	Cholecystolithiasis (cholecystectomy) Choroideremia	None	None
Treatment outcomes				
Chemotherapy-related toxicity and events	Auditory evoked potentials: mild peripheral hearing loss bilateral with a hearing threshold between 40 and 30 dB	Neutropenic fever	Renal failure during HD-MTX Temporarily stop Orkambi due to interaction chemotherapy (dexamethasone, vincristine) - Hyponatremia secondary to SIADH due to Vincristine, oral sodium suppletion - Hypertriglyceridemia due to dexamethasone and PEG-asparaginase, start low fat diet - Tube feeding by persistent weight loss	Neutropenic fever Pancreatitis Dexamethasone induced diabetes Allergic reaction Antibodies against PEG ASPA and Erwiniase
Outcome of treatment	Secondary malignancy Acute myeloid leukemia (M5) diagnosed December 2015 DBH AML NOPHO protocol Age 7 years Complete remission	Cured	Remission	Remission
Duration of follow-up after completion of therapy	10 years	5 years	2 years and 8 months	In maintenance

(Continues)

TABLE 1 | (Continued)

Cystic fibrosis-related information				
Age of diagnosis	1 month	4 years	1 month	1 month
Criteria for diagnosis (Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation)	Blood spot screening elevated trypsine, confirmed by genetics Characteristic gastrointestinal and nutritional abnormalities Two *CFTR* gene mutations known to cause CF on separate alleles	Chronic pulmonary disease Chronic sinusitis Characteristic gastrointestinal and nutritional abnormalities Elevated sweat chloride concentration Two *CFTR* gene mutations known to cause CF on separate alleles	Blood spot screening elevated trypsine, after which abnormal sweat test, confirmed by genetics Characteristic gastrointestinal and nutritional abnormalities Elevated sweat chloride concentration Two *CFTR* gene mutations known to cause CF on separate alleles	Blood spot screening elevated trypsine, after which abnormal sweat test, confirmed by genetics Two *CFTR* gene mutations known to cause CF on separate alleles
CF genotype	DF508 (mother)/306insA (father)	Homozygous DF508 deletion	Homozygous F508del mutation. T-status: 9T/9T	Heterozygoot F508del - 3272-26A→G
Bacterial status at oncology diagnosis	Uncomplicated/not colonized Distal intestinal obstruction syndrome (DIOS) Meconium ileus	Complicated Bacterial colonized No lung transplant	Complicated Bacterial colonization No lung transplant	Uncomplicated/not colonized No lung transplant
Pulmonary function at oncology diagnosis FEV1 (% predicted)	Unknown, without bronchiectasis or colonization	103%, with bronchiectasis and colonized with *Staphylococcus Aureus* and *Pseudomonas Aeruginosa*	97.1%, without bronchiectasis and colonized with *Staphylococcus Aureus*	95%, without bronchiectasis or colonisation
CF treatment and complications at oncological diagnosis	Respiratory physio, dornase alfa, antibiotic and bronchodilation inhalations, pancreatic enzyme supplementation, and multivitamin supplementation	Respiratory physio, dornase alfa, antibiotic pancreatic enzyme supplementation, and multivitamin supplementation Nasal polyps	CFTR modulator Allergic bronchopulmonary aspergillosis Pancreatic insufficiency Cystic fibrosis-related diabetes Chronic sinusitis	Respiratory physio, dornase alfa inhalations, and multivitamin supplementation Chronic rhinitis
New CF complications and treatment started during oncological treatment	Unchanged	Steroid nasal spray *Stenotrophomonas maltophilia* colonization	Colistineb aerosol *Pseudomonas aeruginosa* and *Staphylococcus aureus* colonization	Start *CFTR* modulator and *CFTR* potentiator Colistineb aerosol
Status of CF after oncological treatment (assess impact of cancer treatment on CF)	Stable	Lung function worsened during chemotherapy from 103 to 93%	More neutropenia-related exacerbations	More neutropenia-related exacerbations

Abbreviations: CF, cystic fibrosis; CNS, central nervous system; FEV, forced expiratory volume.

TABLE 2 | Children with cystic fibrosis diagnosed with childhood cases from the international literature.

