# Chest CT in Bronchopulmonary Dysplasia: Clinical and Radiological Correlations

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Summary. Background: Chest CT is very sensitive in assessing pulmonary damage in bronchopulmonary dysplasia (BPD) and radiological findings in BPD are well described. Validated CT scores are available to assess BPD, as available in other pulmonary diseases such as cystic fibrosis. Aim: To investigate whether there is a correlation between radiological pulmonary lesions and relevant BPD clinical data (gestational age, type and duration of mechanical ventilation, and severity of BPD) and assess the usefulness of a CT score in evaluating clinical severity. Materials and Methods: Retrospective study of 19 premature infants with BPD born between 1998 and 2007 who underwent at least one chest CT during their first year of life. A total of 29 CT were blindly evaluated by two radiologists for the presence or absence of pulmonary parenchymal abnormalities described in BPD (areas of decreased attenuation, presence of bullae/emphysema, bronchial wall thickening, bronchiectasis, linear, and subpleural opacities). This score was then compared with the most relevant clinical data. Results: All CT scans showed abnormalities. The most frequent lesion was bronchial wall thickening observed in all patients, followed by linear (89.5%) and subpleural (89.5%) opacities. Areas of decreased attenuation were found in 68.4%. Bullae/emphysema and bronchiectasis were the less frequent item described (26.3% and 21.1%, respectively). The presence of areas of decreased attenuation significantly correlated with BPD severity (P = 0.03). However, there was no significant correlation between the CT score and clinical data. Conclusions: This study demonstrates the potential usefulness of chest CT score to assess the severity of BPD. Areas of decreased attenuation seem the most sensitive item to predict BPD severity. More patients are needed to validate this approach and to evaluate the long-term usefulness of CT scan. Pediatr Pulmonol. 2013; 48:693-698. © 2012 Wiley Periodicals, Inc.

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## INTRODUCTION

Bronchopulmonary dysplasia (BPD), a well-known consequence of prematurity, is associated with a high morbidity and is considered the main cause of chronic lung disease in infancy. Its incidence is inversely related to gestational age (GA) and birth weight (BW).<sup>1</sup> In Switzerland, recent data reported the incidence of BPD to be 13-17% of all preterm births.<sup>2</sup> Initially related to the effects of aggressive mechanical ventilation and oxygen toxicity on the lungs, BPD is a multifactorial process and is now partly attributed to a disruption or an arrest in lung development.<sup>1,3</sup> Since initially described, its incidence has remained stable due to an increase in the survival of extremely premature infants of very low BW.<sup>4</sup> Because of the change in BPD clinical presentation, the National Institute of Child and Human Development (NICHD) proposed a new definition based solely on oxygen use<sup>5</sup>; BPD is now defined as oxygen dependency for at least 28 days after birth, and the severity is graded according to the need for oxygen or <sup>1</sup>Paediatric Pulmonology Unit, University of Geneva Children's Hospital, Geneva, Switzerland.

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ventilatory support at 36 weeks postmenstrual age (PMA). Therefore, the definition is mostly clinical.

Functional evaluation of children suffering from BPD can be performed in specialized research laboratories,<sup>6</sup> whereas radiological evaluation is available in most pediatric centers. Chest CT has been shown to be a more sensitive tool than chest X-ray in assessing pulmonary damage following premature birth, providing an objective evidence of lung injury.<sup>7</sup> Pulmonary parenchymal abnormalities found in BPD are well described and include multifocal hyperlucent area, linear and subpleural opacities, bronchial wall thickening, bullae, and bronchiectasis.<sup>7,8</sup> Multiple scoring systems that analyze some,  $^{9,10}$  or all items,  $^{11,12}$  are available to assess chest CT scan in BPD. Some of these scores have been thoroughly validated.<sup>11,12</sup> Even though most studies show a correlation between clinical severity and radiological scores, there are no radiological prognostic factors usable in the clinical management of BPD.

