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Title; CLINICAL UTILITY OF SURVEILLANCE COMPUTED TOMOGRAPHY SCANS IN INFANTS WITH CYSTIC FIBROSIS¹

Running Title: “CLINICAL UTILITY OF SURVEILLANCE CT IN CF”

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ABSTRACT

Background: In cystic fibrosis (CF), irreversible lung disease arises in early life and is often asymptomatic and unrecognised. Chest computed tomography (CT) scans have been used to detect asymptomatic lung disease in research, however the clinical utility of chest CT is unknown. This study aimed to determine the effect of surveillance CT in early life on the clinical management of patients with CF.

Working Hypothesis: Surveillance CT in early life changes the management of patients with CF.

Method: A medical record review of patients in the AREST-CF cohort who had chest CT at 1 and 3 years of age was performed. Information extracted included CT scan findings and the effect of CT results on clinical management.

Results: The chest CT scans and records of 50 subjects with CF were reviewed. The majority of CT scans (n=75; 75%) were abnormal. N= 31 (31%) of scans overall led to a direct change in management. The number of CT scans needed to be performed to lead to a treatment change was 3.2. The majority (n= 18, 58%) of changes in management were prompted by the finding of bronchiectasis.

Conclusion: To the authors knowledge this is the first study to highlight that early life surveillance CT frequently results in changes in clinical management, and hence may have a role beyond research and in routine care. If this can be shown to contribute to improved outcomes (such as reduced rates of bronchiectasis), then, as radiation doses diminish, chest CT could have an important clinical role.

CLINICAL UTILITY OF SURVEILLANCE COMPUTED TOMOGRAPHY SCANS IN INFANTS WITH CYSTIC FIBROSIS

1. Background

Lung disease is the main cause of morbidity in children with Cystic Fibrosis (CF), with irreversible damage to lung structure¹ and function^{2,3} occurring in early life. Structural lung disease in infants with CF can be asymptomatic and difficult to identify^{4,5} and lung function can be reduced prior to detection by respiratory signs or symptoms.⁶ In addition to difficult detection of early CF lung disease, there is a lack of guidance for clinicians regarding the use of certain therapies in the preschool age group. For example, international guidelines recommend the use of mucolytics (dornase alpha and hypertonic saline) in all children with CF over 6 years old, including those with mild lung disease.⁷ However, there are few recommendations for infants or children younger than 6 years of age. Given the insensitivity of clinical findings and lack of guideline recommendations for young children with CF, clinicians may find objective information from investigations helpful in aiding clinical management.

Chest computed tomography (CT) scans are the most sensitive marker of lung disease in infancy.⁸⁻¹⁰ However, routine surveillance CT scans are currently used largely in research only. In this novel study we aimed to assess the clinical utility of surveillance chest CT scans in pre-school children with CF, by evaluating if CT scans at these ages changed clinical practice.

2. Method

A retrospective medical record review was undertaken in a random sample of 50 patients with CF cared for at The Royal Children's Hospital in Melbourne, Australia. Ethics approval and informed consent was obtained as part of the AREST-CF study. Subjects underwent volume-controlled chest CT scans, under general anaesthesia, at 1 year and 3 years of age according to the standard operating procedures of AREST-CF.¹ Although CT scans are routinely part of clinical care, only patients who were enrolled in the AREST-CF study were included in this study as they were covered by ethics approval and their parents had given informed consent for their children to be used in research studies.

Medical record review was performed by two clinicians involved in the care of patients with CF. Data extracted from medical records included CT scan findings. Based on paediatric radiologist's report, CT scans were categorised as: 'normal', 'bronchiectasis' or 'other CF related changes' (such as mucus plugging, bronchial wall thickening, significant atelectasis, and air-trapping). Minor atelectasis of the dependent lobes, that was likely due to complication of general anaesthesia was not included in the other CF related changes category. If a patient had both bronchiectasis and other CF related changes, they were recorded only in the bronchiectasis group. The CT scans were also reviewed by the CF team (a minimum of three physicians) to ensure they agreed with the radiology report, and where there was disagreement, after discussion between the CF team and radiologist, the report was amended. The categories in the study were chosen, as opposed to a CF CT score, as they mimic the pragmatic way the CT scans are reported and used clinically. Information was also collected on the effect of CT scans on subsequent treatment, with options including; 'no change', 'hospital admission' (for intravenous antibiotics and in-patient

physiotherapy) and prescription of 'mucolytics' (dornase alpha, hypertonic saline and mannitol) or 'corticosteroids'.

