CT Imaging Assessment of Response to Treatment in Chronic Pulmonary Aspergillosis Link

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Reference (Published version):
Godet, Cendrine; Laurent, Francois; Bergeron, Anne; Ingrand, Pierre; Beigelman-Aubry, Catherine; Camara, Boubou; Cottin, Vincent; Germaud, Patrick; Philippe, Bruno; Pison, Christophe; Toper, Cecile; Carette, Marie France; Frat, Jean-Pierre; Beraud, Guillaume; Roblot, France & Cadranel, Jacques(2016) CT Imaging Assessment of Response to Treatment in Chronic Pulmonary Aspergillosis. In: CHEST, 150(1), p. 139-147

DOI: 10.1016/j.chest.2016.02.640
Handle: http://hdl.handle.net/1942/22551
Computed Tomography Assessment of Response to Treatment in Chronic Pulmonary Aspergillosis

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PII: S0012-3692(16)01259-9
DOI: 10.1016/j.chest.2016.02.640
Reference: CHEST 317

To appear in: CHEST

Received Date: 29 October 2015
Revised Date: 9 December 2015
Accepted Date: 2 February 2016


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
COMPUTED TOMOGRAPHY ASSESSMENT OF RESPONSE TO TREATMENT IN CHRONIC PULMONARY ASPERGILLOSIS

Running title: Assessing CPA treatment outcome

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ACHROSCAN study group (CT-SCAN evaluation of CHRONic pulmonary Aspergillosis): for a complete list of the study group members, please refer to the Acknowledgements section.

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Conflict of interest:
Cendrine Godet: received consultancy or speaker fees, travel support from Pfizer, Astellas, Gilead, MSD, SOS Oxygene and ISIS Medical.
Anne Bergeron: received advisory board fees from MSD and Pfizer, speaker fees from MSD, Pfizer and Gilead and travel support from Vitalair.
Vincent Cottin: reports personal fees from Actelion, personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from Gilead, personal fees from GSK, personal fees from Intermune / Roche, personal fees from Novartis, personal fees from Roche, personal fees from Sanofi, personal fees from Biogen Idec, outside the submitted work; and Dr. Cottin's wife is an employee of Sanofi Pasteur.
Patrick Germaud: received consultancy or speaker fees and travel support from Pfizer and
Novartis.

Christophe Pison: received honoraria from Pfizer for speaking activities.

France Roblot: received consultancy or speaker fees and travel support from Astellas, Gilead and Pfizer and is president of French Infectious Diseases Society (SPILF).

Jean-Pierre Frat: reports personal fees from SOS OXYGENE, outside the submitted work.

François Laurent, Pierre Ingrand, Catherine Beigelman-Aubrey, Boubou Camara, Bruno Philippe, Cécile Toper, Marie France Carette, Guillaume Béraud, Jacques Cadranel have nothing to disclose.

**Source of the support:**

This study was funded by grants from Pfizer, Paris, France; ASTELLAS Pharma SAS, France; SOS Oxygène, Nice, France; ISIS Médical, France; AADAIRC, Poitou-Charentes, France. The funder of the study provided access to the Research database, which included collection and management of data. The funder of the study had no role in study design, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

**Notation of prior abstract publication/presentation:**

Patients included in this study are part of an ACHR OSCAN database. One part of this database was the subject of a recent publication in the European Respiratory Journal (Godet C, Laurent F, Béraud G et al; for ACHROSCAN study group. Phenotyping chronic pulmonary aspergillosis by cluster analysis. *Eur Respir J*. 2015 Sep 17. doi: 10.1183/13993003.00869-2015). The results presented in the submitted manuscript do not overlap with the results presented elsewhere.