Oncological information							
Age of diagnosis (year of diagnosis)	Birth (1983)	1 year (1983)	13 years (2007)	5 years (2016)	16 years (2017)	9 years (2023)	2 years (2025)
Country	USA	USA	USA	Germany	Australia	USA	Turkey
Sex	Male	Male	Male	Male	Male	Female	Female
Tumor diagnosis	Neonatal neuroblastoma	Neuroblastoma	Moderately differentiated adenocarcinoma	Osteoblastic osteosarcoma	Malignant fibrous histiocytoma type osteosarcoma	Askin tumor (Ewing/PNET sarcoma)	Bilateral Wilms tumor
Tumor genetics	—	—	—	—	—	*EWSR1* gene (22q12)	—
Presenting symptoms	Respiratory distress Bulky stool	Respiratory distress Diarrhea	Abdominal pain, pneumaturia and passing fecal materials during urination	Swelling of the left upper arm	Three-month history of a progressively painful swollen right ankle	Persistent right lung lesion post pneumonia consolidation and a rib lesion	Abdominal mass
Describe prediagnosis course if relevant	Dyspnea at birth	Dyspnea at birth					
Tumor site	Paraspinal thorax	Paraspinal thorax	Cecum	Left proximal humerus	Right distal tibia	Rib right thorax	Bilateral kidneys
Stage	Stage 1 (Stage L1)	Stage 1 (Stage L1)	Stage 2	—	Localized	Metastatic	Stage 5
Risk classification	Low-risk	Low-risk	—	—	Standard-risk	High-risk	—
Site of metastases	None	None	Direct spread	None	None	Liver	None
Treatment protocol	Watch and wait	Surgery only	Adult protocol for colon cancer using 12 cycles of oxaliplatin, 5-FU, and leucovorin	Euramos-1 protocol Neoadjuvant induction chemotherapy of cisplatin, doxorubicin, and high dose methotrexate, surgery (osteosynthesis) and consolidation therapy	Protocol AOST0331 Neoadjuvant induction chemotherapy of cisplatin, doxorubicin and high dose methotrexate, surgery and consolidation therapy	EURO-EWING 99 protocol and resection sixth and seventh rib lower lobe lobectomy	SIOP-type protocol

(Continues)

TABLE 2 | (Continued)

Family history	None	None	Breast cancer	None	None	None	None
Significant events during treatment course	None	None	Myelosupression	No pulmonary exacerbations	Pulmonary exacerbation New Mycobacterium intracellular infection and abscesses	Malnutrition Persistent exacerbations of infections	None
Comorbidities independent from cystic fibrosis	None stated	None stated	None stated	None stated	None stated	Feeding problems	None stated
Oncological complications during treatment	None stated	None stated	None stated	Postoperative compartmental syndrome	None stated	None stated	None stated
Cystic fibrosis information							
Age of diagnosis	2 months	6 months	Not stated	6 weeks old	2 months	3 months	Neonatal period
Criteria for diagnosis Diagnosis of CF: Consensus Guidelines from the Cystic Fibrosis Foundation)	Absent stool trypsin Positive sweat test	Sweat test	Not stated	Newborn screening heel prick test and confirmed with a sweat test	Newborn screening heel prick test	Sweat test Sequencing of the *CFTR* gene Persistent bronchopneumonia, chronic diarrhea, and failure to thrive Pseudo-Bartter syndrome	Immune reactive trypsinogen testing Sweat test Genetic confirmation
CF genotype	—	—	Not stated	Homozygous for F508 genotype	Homozygous for F508 genotype	Heterozygous for F508 genotype Mutations c.54_273del (exons 2 + 3) and c.1521_1523del (exon 11)	Heterozygous for F508 genotype
CF status at oncology diagnosis	Newly diagnosed Respiratory distress Bulky stool	Newly diagnosed Respiratory distress Diarrhea	Not stated	None	Progressive bronchiectasis	Feeding problems and repeated pulmonary infections	None
Lung transplant status	Not transplanted	Not transplanted	Not transplanted	Not transplanted	Not transplanted	Not transplanted	Not transplanted

(Continues)

TABLE 2 | (Continued)