To determine if treatments were prompted by CT scan findings, all medical documentation was reviewed including: hospital admission medical notes, outpatient clinic notes and annual review meeting documentation. The annual review meeting is a multi-disciplinary CF team meeting, designed to review all aspects of a patient's care and make treatment decisions. The meetings are documented on a proforma, which includes comments for review of chest CT scans and subsequent treatments or management. After initial data collection, those patients identified as having a management change based on CT result, had their medical record re-checked to ensure this assessment was correct. In cases where there was doubt as to whether the CT scan findings led to a change in treatment, it was recorded as 'no change'.

3. Results

50 patients (60% male) were included with a median age of 5.5 years at the time of data collection (range 3.25-11.9). Data were collected during the months of February to April 2017 and are summarized in Table 1.

33/50 patients (66%) had an abnormality detected on CT at 1 year of age and 42/50 (84%) had an abnormality at 3 years. Only 25/100 (25%) of all CT scans performed were reported as normal. (See Figure 1). Of the 8 patients with normal CT at 3 years, 3 patients had previously had an abnormal scan (with all having other CF related changes). The majority of

'other CF related changes' were airway wall thickening and air trapping, whilst mucus plugging was only seen in conjunction with bronchiectasis.

22/50 (44%) of subjects had a treatment decision based on CT scan findings; 9/50 (18%) had a hospital admission and 4 of these proceeded to have regular admissions, 20/50 (40%) started a mucolytic and 2/50 (4%) commenced corticosteroids for treatment of allergic bronchopulmonary aspergillosis (see Figure 2).

The proportion of CT scans resulting in a treatment change was 18/50 (36%) of CT scans at 1 year and 13/50 (26%) of CT scans at 3 years respectively. Overall the majority (18/31, 58%) of treatment changes were prompted by the finding of bronchiectasis, whereas 13/31 (42%) of changes were prompted by other CF related changes. At 1 year, 7/18 (39%) of management changes were prompted by bronchiectasis, and 11/18 (61%) by other CF related changes. At 3 years, 11/13 (85%) of management changes were due to bronchiectasis and 2/13 (15%) were due to other CF related changes. The number of CT scans needed to be performed to lead to a treatment change was 3.2.

Regarding the effect of changes in management at 1 year of age on 3 year old CT scan result, of the 18 patients who had a change in management; 2 patients had improvement on CT at 3 years (1 went from bronchiectasis to normal, 1 from 'other CF related changes' to normal), 9 patients had the same CT classification, and 7 showed progression from other 'CF related change' to bronchiectasis.

4. Discussion and Conclusion

In this study we identified that clinicians frequently respond to results of CT chest findings in pre-school children by changing treatment regimens, including ordering admission for intensification of treatment and introduction of mucolytics. As abnormalities detected on chest CT scans at 1 and 3 years of age were very common, changes in treatment occurred frequently and the number of scans needed to result in a treatment change was 3.2. The identification of bronchiectasis on the CT scan was the most common finding that resulted in a treatment change, but in infants findings such as mucous plugging were relatively more likely to result in a treatment change. Although, the CT results at 3 years showed more severe disease, more changes in management were based on the results of CT at 1 year. This may be due to clinicians responding to more subtle changes at 1 year and even when CT at 3 year showed more severe disease, the patients were already on 'maximal' appropriate therapy.

There are several important limitations of this study, including a small and random sample, the limitations of a retrospective medical record review, and the fact it is a single centre study. Random sampling has the potential to bias the findings; for example, if the sample had more severe structural lung disease than average the effect on treatment decisions would be overestimated. When comparing the CT scan findings to those in the wider AREST-CF cohort, however, it appeared that the cohort of children in this study had milder structural lung disease. Sly *et al*¹ reported that 31% of children had bronchiectasis at 12 months and 61% had it at 3 years, whereas in this group only 18% had bronchiectasis at 12 months and 34% at 3 years. It is harder to compare the rates of other CF-related CT changes as Sly *et al*¹ did not report this. Given that the cohort included in this study had less bronchiectasis than the wider cohort, this would bias the results to underestimate the effect

of CT scans on clinical decision-making. Retrospective reviews of medical records can be open to bias, from inaccurate interpretation of documentation. However, the methods used in this study (whereby inconclusive records were recorded as 'no change' in treatment) would also have resulted in an underestimation rather than overestimation of the true effect. The study was based at a single centre with experience in obtaining high quality CT scans, and using results to aid clinical decision making. If a similar approach was used at a centre with less experience the effect of CT scans may be different due to either the quality of the CT scans obtained, or the familiarity of the CF team in factoring results into decision making.

