'To CT or not to CT? That is the question': outcome surrogates for surveillance in childhood cystic fibrosis

Carolyn Young, Catherine Owens

The benefit of the increasing utility of CT has been promoted as a potential long-term outcome surrogate for monitoring patients with cystic fibrosis (CF), and is recognised as a crucial part of CF research.[1] The study by the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) on the use of thin-section CT highlights the sensitivity of this imaging modality in providing insight into the early development of CF lung disease. The factors associated with the development and progression of structural lung disease in infants and preschool children diagnosed by the newborn CF screening programme[2] are described.

The argument for the increasing use of annual CT of the thorax as an outcome surrogate for measuring and monitoring the progression of lung disease in patients with CF is the ability of CT to detect subtle, salient lung parenchymal changes, as opposed to using conventional plain chest radiography or spirometry. However, lung clearance index (LCI), being more effective than spirometry, has been found to be as sensitive as high-resolution CT (HRCT) in detecting early lung abnormalities in infants, and together they compliment each other in providing markers for early CF lung disease in children.[3] Application of LCI is suitable in all age groups, which suggests its potential as an outcome measure to monitor progression of disease throughout the life of patients with CF, and thus help reduce the cumulative radiation dose.[4 5] It is suggested that, in clinical practice, LCI should be the first line of investigation to assess the presence of CF lung disease, and that HRCT should only be performed when LCI is normal. This is because a normal result on either measure is not predictive of a normal result in the other.[3] This approach would reduce unnecessary CT imaging and the ensuing associated radiation burden. It is estimated that the lifetime risk of subsequent malignancy associated with the use of HRCT of the thorax in a 2-year-old girl is 24 per 100 000, and 6 per 100 000 in boys.[6]

Because CF is a multisystem disorder, patients are often required to undergo numerous diagnostic and interventional procedures involving the use of ionising radiation throughout their life. This is in addition to potential chest CT imaging every year. This annual accumulation of diagnostic radiation exposure will ultimately increase the patient's lifetime risk of developing thoracic and abdominal malignancies in later life.[7] This is especially pertinent when life expectancy for patients with CF is increasing due to improved therapeutic intervention. The risk of developing a malignancy can be minimised if surveillance chest CT is carried out every 2–3 years (instead of annually) in lieu of plain chest radiography, as reported by a large European CF treatment centre.[8]

Although the increasing use of chest CT is controversial because of the potential risks of radiation exposure, the benefit as an outcome measure in CF clinical trials is well documented. The detection rate of bronchiectasis and evidence of air trapping in the AREST CF study using a limited three-slice CT scan protocol is noteworthy even though there is a possibility of underestimation in the findings. This is as a result of limited sampling of lung parenchyma in the three-slice technique. The other important question raised is whether there was true resolution of early detected 'bronchiectasis'. Despite this, bronchiectasis was detected in 75% of patients, with extent of bronchiectasis increasing in 63% of patients at follow-up. Air trapping was noted in 88% of patients, with increase in extent seen in 46% of patients at follow-up.

Therefore, in spite of early detection and interventional therapies, bronchiectasis was shown to persist and indeed progress, raising the question as to the effectiveness of the current standard treatment. However, novel therapies are emerging for adults with CF and have been described to use small molecule correctors and potentiators,[9 10] all of which necessitate the use of more sensitive and accurate markers of disease status and progression, and perhaps even regression.

An important point to note from the AREST CF study is the demonstration of an association between persistence and progression of bronchiectasis and air trapping in the presence of neutrophilic inflammation and pulmonary infection. That is, when infection and inflammation are present at the time of the initial scan, they are indicative for the future development of structural lung disease. Thus, and very importantly, early clinical detection and eradication of infection may prevent further structural lung changes. More importantly, respiratory symptoms were found not to be associated with an increased rate of persistence or progression of bronchiectasis and air trapping (although admittedly the cohort of children with symptoms was small at the time of CT imaging, and therefore cannot be relied upon to identify children at risk of future lung disease). Therefore one may postulate whether there is a necessity to carry out bronchoscopy with bronchoalveolar lavage, in addition to CT imaging, or whether screening by HRCT alone is sufficient as an outcome measure in clinical trials or is performed purely to document disease progression.