Pulmonary function at oncology diagnosis FEV1 (% predicted) Bronchiectasis Bacterial colonization: if yes, which bacteria	Not tested	Not tested	Not stated	*Staphylococcus aureus*	FEV1 of 3.8 L (93.9%) *Staphylococcus aureus Pseudomonas aeruginosa*	*Pseudomonas aeruginosa Staphylococcus aureus*	Not tested
CF treatment at time of oncological diagnosis				Secretolysis using inhalation with hypertonic saline and acetylcysteine, salbutamol and ipratropium bromide, physiotherapy, pancreatic enzyme replacement (PERT), and vitamin replacement therapy and cefuroxime prophylaxis			
New CF treatment started during oncological treatment	—	—	—	—	—	CFTR modulator therapy with elexacaftor/ Teza-caftor/ivacaftor	—
Status of CF after oncological treatment (assess impact of cancer treatment on CF)	Comparable to prediagnosis	Comparable to prediagnosis	Not stated	Comparable to prediagnosis	Improved pulmonary function	Persistent lung infections and malnutrition	Comparable to prediagnosis
Lung function after oncological treatment FEV1 (% predicted) New bronchiectasis: Bacterial colonization: If yes, which bacteria	*Staphylococcus aureus Klebsiella pneumoniae Pseudomonas aeruginosa Pseudomonas maltophuilia*	—	—	—	4.15 L (102.3% predicted) *Mycobacterium intracellular infection*	Comparable to prediagnosis	—

Abbreviations: CF: cystic fibrosis, FEV: forced expiratory volume.

can also obscure cancer-specific signs on radiological imaging. Given these findings, it is imperative for healthcare providers to maintain vigilant monitoring for potential malignancies in PwCF, especially when persistent or unexplained symptoms arise. The importance of early detection and intervention in improving cancer-related outcomes for this vulnerable population cannot be overstated.

Between 2004 and 2022, there were 9618 children aged 0–18 years diagnosed with cancer in Belgium of which only four were PwCF. Although the sex-distribution for childhood cancers in CF were equal. Most studies on overall cancer risk in CF, focused on adults with gastrointestinal or colorectal malignancies, show an equal or male-predominant distribution [23, 24]. The mean age of the four Belgian patients was 8.2 years compared with 4–6 years globally. All four children were cured or in remission from their malignancies, which is in line with the 83% 10-year overall survival for children under 16 years documented in Belgium. One patient, 25%, developed a secondary malignancy which is higher than the 5–10% cumulative incidence rate over 30 years recorded in children. Although the pulmonary function of the group changed approximately by 10% each, the values remained within normal values for their age groups. The outcomes for PwCF diagnosed with childhood cancer are comparable to non-CF patients treated for childhood cancer, but the very small sample size makes it statistically unreliable for the purpose of drawing conclusions.

In the pediatric cases, solid tumors were observed to be particularly prevalent, with neuroblastoma and osteosarcoma being most encountered, but the data cannot show any specific tumor-type predilection in children, because the numbers are far too small. *CFTR* has also been demonstrated to function as a tumor suppressor gene in the intestine, when not functioning, leads to gastrointestinal malignancies in adults [25, 26]. Neuroblastoma, a pediatric cancer, originates from neural crest derivatives, while osteosarcoma arises from mesenchymal bone precursors, both relying on *CFTR* in maintaining physiological homeostasis [25, 26]. *CFTR* is not associated in the pathogenesis of either conditions; therefore, we postulate that the finding is coincidental or a reporting bias due to the limited number of cases published.

The impact of the pathophysiology of CF, such as persistent neutrophilic inflammation, immune dysregulation, and auto immune-like responses, on oncological treatment can potentially worsen the CF bacterial status and limit optimal oncological care during treatment. One such example is the overreaction to foreign proteins, like asparaginase (an enzyme derived from bacteria, often *E. coli* or *Erwinia*), which was also evident in the fourth Belgian patient. The patient diagnosed with B-ALL developed allergies as well as antibodies, or silent inactivation, against E coli asparaginase and Erwinia asparaginase. The likelihood of developing allergic reactions against E coli asparaginase is 3–37% [27], developing antibodies against E coli asparaginase 30–70% [28] and antibodies against Erwinia asparaginase 8–38% [29, 30]. The likelihood of a single patient developing all these reactions is approximately 5–8% [30]. In a disease that predisposes to immunological comorbidities, such as CF, it is imperative that patients are observed with utmost vigilance.

In the context of concurrent management of CF and a childhood malignancy, there is an increased requirement for patient-directed management and supportive care. This includes antimicrobial prophylaxis (see Table 3) and CF-disease modulators due to repeated infections during neutropenia.

3.3.1 | Infection Screening and Antimicrobial Therapy

Infection prevention strategies are imperative to reduce the burden of respiratory infections. Given the potential preexisting colonization of PwCF with pathogens at the time of diagnosis and at the onset of chemotherapy-induced neutropenia, the threshold for antimicrobial therapy should be lower than in non-CF patients with empirical antibiotic strategies adapted to colonization [31–34]. No universal guidelines mandate screening for *all* children diagnosed with cancer, but it is recommended for those at high infection risk or patients with specific comorbid diseases. Therefore, we recommend establishing the colonization pattern of all PwCF diagnosed with childhood cancer.