We hypothesize that clinical data correlated with radiological score. We aimed to evaluate pulmonary parenchymal abnormalities found in BPD by using a validated chest CT score,<sup>11</sup> to correlate radiological findings with disease severity and clinical characteristics, and to determine the potential usefulness of HRCT findings in the evaluation of BPD.

## MATERIALS AND METHODS

#### Patients

We retrospectively studied preterm infants born between 1998 and 2007 at the Geneva University Hospital. Study selection criteria were a diagnosis of moderate to severe BPD, and at least one chest CT performed either routinely or because of a protracted clinical course. BPD was defined following the NIH recommendations as "supplemental oxygen use for at least 28 days," and severity was graded according to the need for oxygen or ventilatory support at 36 weeks PMA.<sup>5</sup> The study was approved by the human research ethics committee of the University Hospital of Geneva. Because this study was retrospective and involved only medical charts and imaging review, the ethics committee of the Institution did not require parental consent but only the study approval.

## **CT Protocol**

Children were sedated with halogenated sevoflurane gas to maintain spontaneous breathing. If required, they were assisted by facial mask ventilation. Apnea was induced with intravenous Propofol or Alfentanyl. Highresolution CT scans were performed with a Siemens Sensation 64, a GE medical systems highspeed CT or a Philips MX 800 CT obtaining 1-mm section at 5- or 10mm intervals from the apex to the diaphragm. This dataset is generally used for CT scan when performed to assess chronic lung disease in order to minimize the radiation dose. Full inspiration was obtained with positive pressure, and expiration without respiratory support. Lung window settings were used for the display. Scan parameters used were between 80 and 140 for kV (median 120) and between 50 and 200 for mAs (median 100). Before 2008, there was a great dispersion between the different centers in the product dose length (PDL) delivered to the patients. First recommendations were made according to Verdun survey in 2008<sup>13</sup> and Swiss official recommendations were published by OFSP (Office fédéral de la santé publique) in 2010. CT images were evaluated for the presence of pulmonary abnormalities described in BPD<sup>7,14</sup> using Fleishner's glossary of terms.<sup>15</sup> Areas of decreased attenuation were defined as diminished lung density resulting from hypoperfusion, bullous emphysema as bullous destruction of the lung parenchyma, bronchial wall thickening as bronchovascular interstitial thickening, subpleural opacities as small triangles with a pleural base and an internal apex, linear opacities as continuous thickening of peribronchial area, and finally bronchiectasis as bronchial dilatation with respect to the accompanying artery, lack of tapering of bronchi, or identification of bronchi within 1 cm of the pleural surface.

CT scans were evaluated for the number of affected lobes for each pulmonary abnormality. The absence of lesions was scored zero and their presence was graded from one to six according to the number of affected lobes (lingula included). The CT scores ranged from 0 (no abnormalities) to 36 (each abnormality in all 6 lobes), such that a higher score reflected more severe disease. According to Aukland et al.,<sup>11</sup> the option to base the scores on findings in the different lung lobes instead of lung segments makes the scoring process less complex, reducing the risk of inaccuracies. The CT scans were blindly reviewed by two radiologists, first independently, then by consensus in case of discrepancy. We report only the consensus scores.

## **Neonatal Data**

Neonatal data was obtained from the medical records of the neonatal intensive care unit. Variables such as GA, BW, type/duration of mechanical ventilation, and oxygen supplementation were analyzed.

Other potential contributing factors known to increase the risk of BPD such as chorioamnionitis, necrotizing enterocolitis (NEC), hyaline membrane disease (HMD), patent ductus arteriosus (PDA), and neonatal sepsis were also recorded.<sup>2,16</sup> Medical interventions (surfactant, ante-postnatal steroids, and diuretics) and two significant clinical parameters,  $pCO_2$  and respiratory rate at 28 days and 36 weeks PMA, respectively, were also analyzed.