Some of the results of our study have been previously reported in the form of an abstract at the ERS International Congress 2015, Amsterdam Netherlands, 26-30 September (Godet C, Laurent F, Bergeron A et al. Computed tomography assessment of response to treatment in

Abbreviations: CPA = Chronic Pulmonary Aspergillosis; CT = computed tomography; ABPA = allergic bronchopulmonary aspergillosis; IPA = invasive pulmonary aspergillosis; SA = simple aspergilloma; ICC = Interclass Correlation Coefficient; CI = confidence interval; COPD = chronic obstructive pulmonary disease.
**ABSTRACT:**

**Background:** Long-term antifungal therapy is usually the only treatment option for Chronic Pulmonary Aspergillosis (CPA). However, response rates are difficult to compare because the reported clinical, mycological or radiological criteria are not standardized. Objective parameters are therefore needed. To define the most relevant computed tomography (CT) variables in assessment of response to treatment, we investigated changes over time in CT variables.

**Methods:** Changes in CT variables were assessed by systematic analysis of the CT findings of 36 patients at diagnosis and 6 months after initiation of treatment. The relevant radiological variables were determined by selecting those showing significant changes over time. Two experienced thoracic radiologists independently performed CT-scan analyses blinded for clinical and serological response. Inter-reader agreement and concordance between radiological and clinical response were evaluated.

**Results:** Out of the 36 patients, seven clinically deteriorated on therapy. Significantly evolving radiological variables were cavity and pleural wall thickening (P<0.05), which were associated with clinical improvement. There was a strong association between fungus ball disappearance and cavity/pleural wall thickening reduction and clinical improvement (P=0.04). There was poor agreement between size changes of cavities or nodules, and clinical evolution (Cohen’s κ, -0.13 to -0.24).

**Conclusions:** Variations in cavity and pleura wall thickness may be the most relevant CT variables for assessing response to treatment. Loss of fungal ball is strongly associated with clinical and radiological improvement, but cavity size changes are unrelated to CPA evolution. All these CT variables may be applied in future clinical trials to assess treatment outcome.

**Key words:** Chronic pulmonary aspergillosis, computed tomography, CT, radiological
response, treatment outcome.
INTRODUCTION

Aspergillus infection-related pulmonary disease may present with various aspects. Overall, three clinical conditions can be distinguished: allergic bronchopulmonary aspergillosis (ABPA), caused by the bronchial colonization of Aspergillus spp. in patients with asthma and cystic fibrosis; acute invasive pulmonary aspergillosis (IPA) affecting severely immunocompromized patients, and the chronic forms of pulmonary Aspergillus infection, usually referred to as Chronic Pulmonary Aspergillosis (CPA).\textsuperscript{1,2} CPA is a debilitating syndrome characterized by slowly progressive lung cavitation in patients with pre-existing structural lung diseases, even though other patterns have also been identified.\textsuperscript{3} Aside from surgical simple aspergilloma (SA), long-term antifungal therapy, lasting at least six months, is usually the only treatment option available.\textsuperscript{2} Even if the efficacy of systemic antifungal treatments has been assessed, the criteria for defining response to treatment have pronouncedly varied between studies.\textsuperscript{3-15} Clinical criteria for assessing response to treatment, such as improvement in daily life activities and health status, are subjective and standardized respiratory sample processing to define eradication of Aspergillus in the respiratory tract is lacking.\textsuperscript{8,13,16} Other authors have proposed CT-scan criteria for assessing response to treatment, but their criteria were predetermined rather than based on thorough and independent analysis of CT features, and they differed from one study to another.\textsuperscript{4,8,13} The most common predetermined variables used in the previous studies to define radiological response included cavity and pleural wall thickening, size/number of cavities and fungus ball and presence or not of pericavitary infiltrates. However, pericavitary infiltrates were not well-defined and pericavitary thickening or cavities was not considered in all the studies.\textsuperscript{4,8,13} The aim of the present study was to assess changes over time in CT variables in order to define the most relevant CT variables in assessment of response to antifungal therapy in CPA
(SA excluded). Evolution of radiological variables was also evaluated in terms of concordance with the observed clinical response.