Bronchoscopy with bronchoalveolar lavage (BAL) in childhood cancer patients, although safe with a high diagnostic yield, is not routinely indicated, but depends entirely on clinical indications. The CF-based indications for the frequency of BAL are thus indicated during oncological management with additional screening per indication during acute episodes.

Invasive fungal and mold infections add to both short- and long-term morbidity and mortality in pediatric oncology [1]. *Aspergillus fumigatus* has also been associated with worse respiratory outcome in PwCF [35]. However, treatment with prophylactic antifungals remains controversial and does not correlate with enhanced pulmonary function [36]. Yet, repeated or prolonged episodes of neutropenia due to chemotherapy or stem cell transplantation are indications for prophylactic antifungal treatment during oncological management, independent of CF status.

3.3.2 | Supportive Care

During both intensive and maintenance chemotherapy treatment, a number of mitigation strategies are of vital importance as supportive care for the oncological management, but also to prevent deterioration of the clinical CF status (*see* Table 3) [37]. It is important to provide aggressive nutritional support to maintain already increased cellular demands. Physiotherapy should preventatively be initiated to prevent both pulmonary and musculo-skeletal deterioration [38]. Close surveillance of organ functions should be regularly planned based on combined tumor-specific protocols and CF-guidelines [37].

Continuous pharmacovigilance is imperative when prescribing therapy for PwCF. Polypharmacy in CF necessitates dosage adjustment due to potential CYP450 induction or inhibition. Concomitant administration with chemotherapeutic and supportive agents increases the likelihood of pharmacological interactions, including QT prolongation, nephrotoxicity, and hypersensitivity reactions [39]. Such interactions may compromise treatment

TABLE 3 | Antimicrobial prophylaxis considerations and mitigation strategies during immunosuppressive therapy with GRADE strength of recommendation and level of evidence [30–33].

Prophylaxis	Reason	Recommendations
Infection-related considerations		
Bacterial infections	Prevent Gram-negative (e.g. *Pseudomonas aeruginosa*) and Gram-positive infections during neutropenia; CF patients often colonized	During prolonged chemotherapy-related high-risk neutropenia (absolute neutrophil count <500/μL) start levofloxacin [moderate, Level II]
Fungal infections CF may predispose to *Aspergillus*	Patients at high risk for *Candida* and *Aspergillus* infections with chemotherapy-induced neutropenia or mucositis	During AML treatment or HSCT with prolonged neutropenia start Fluconazole for *Candida* or Posaconazole preferred for broader coverage [high, Level I] Echinocandins or a mold-active azole [high, Level I]
Viral infections	Reactivation of HSV or VZV during chemotherapy; immunocompromised state increases severity.	Oral valaciclovir or aciclovir prophylaxis in HSV/VZV-seropositive patients receiving intensive chemotherapy [high, Level I]
Pneumocystis jirovecii Chemotherapy-related immunosuppression increases infection risk	High risk with lymphopenia, steroids, or certain cancer regimens and HSCT	Trimethoprim–sulfametoxazol is first line. Alternatives: pentamidine, dapsone, atovaquone if trimethoprim–sulfametoxazol is not tolerated.
Mycobacterial infections No routine screening during oncological management, but increased in CF	Nontuberculous mycobacteria common in CF but no routine prophylaxis unless prior history or high risk	Consider azithromycin in select CF patients with recurrent nontuberculous mycobacteria, but caution with resistance/side effects [low-moderate, Level III-IV]
Supportive care considerations		
Immunoglobulin replacement	CF may impair mucosal immunity; chemotherapy impairs humoral immunity.	Intravenous immunoglobulins if IgG <400 mg/dL or with recurrent infections. C Special consideration in B-cell depleting therapy like rituximab [moderate, Level II]
Vaccination Vaccination during chemotherapy may result in suboptimal immune responses and not advised	Prevent vaccine-preventable infections (e.g., influenza, pneumococcus, and seasonal infections like COVID-19)	Annual flu vaccine, PCV/PPSV23, COVID-19 vaccine. Avoid live vaccines during intensive immunosuppression and chemotherapy treatment [high, Level I]
CF-specific inhaled antibiotics	Chronic colonization with *Pseudomonas* or *Burkholderia* in CF patients or at physician discretion for MRSA, *Achromobacter xylosidans*, *Stenotrophomonas maltophilia*, and NTM infections	Continue if previously prescribed for airway suppression; evaluate on a case-by-case basis during cancer treatment; the threshold to commence inhaled antibiotics should be lower during oncology treatment.
Mitigation strategy		
Infections	Employ strict neutropenic precautions and close infection surveillance [high, Level I] Perform frequent respiratory sampling of sputum cultures or throat swabs for surveillance [high, Level I] Treat respiratory infections immediately and aggressively, initiate eradication therapy even if the patient is asymptomatic [high, Level I] There should be a lower threshold to initiate antibiotics in CF patients with fever or neutropenia with investigations directed to a potential source [moderate, Level II–III]. Maintain heightened vigilance for atypical CF pathogens like *Burkholderia cepacia* or *M. abscessus* [moderate, Level III]	