An important consideration when evaluating the utility of CT scans is potential adverse events, including ionizing radiation exposure and the effect of general anaesthesia. It was outside the scope of this study to analyse these events. Extensive work has been undertaken to minimise radiation dose in the CT scans used in the study with specific low dose protocols developed. The current dose for a CT scan, and hence risk of adverse event, is extremely low.^{11,12} In the future, questions regarding the long-term effects of general anaesthesia in early life may be explained by the CF GAIN study, which has now completed data collection.¹³

It was also beyond the scope of this study to compare the potential clinical utility of CT scans and other investigations. Other potentially clinically useful investigations in young children with CF include alternate imaging modalities (chest X-RAY, or magnetic resonance imaging) and infant pulmonary function tests. In the research setting, CT has been shown to be the most sensitive tool to detect lung disease in young children with CF and hence will

likely be the most useful clinically.⁸⁻¹⁰ Despite this, future work should examine the clinical utility of alternate investigations.

Despite the limitations, these data demonstrate that by identifying early and clinically undetectable lung disease in CF, the finding of either bronchiectasis or other CF related changes on surveillance chest CT scans change clinical management by allowing implementation of treatments aimed at preserving respiratory health. The study showed that for every 3.2 scans undertaken at 1 or 3 years of age there resulted a treatment change. This provides evidence to support further evaluation of surveillance CT scans as a clinical tool in infants and young children with CF, ideally via a prospective multi-centre study with a larger sample size. A future study should also include evaluation of the negative aspects of carrying out CT scans in this age group (including general anaesthesia). Although treatment changes were introduced, there is as yet no evidence that these are beneficial. It would also be important to assess whether CT-initiated changes in clinical management alter long-term outcomes (such as limiting onset or progression of structural lung disease, lung function, and quality of life). If chest CT scans can be shown to contribute to improved outcomes in CF (such as reduced rates of bronchiectasis), then, as the associated radiation doses diminish further, chest CT could have an important clinical role in CF.

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Table 1. Summary of Patient Demographics, Result of Computed Tomography Scans, and Effect of Computed Tomography Scans on Clinical Management

Patient Demographics	
Male, n (%)	30 (60)
Age, years, median (range)	5.5 (3.25-11.9)
CT findings at 1 year	

Normal CT at 1 year, n (%)	17 (34)
CF-related changes on CT at 1 year, n (%)	24 (48)
Bronchiectasis on CT at 1 year, n (%)	9 (18)
Abnormal CT at 1 year, n (%)	33 (66)
Effect of CT at 1 year	
Hospital admission due to CT at 1 year, n (%)	3 (6)
Mucolytic started due to CT at 1 year, n (%)	16 (32)
Steroids started due to CT at 1 year, n (%)	0 (0)
CT at 1 year that yielded management change, n (%)	18 (36)
CT findings at 3 years	
Normal CT at 3 years, n (%)	8 (16)
CF-related changes on CT at 3 years, n (%)	25 (50)
Bronchiectasis on CT at 3 years, n (%)	17 (34)
Abnormal CT at 3 years, n (%)	42 (84)
Effect of CT at 3 years	
Hospital admission due to CT at 3 years, n (%)	6 (12)
Mucolytic started due to CT at 3 years, n (%)	4 (8)
Steroids started due to CT at 3 years, n (%)	2 (4)
CT at 3 years that yielded management change, n (%)	13 (26)
Patients with management changes due to CT, n (%)	22 (44)

Patient Demographics	
Male, n (%)	30 (60)
Age, years, median (range)	5.5 (3.25-11.9)
CT findings at 1 year	
Normal CT at 1 year, n (%)	17 (34)
CF-related changes on CT at 1 year, n (%)	24 (48)
Bronchiectasis on CT at 1 year, n (%)	9 (18)

Abnormal CT at 1 year, n (%)	33 (66)
Effect of CT at 1 year	
Hospital admission due to CT at 1 year, n (%)	3 (6)
Mucolytic started due to CT at 1 year, n (%)	16 (32)
Steroids started due to CT at 1 year, n (%)	0 (0)
CT at 1 year that yielded management change, n (%)	18 (36)
CT findings at 3 years	
Normal CT at 3 years, n (%)	8 (16)
CF-related changes on CT at 3 years, n (%)	25 (50)
Bronchiectasis on CT at 3 years, n (%)	17 (34)
Abnormal CT at 3 years, n (%)	42 (84)
Effect of CT at 3 years	
Hospital admission due to CT at 3 years, n (%)	6 (12)
Mucolytic started due to CT at 3 years, n (%)	4 (8)
Steroids started due to CT at 3 years, n (%)	2 (4)
CT at 3 years that yielded management change, n (%)	13 (26)
Patients with management changes due to CT, n (%)	22 (44)

Table 1. Summary of Patient Demographics, Result of Computed Tomography Scans, and Effect of Computed Tomography Scans on Clinical Management

Figure 1

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Figure 2

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