## **Statistical Analysis**

The clinical characteristics, the clinical data and the CT findings were described by percentage or median (with range). The radiological items (scored on a scale 0-6) were compared to the binary clinical data (BPD severity, surfactant, corticosteroids using a Fisher exact test. The median number of affected lobes according to BPD severity was analyzed using a Mann–Whitney *U*-test. Associations between the radiological items and the quantitative clinical data (GA, BW, duration of CPAP, duration of O<sub>2</sub>, respiratory rate, and pCO<sub>2</sub> at 28 days and 36 weeks PMA) were explored using linear regression models. Comparisons between sub-groups were performed using Fisher exact tests or Mann–Whitney's *U*-tests.

The radiological items were binarized into categories: absent (score of zero), or present (score of one or more). The positive predictive value of each radiological item in the prediction of BPD severity was assessed (proportion of severe patients among the patients with a score >0). The confidence intervals (95%) were obtained by the Clopper–Pearson method.

The global agreement of CT findings between the two readers was assessed by the Cohen's Kappa coefficient interpreted on the Landis and Koch scale: the agreement is almost perfect for a Kappa statistic beyond 0.80, substantial between 0.60 and 0.80, moderate between 0.40 and 0.60, fair between 0.20 and 0.40, and slight below 0.2.

## RESULTS

## **Study Patients**

According to Geneva's Maternity Hospital database, a total of 3,717 preterm infants (under 37 weeks GA) were born between 1998 and 2007, representing 10.4% of all births. Among these, 88 (2.4%) developed moderate or severe BPD according to the NICHD definition.<sup>5</sup>

Nineteen premature infants (10 boys, 9 girls) who underwent at least one chest CT were included in the study group. Median GA at birth was 26.1 weeks (range, 24.3–33.3) and median BW was 740 g (range, 510–1,370). Six patients (31.6%) were classified as moderate BPD (supplemental oxygen use  $\geq$ 28 days and oxygen <30% at 36 weeks PMA or discharge) and 13 patients (68.4%) as severe BPD (supplemental oxygen use  $\geq$ 28 days and oxygen >30% and/or CPAP at 36 weeks PMA or discharge). Median age at the first CT was 14.6 months (range, 1.5–53.7). Patient characteristics are summarized in Table 1.

## **CT Findings**

Nineteen patients underwent at least one chest CT at the median age of 14.6 months (1.5–53.7). Four patients had two or three imaging studies performed at the median age of 19.5 months (3.9–63.7) for the second one and 80 months (24–99) for the third one.

All CT scans showed abnormalities. The most frequent abnormality was bronchial wall thickening in all patients (100%; Fig. 1a). Linear and subpleural opacities were observed in 17 cases (90%). Areas of decreased attenuations were detected in more than half of the patients (69%; Fig. 1b), and only five patients (26%) presented emphysema. Bronchiectasis was visible in only four cases (21.1%).

The presence of bronchial wall thickening affected at least four lobes for all patients, whereas the presence of all other items was more variable. For the lesions including bronchial wall thickening, linear opacities, subpleural opacities, and emphysema/bullae, the proportion of patients who had at least one lobe affected was similar between severe and moderate BPD (P = 1).

In the four patients who had more than one chest CT (between 10.6 and 43.2 months later), the lesions remained fairly stable over time, with poor improvement, and no further evolution.

#### Interobserver Reproducibility

Agreement of CT findings between the two reviewers was further evaluated using the Cohen's kappa indice. Bronchial wall thickening, bronchiectasis, and subpleural opacities showed high concordance (Cohen's kappa ranged from 0.79 for bronchial wall thickening to 0.99 for emphysema/bullae). Concordance was inferior but still substantial for the items attenuation (Cohen's kappa = 0.62) and linear opacities (Cohen's kappa = 0.71).

#### **Correlation Between CT Findings and Clinical Data**

There was no significant correlation for the comparison of each radiological item from the baseline CT,

#### TABLE 1—Clinical Characteristics

	N = 19
Sex (M/F)	10/9
GA (weeks)	26.1 (24.3–33.3)
BW (g)	740 (510–1,370)
BPD severity	
Moderate	6
Severe	13
Age at 1st CT scan (months)	14.6 (1.5–53.7)

GA, gestational age; BW, birth weight. Data are presented as median (range).