(Continues)

TABLE 3 | (Continued)

Prophylaxis	Reason	Recommendations
Lung function	Close pulmonary monitoring, baseline pulmonary function tests, chest physio support [high, Level I]	
Medication dosing [78]	Evaluate drug interactions and adjust according to international guidelines; adjust based on pharmacokinetics and therapeutic drug monitoring [high, Level I]	
Nutrition [38]	Aggressive enteral or parenteral nutritional support [moderate, Level II]	
Hepatic/gastrointestinal problems [79]	Monitor liver functions, use pancreatic enzyme therapy, adjust hepatotoxic medication [high, Level I]	
Chemotherapy can cause chemical transaminases and predispose to liver cel damage	If there is evidence of cholestasis or rising liver enzymes, consider adding ursodeoxycholic acid [low to moderate, Level II–III]	
	Vincristine can cause constipation during treatment. Use laxatives and stool softeners proactively in CF patients at risk for constipation or distal intestinal obstruction syndrome [high, Level I].	
	Ensure adequate hydration and early use of osmotic agents. If a severe obstruction occurs, bowel washouts might be necessary but avoid enemas or bowel washouts during neutropenia due to infection risk [high, Level I].	
Psychosocial problems [80]	Provide comprehensive psychosocial support involving the CF care team, oncology team, and mental health professionals [Moderate, Level II]	

Abbreviations: CF: cystic fibrosis, AML: acute myeloid leukemia, HSCT: hemopoietic stem cell transplant.

adherence and modify oncolytic pharmacokinetics or dosing efficacy [40].

CFTR modulator therapy lowers the requirement for adjunctive symptomatic treatments, thereby reducing therapeutic burden. However, overlapping toxicities, such as hepatotoxicity and neuropsychiatric effects, are shared with oncologic regimens [1]. Given that *CFTR* modulators undergo extensive metabolism via CYP3A4 and CYP3A5, the potential for clinically relevant drug–drug interactions, particularly with CYP3A4 modulators, underscores the necessity for heightened awareness in therapeutic management [1].

3.4 | Respiratory Diseases in CF

The complexity and potentially deadly nature of respiratory infections in CF is further compounded by the presence of polymicrobial infections during neutropenic events due to chemotherapy [41]. The early and precise detection of pathogens remains important and therefore frequent respiratory sampling is suggested, ideally by expectorating sputum especially when testing for bacterial and atypical infections, although oropharyngeal swabbing also has a good yield in viral infections [41]. It is imperative that sampling is performed both as surveillance and active identification of organisms during pulmonary exacerbations [41]. During oncological management, especially during neutropenia, combined sampling of sputum and swabbing is advised, as is pathogen-specific testing using the most sensitive PCR techniques. In most oncological diagnoses, CT-imaging of the lungs is part of the standard diagnostic work-up. In cases where it is not, a multidisciplinary team decision should guide the indication for CT-imaging [42].

Prophylactic and targeted treatments should be based on CF disease severity and oncological treatment at cancer diagnosis [41, 43]. *Pseudomonas aeruginosa* infections require immediate antibiotic treatment, regardless of symptoms, with the eradication of the infection being the primary objective [41, 43]. While the protocols for other pathogens are less clearly defined, increased vigilance is advised for organisms, such as *Mycobacteroides abscessus* and *Burkholderia cepacian* [1]. Antimicrobial susceptibility testing is a poor predictor of clinical response and treatment should be guided by the pathogen and clinical response [44, 45]. The duration of treatment has been the subject of debate in CF, but mostly exists of a 10- to 14-day course [46]. Established airway clearance techniques and use of mucoactive agents in PwCF apply in equal measure during oncological treatment [46–48].