Another important association identified from the AREST CF study is the link between infants with the more severe CFTR genotype and more rapid progression of lung disease. This raises the question as to whether intervention can selectively be based on genotype findings alone. It would thereby perhaps appear prudent to carefully document disease progression by HRCT in this subgroup. There are strong arguments in favour of the use of CT in monitoring and quantifying lung disease in children with CF. However, the need to minimise radiation dose exposure is paramount, particularly in young children.

Cardio-thoracic Imaging Unit, Great Ormond Street Hospital for Children NHS Trust, London, UK

Correspondence to Dr Catherine Owens, Cardio-thoracic Imaging Unit, Great Ormond Street Hospital, London WC1N 3JH, UK; owensc@gosh.nhs.uk

The current trend in CF research trials (to which the authors have alluded) is to acquire a volumetric CT dataset of the entire thorax in inspiration and expiration. The advantage of acquiring this more robust dataset is a more precise evaluation of the entire lung parenchyma with improved understanding of the disease process in young children. The disadvantage is an additional threefold to fourfold increase in radiation burden. A compromise (as used in our clinical practice) is to perform a volumetric end-inspiratory acquisition followed by a limited interspaced three-slice end-expiratory CT protocol in children with known CF, or in those in whom lung disease is suspected or visualised on the inspiratory CT images.

As the most common lung parenchymal abnormality is air trapping in young children with CF (best defined by end-expiratory chest CT), Loeve et al[11] discussed the possibility and adequacy of fully evaluating CF-related structural lung abnormalities from a single end-expiratory volumetric dataset, thus achieving a 75% radiation dose reduction (compared with full inspiratory and additional expiratory datasets). However, clinicians must be confident that all the necessary diagnostic information is available from a single volumetric end-expiratory CT protocol to ensure an accurate diagnosis can be made when reviewing the images. Conventional standardised data for measuring bronchial wall thickness and dilatation (to assess bronchiectasis) have been established for inspiratory (and not expiratory) datasets. This will be a confounding factor when establishing new thresholds to long established criteria for diagnostic CT purposes.

It is pertinent to mention the difference in CT scanning technique and parameters used by the two participating institutions in this clinical study. The use of 120 kVp is no longer advocated in young children, especially when using a multi-slice CT scanner. From our experience and from that of Loeve et al,[11] the use of 80 or 100 kVp would have been sufficient, providing equally diagnostic and high-quality images (images which are 'fit for purpose') in this age group at a much lower radiation dose.

There was also a discrepancy in CT tube currents (mAs) (and therefore the estimated CT dose index—a measure of radiation exposure during the CT scan) between the two institutions. A 133% and 94% mAs increase was noted at the Perth centre for the inspiratory and expiratory series, respectively, with patients receiving twice the radiation dose as those at Melbourne. It is our experience that when CT imaging is carried out under controlled ventilation with the lungs held at full inspiration, the CT tube current could be further reduced without degradation of image quality due to the improved inherent contrast in the lung parenchymal tissue.

A crucial point to remember when carrying out multicentre trials is to standardise the CT scanning protocol (which is possible even with CT scanners from different manufacturers) so that the children recruited into trials are treated equally, receiving a similar radiation dose. More importantly, it cannot be overemphasised that image quality should be consistent across sites, enabling clinicians to review images that are of similar resolution and allowing unbiased scoring of the data.

If we are to advocate the routine use of CT imaging as a surrogate outcome measure for patients with CF,[12] we must justify and optimise the examination parameters. The development and use of a low-dose imaging technique should be 'fit for purpose', that is, diagnostic images acquired with radiation doses 'as low as reasonably achievable', thus ensuring children are not subjected to overexposure to radiation that is an increased risk with no additional benefit.

AREST CF's ongoing research, which is using revised CT scanning and dose optimisation techniques as described, assumes that a fourfold increase in radiation dose will result if the chosen transition is made to volumetric CT data acquisition in inspiration and expiration. Clearly any potential benefit gained from a more sensitive (whole lung sampling volumetric) scanning technique carries with it an increase in radiation exposure, which will pose an additional risk to the patient. It will be of interest to follow the progress of this piece of essential longitudinal research in patients with CF.

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Correction

Young C, Owens C. 'To CT or not to CT? That is the question': outcome surrogates for surveillance in childhood cystic fibrosis. *Thorax* 2012;**67**:471—2

The following sentence should read:

However lung clearance index (LCI) being more effective than spirometry has been found to be as sensitive as HRCT in detecting early lung abnormalities, in a group of school age (8 year old) children, and together they compliment each other in providing markers for early CF lung diseases in children.[3]

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