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Fig. 1. a: 13 months old boy with severe BPD. Inspiratory axial CT showing regions of attenuation (arrowheads), parenchymal linear opacities (black arrow), bronchial wall thickening, and bronchiectasis (white arrow). b: 3 years old girl with severe BPD. Inspiratory axial CT showing regional attenuations (arrowheads). The pulmonary vessels caliber in those areas are smaller. Bronchiectasis (white arrows) is also noted.

individually and as a total score, to the clinical data. However, when comparing the radiological items to BPD severity, there were significantly more areas of decreased attenuation in severe BPD compared to moderate (P = 0.046; Fig. 2). Furthermore, there were significantly more lobes showing decreased attenuation according to BPD severity (P = 0.03). Differences in other parenchymal abnormalities and median composite score were not statistically different between moderate and severe BPD (Table 2).

The positive predictive value of each radiological item assessed by binary categorization was good to excellent to predict BPD severity: subpleural and linear opacities: 70.6% (44.1–89.7), bronchectasis: 100.0% (39.8–100.0), emphysema: 80.0% (28.4–99.5), and attenuation: 84.6% (54.6–98.1).

## **Risk Factors and Medical Interventions**

The highest risk factor for severe BPD was the presence of HMD (P = 0.004). 13/19 patients had PDA. The ratio of PDA in severe (9/13) and moderate BPD (4/6) was not different and the number of clinical sepsis, NEC and chorioamnionitis were not significantly relevant.

The most important drug therapies used in the prevention and management of BPD were analyzed. To the



Fig. 2. Distribution of parenchymal abnormalities according to BPD severity.

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exception of surfactant used more often in patients with severe BPD (P = 0.02), there was no significant difference in the administration of diuretics between moderate and severe BPD (used in all children, 100%), or steroids (prenatal P = 0.52, postnatal P = 0.62).

## **Respiratory Support**

All patients with moderate and severe BPD required oxygen supplementation and CPAP during their neonatal period, while 79% were mechanically ventilated. Mechanical ventilation (MV) was more frequent in severe BPD, but median duration of MV was similar between severe and moderate BPD (21.5 days vs. 26 days, respectively). The use of CPAP was longer in severe BPD. There was no difference in the mean duration of oxygen therapy.

## **Prognosis Data**

Median pCO<sub>2</sub> was significantly higher at 36 weeks PMA for severe BPD patients compared to moderate (7.9 kPa vs. 6.27 kPa, P = 0.03), but not at 28 days PMA when BPD was diagnosed (7.4 kPa vs. 7.29 kPa, respectively).

## TABLE 2—Number of Affected Lobes According to BPD Severity

	Moderate BPD, N = 6 lobes	Severe BPD, N = 6 lobes	$P^1$
Bronchial wall thickening	6 (6–6)	6 (4–6)	0.32
Linear opacities	5 (0-6)	3 (0-6)	0.85
Subpleural opacities	3 (0-6)	4 (0-6)	0.56
Attenuations	0 (0–5)	2 (0-6)	0.03
Bullae	0 (0-4)	0 (0-6)	0.5
Bronchiectasis	0 (0–0)	0 (0-4)	0.14
Median composite score <sup>2</sup>	12 (9–27)	18 (8–24)	0.28

<sup>1</sup>Mann–Whitney *U*-test. Data are presented as median (range).

<sup>2</sup>Median composite score on 6 lobes  $\times$  6 radiological items = total score of 36.

Median respiratory rate was comparable in the two groups (49/min at 28 days and 50 at 36 weeks PMA for moderate BPD vs. 44 and 55/min, respectively for severe BPD).

### DISCUSSION

In this retrospective study, we used a validated chest CT score<sup>11</sup> to describe pulmonary parenchymal abnormalities found in BPD, and we correlated radiological findings to disease severity and clinical characteristics. We assessed the score's usefulness in predicting the severity of BPD.