3.5 | Cardiopulmonary Toxicity Considerations

PwCF face significant risks when receiving cardiopulmonary-toxic chemotherapy due to their compromised lung function and systemic vulnerabilities [49, 50]. Chemotherapy agents, such as bleomycin, busulfan, and anthracyclines, can exacerbate existing lung damage, causing pneumonitis, fibrosis, or heart dysfunction [49, 50]. The reduced pulmonary reserve increases the possibility of severe respiratory complications, while the chronic inflammatory state and nutritional deficiencies heighten susceptibility to cardiotoxic effects, such as cardiac failure or arrhythmias [49, 50]. Detecting these symptoms remain challenging since dyspnea and fatigue overlap with baseline CF manifestations. A comprehensive array of preventive measures has been established, encompassing thorough baseline assessments of lung function and cardiac status, followed by close monitoring throughout the treatment period [49, 50]. Adapting treatment to reduce cardiopulmonary toxicity, adjusting doses, and providing aggressive pulmonary support and nutritional optimization should continuously be discussed in a multidisciplinary team involving pulmonologists, cardiologists, oncologists, and dieticians [49, 50].

During oncological management lung function tests are indicated once after treatment completion with additional lung function tests indicated per clinical indication or in chemotherapy regimens with specific pulmonary side effects, such as bleomycin [51, 52]. Performing lung clearance index measurements through multiple breath washout is a valuable method for monitoring ventilation inhomogeneity in PwCF, but its potential application during oncology treatment is still being investigated [53]. It is highly recommended and increasingly being used in children over 3-years old, especially with conditions like CF [54]. In oncological management, it may potentially be more beneficial, because it is more sensitive to early small airway disease than spirometry, requires only tidal breathing without active patient cooperation, and is feasible in unsedated children [54].

Although global consensus guidelines are yet to be established, cardiac ultrasound to evaluate cardiac function and anomalies are standardly done before initiation and after completion of chemotherapy, with increased frequency during doxorubicin therapy, lung irradiation, and stem cell transplant [55]. During late-effects management a cardiac evaluation is indicated every 5 years. In summary, the frequency of pulmonary evaluations should be based on CF-guidelines and cardiac evaluations according to pediatric oncology guidelines, based on the highest frequency of evaluations respectively.

3.6 | Hepatogastric Considerations in CF and Oncology Treatment

PwCF have been shown to exhibit a marked increase in energy demands due to chronic inflammation, malabsorption, and persistent pulmonary infections [56]. Cancer treatment further exacerbates this demand, as chemotherapy and radiotherapy increase metabolic stress. This necessitates close monitoring of caloric intake, protein consumption, and micronutrient supplementation to prevent malnutrition, which can negatively impact both CF and oncological outcomes [56].

CF patients with pancreatic insufficiency require pancreatic enzyme replacement therapy (PERT) to ensure adequate digestion and absorption of fats and proteins [57]. Oncology treatments, especially those affecting the gastrointestinal tract, can further impair enzyme function and nutrient absorption, increasing the risk of malnutrition [57]. It is essential to adjust PERT dosages in response to weight changes, altered stool consistency, or worsening malabsorption [57].

During oncological treatment, there is an increased risk of hepatotoxicity predisposing CF patients, who are already at an increased risk to develop liver disease, characterized by fibrosis, cholestasis, and cirrhosis [58]. Many chemotherapeutic agents, particularly methotrexate, vincristine, busulfan, and tyrosine kinase inhibitors, are hepatotoxic, thereby potentially exacerbating pre-existing liver dysfunction. Close monitoring of liver enzymes and bilirubin levels are crucial [59]. Ursodeoxycholic acid administration may be considered during oncological management for patients with cholestasis to promote bile flow and reduce liver inflammation especially during stem cell transplant [59].

PwCF have an increased predisposition to pancreatitis, primarily in pancreatic-sufficient individuals with CF, due to pancreatic duct obstruction and genetic factors, compared with non-CF patients. Certain chemotherapeutic agents, such as L-asparaginase, 5-fluorouracil, and corticosteroids, further elevate this risk [60]. Therefore, symptoms such as abdominal pain, nausea, and vomiting should not only be evaluated from an oncological perspective, but also in the context of CF complications [60]. Avoiding unnecessary pancreatic-toxic medications and maintaining hydration within the limitations of CF disease are essential preventive strategies [61]. The development of these complications may occur within hours, with or without symptoms, such as abdominal pain and vomiting, or silently over the course of a month, as is the case with pancreatic cysts [62]. Considering these observations, we propose regular screening, as illustrated in Table 4.

Gastrointestinal dysmotility in CF increases the likelihood of constipation and distal intestinal obstruction syndrome (DIOS), which can be worsened by chemotherapy, such as vincristine, dehydration, opioid pain management, and reduced physical activity [58]. Laxatives should be used proactively in at-risk patients [58]. Bowel washouts may be required in severe DIOS cases, but are not recommended during periods of neutropenia as this may cause life-threatening infections [58].

Small intestinal bacterial overgrowth (SIBO), present in 30–70% of children with CF [63], where intestine has increased permeability due to chronic inflammation and dysbiosis [61]. Clinical signs attributed to SIBO are abdominal bloating, diarrhea, malabsorption, bacterial translocation, and sepsis, especially in neutropenic patients [56, 61]. This may be increased during episodes of chemotherapy-related mucositis. Therefore, intravenous antibiotics should be prioritized for febrile episodes in these patients and the threshold for feces-related investigations should be low [61]. The utilization of probiotics in patients receiving chemotherapy remains a subject of debate, but is not generally recommended [64].

3.7 | Endocrinological and Dietary Considerations in CF During Oncological Treatment

During oncological therapy, infections, stressful procedures, such as surgery, and drug-related allergic reactions may affect glucose metabolism due to stress responses in the body [65, 66]. Radiotherapy or surgery to especially the hypothalamus and hypophysis or any hormone-producing or -regulating organ can reduce the capacity of the body to regulate hormones further n PwCF who potentially already have a reduced capacity. Glucose tolerance in PwCF should be tested annually using a 2-h 75-g oral glucose tolerance test, starting at 10-years old with additional testing per clinical indication during oncological treatment [66].

In combination with oncological treatment, PwCF with exocrine pancreatic insufficiency have an insulin deficiency that worsens with age, and insulin secretion is reduced even in those with normal glucose tolerance [59, 60]. With impaired glucose tolerance, diabetes become more prevalent, a condition known as CF-related diabetes [59, 60]. In CF, as in diabetes, the insulin response to a glucose load or meal is reduced in amplitude and delayed

TABLE 4 | Toxicity screening suggestions during pancreatic-toxic chemotherapy administration

Investigation	Frequency	Motivation
Electrolytes and liver enzymes	Weekly	Secretory and hormonal dysregulation with concomitant hepatotoxicity, prone to hyponatremia and hypokalemia
Lipase or amylase	Weekly	Predisposition to pancreatitis
Abdominal ultrasound	Monthly	Development of pancreatic cysts
Urine glucose monitoring	Weekly	Endocrine function deregulation

compared with healthy individuals, while basal insulin secretion is relatively preserved [61]. The primary cause of impaired glucose tolerance in CF is insulin deficiency, which should be treated with insulin [59, 60]. Patients receiving oncological treatment with poor nutritional status have poorer outcomes. Therefore, identifying CF-related diabetes in need of insulin is paramount as insulin improves lung function and nutritional status in PwCF [61]. In oncology care, monitoring glucose levels and informing the pediatric endocrinologist is essential because certain chemotherapy drugs (e.g., dexamethasone) can affect glucose metabolism, and nonchemotherapy agents or hyperhydration may be given in glucose-containing solutions [59, 61].

When PwCF do develop hypoglycemia, the internationally recommended algorithms for the diagnosis of the underlying cause should be followed [65, 67]. Diabetic ketoacidosis (DKA) is rare in CF-related diabetes but can still occur [65, 66]. The treatment of DKA should be performed in accordance with national or institutional guidelines [67].

With pre-existing CF-related diabetes, or during the development of diabetes secondary to oncological treatment, the dietary advice is not the same as in other forms of diabetes and that a "diabetes diet" may not be indicated. Families should be discouraged from reducing calorie intake to avoid insulin treatment. During oncological treatment, chemotherapy-induced nausea and vomiting, gastrointestinal infections or radiotherapy, and surgery-related procedures will reduce intake, all measures to promote caloric intake should be preserved. These include antiemetics, management of mucositis and infections, and maintaining a low threshold to place a naso-gastric or nasoduodenal feeding tube [67]. Guidance from a dietician regarding adequate nutrition remains a priority, and a diet high in calories and fats, comprising 35–40% of calories, should be continued [67]. This combination optimize diabetes regulation and promote weight gain, which is essential to counter the catabolic effect of the tumors and oncological treatments. Food intake should not be reduced to regulate blood glucose levels, but meals and snacks should be eaten regardless of blood glucose levels to promote continuous regulation [67]. Protein intake should be 1.5–2.0 times the daily recommended intake [67]. A high salt diet, especially in warm conditions and/or with increased sweating, should be maintained [67]. If the loss of weight exceeds 10% of the body weight at diagnosis despite oral or naso-tube feeding, intravenous feeding must be started.