Thoracic CT allows good assessment of lung morphology. Moreover, it is a very sensitive method to detect and quantify lung disease. Indeed, in cystic fibrosis (CF), CT imaging is known to correlate with clinical measures of disease severity and to correspond to path-ological findings.<sup>17</sup> In BPD, previous studies have shown that all survivors born before the mid-1990s had abnormalities on CT scanning, whether they still presented pulmonary signs or symptoms<sup>7</sup> or not.<sup>8,18</sup> Nowadays, the CT scores of BPD patients compared with those of healthy control subjects are significantly higher in children with persistent chronic lung disease of infancy, and correlate significantly with the number of days of supplemental oxygen,<sup>19</sup> reflecting more severe disease. Likewise, in a prospective study evaluating infants with BPD with a more complex CT analysis grid, there was a significant correlation between CT scores and the duration of oxygen supplementation, but not with the duration of mechanical ventilation.<sup>10</sup>

The most frequent abnormal CT findings described in BPD are well-defined linear opacities, areas of decreased lung attenuation, and triangular subpleural opacities. Associated pathologic features are strands of atelectasis extending to the pleura for linear opacities, and small airway obstruction leading to obstructive emphysema for reduced attenuation.<sup>7,20</sup> In our patient population, the most frequent abnormality was bronchial wall thickening, suggesting that there might be airway changes with peribronchial and peribronchiolar fibrosis, added to the dysregulation of lung morphologic maturation with an arrest at the canalicular phase of lung development and simplified alveolar septation.<sup>21</sup> Thus, BPD is a chronic disease involving lung parenchyma and airways.

Interestingly, bronchiectasis was only rarely found in our population and did not predict any clinical outcome. However, the presence of bronchiectasis was associated with BPD severity even more significantly when combined with areas of attenuation.

In our retrospective analysis, the single item which correlates significantly with BPD severity was the presence of areas of decreased attenuation. Similarly, in the first study looking at correlations between CT and clinical findings,<sup>9</sup> only the extent of hyperaeration correlated to clinical severity, even if the clinical items evaluated are not part of the BPD grading system now in use. Thus, hyperaeration possibly reflects a decreased number of functional alveoli, consequently playing an important role in the impairment of pulmonary function and BPD severity. Therefore, the item attenuation could be most useful to predict the severity of BPD.

Chest X-rays abnormalities found in BPD are known to gradually improve in the long term.<sup>16</sup> Little is known about the evolution of CT scan abnormalities. Although follow up of radiological lesions was not the purpose of this retrospective study, in the four patients who had repeated chest CT in a relatively short time, the lesions remained stable with poor improvement and no further degradation. Indeed, according to Aquino et al.,<sup>18</sup> abnormal findings on high resolution CT scans were described in 92% of children and adolescents with a past history of BPD. The correlation between CT scan and functional evolution should be addressed in further prospective studies.

Moreover, the risks of irradiation during CT should not be underestimated despite using automatic exposure systems and age-based Diagnostic Reference Levels (DRL) as advocated by Verdun.<sup>22</sup>

The comparison of chest CT findings and pulmonary function tests in BPD survivors has shown conflicting results. Aukland et al.<sup>11</sup> found a significant association between decreased maximal expiratory flow rates and HRCT scores. On the contrary, Sarria et al.<sup>19</sup> found that CT score was more accurate in discriminating between the patients with CLDI and the controls, even if BPD survivors had lower forced expiratory flows. CT imaging, with an appropriate evaluation grid, is certainly complementary to pulmonary function testing in the evaluation of BPD patients and both methods offer different assessments of the lungs.

The major drawbacks of this study come from its retrospective nature and the small sample size, limiting significant correlations with clinical data and outcomes such as rehospitalization or death.

In conclusion, the reading and interpretation of pulmonary CT findings in BPD according to a validated score is easily feasible. It can be useful in assessing the severity of this disorder, and areas of decreased attenuation seem to be the most sensitive radiological item to predict BPD severity. However, this cannot be used at the present time to predict BPD evolution. As CT requires sedation and provides the child with radiation exposure, this exam should be performed when CT findings are expected to have direct impact on clinical management. We suggest the acquisition of further prospective data to better evaluate the impact on treatment and outcome of BPD patients before implementing routine chest CT in their management.

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