Fat-soluble vitamin deficiencies must be monitored, as these nutrients are crucial for immune function and tissue repair [67]. There should be a low threshold to supplement PwCF, given that physiological doses do not impair the efficacy of chemotherapy agents, but support normal organ functions and prevent complications [68].

3.8 | Fertility

Males with CF are infertile in approximately 97–98 % of cases due to congenital bilateral absence of the vas deferens, but many can produce spermatozoa and achieve biological fatherhood via assisted reproductive technologies [69]. Females with CF remain in general fertile, but may experience fertility problems due to thickened cervical mucus, irregular or absent ovulation [70].

In addition to CF-related infertility, chemotherapy can further decrease the fertility potential in pediatric patients [71]. Therefore, counseling from a fertility expert should be offered before start of oncological treatment to ensure future reproductive prospects [71].

3.9 | Outcomes Considerations

Survival outcomes for PwCF who underwent oncological treatment during childhood are poorly documented in the literature. To predict the potential outcomes when combining long-term survivorship data for both diseases, it is necessary to consider the patients' risk for premature mortality due to decreased pulmonary and cardiac reserves and increased late effects burdens. Therefore, clinicians should be especially vigilant in long-term monitoring and aggressive management of organ dysfunction, secondary malignancy screening, and multidisciplinary care for CF patients who survived childhood cancers. This includes advance care plans and palliative care strategies.

CF patients who undergo oncological treatment may be predisposed to increased risks of developing secondary malignancies due to posttreatment chronic inflammation, frequent infections, and oxidative stress that can contribute to mutagenesis [72]. This is further exacerbated by the interaction of *CFTR* mutations with DNA repair genes or cancer susceptibility loci [4]. Post lung transplantation PwCF are at a 10-fold increased risk to develop secondary malignancies compared with non-CF transplant recipients [73]. Posttransplant lymphoproliferative disease (PTLD) in PwCF was 1.66 higher than in non-CF patients and gastrointestinal malignancies were 20 times higher [73]. Since the average age for lung transplantation is 20 years, limited

pediatric data are available [74]. Yet, the incidence of posttransplant malignancies in children and adolescents is lower and mainly limited to PTLD [73, 74]. For children with CF and treated for cancer, there isn't convincing evidence that either the event free survival or overall survival differs from patients without CF diagnosed with childhood independent from specific cancer types. Of importance is the higher incidence of certain cancers, especially after transplant, and management complexity since CF itself can predispose patients to increased oncological treatment toxicity, particularly for therapies that affect the lungs. This increases in cases with established pulmonary fibrosis. The increased risk of toxicity can limit the dosage and duration of oncological treatment, which could impact the effectiveness of the treatment itself [75, 76].

3.10 | Recommendations for Research

Not all recommendations related to the comanagement of CF and malignancies have been validated by clinical trials and are based on either CF or oncological guidelines without evidence when synchronous diseases occur. The establishment of registry-level efforts is imperative for the documentation of childhood cancer diagnoses and survival in CF cohorts. The objective of this initiative is to integrate data across oncology and CF registries to track outcomes longitudinally. Short- and long-term CF-specific survivorship care plans should be developed based on the current knowledge of both disease entities in anticipation of compounded risks for early cardio-respiratory disease and an increased awareness for secondary cancer screening.

4 | Conclusion

Although there is currently no evidence in the literature yet that overall childhood cancer risk in CF is increased, but the key issue with the synchronous presentation of childhood cancer in CF, is management complexity. The administration of oncology treatment presents multiple challenges to the CF pathophysiology, including nutritional depletion, hepatotoxicity, pancreatitis risk, bacterial and fungal infections, and gastrointestinal complications. The employment of a multidisciplinary team approach is essential to optimize patient outcomes. Monitoring and proactive management of complications can promote optimal oncological treatment while limiting complications to PwCF. Individualized care plans should address diagnostic challenges, modify treatment protocols to minimize toxicity, increase supportive care, and emphasize comprehensive, long-term follow-up tailored to the dual disease burden.

Author Contribution

JvH conceptualized and designed the study. All authors collected data and wrote the manuscript. JvH performed the statistical analysis. All authors contributed data, critically reviewed, and revised the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data may be requested on reasonable request within the determinations of ethical committees.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File: pbc70295-sup-0001-TableS1.docx.