**Patients and Methods**

**Study design**

Between January 2002 and December 2011 we conducted a retrospective study in eight chest departments of French university hospitals (ACHROSCAN database). The study was approved by the research-oriented Ethics Committee (DR-2012-304) of Poitiers, France.

**Subjects**

All subjects who satisfied the CPA definition\(^3\) excluding simple aspergilloma and had a whole thorax CT at time of diagnosis and six months after treatment were included in the study. The 6-month follow-up CT corresponded to the minimum duration of antifungal treatment for CPA.\(^2\)

Inclusion, exclusion criteria and clinical data collection are detailed in e-Supplemental Material.

**CT variables and measurement**

CT images were independently reviewed by two chest radiologists (FL, CBA) blinded to the clinical data, and who reached a final decision by consensus. The initial CT examination and the 6-month CT were analyzed jointly. The following features were collected in each lung: number/volume of cavities, maximal cavity wall thickness; number/volume of fungus balls; maximal thickness and extent of pleural thickening; presence of pleural effusion, calcifications, and pneumothorax. Alveolar consolidation, ground-glass attenuation, and
nodules were also assessed. Finally, lobar collapse(s) and bronchiectases including severity and locations were recorded. Labelled examples of patients with various item measurements are shown in e-Figure 1 (see e-supplemental material).

Significance of changes was defined as at least 30% for volume of the fungus ball or cavities, 20% for cavity wall and pleural thickening, with a minimum of 2 mm. These criteria took into account the limited reproducibility of measurements on CT images.\textsuperscript{17,18}

**Clinical and radiological classifications**

The clinical categories of response commonly used in previous studies\textsuperscript{4,8} were based on assessment after six months of treatment of the patient’s sense of well-being, weight gain, improvement in cough, expectoration, haemoptysis, fever, fatigue, chest pain, and dyspnea. Worsening was defined by aggravation of at least one symptom or weight gain <3 kg; Improvement by attenuation of at least one symptom or weight gain \( \geq 3 \) kg; stable, otherwise.

Evolution of the selected CT variables was divided into two categories: stable or improved, and deteriorated, according to the changes observed on CT findings (see e-supplemental material).

**Statistical analysis**

Qualitative data are presented as number of patients and percentage. Quantitative variables are presented as means ± SD.

To identify any selection biases resulting from inclusion based on the availability of the 6-month follow-up CT, characteristics of included patients were compared to those of the others registered in the database with Chi-squared test, or Fisher’s exact test for proportions, and Student’s t-test or a nonparametric rank for means.
Changes of radiological variables between 0 and 6 months were assessed using McNemar or binomial exact test for paired proportions and nonparametric Wilcoxon test for paired means. Agreement of radiological variables with the observed clinical response were quantified by Cohen’s kappa coefficient\textsuperscript{19} (see e-supplemental material); this analysis included variables selected on the basis of a significant change at 6 months, and variables which did not change significantly, but which had been selected in previous studies\textsuperscript{4,8,13} to define radiological response. McNemar’s test or exact binomial tests were used as tests of symmetry of discordant observations. Univariate and multivariate associations between clinical response and radiological variables were assessed using Fisher’s exact test and logistic regression analysis respectively. Odds ratios were computed with their 95% confidence intervals. A P-value of less than 0.05 was considered to be statistically significant. Data analysis was performed with SAS software (version 9.4, SAS Institute, North Carolina, USA).

RESULTS

Patient characteristics

Thirty-six out of the 127 patients enrolled in the ACHROSCAN database satisfied the inclusion criteria. No significant difference was found, in terms of clinical characteristics at entry, between the whole study population and patients included in the database who did not satisfy the inclusion criteria (CT follow-up at six months) (Table 1). Patients had a mean age of 58 ± 12 years and were more frequently males (61.1%). The most common underlying conditions were previous history of pulmonary tuberculosis in 14 patients (38.9%) and chronic obstructive pulmonary disease (COPD) in 11 (30.6%). Thirty patients (83.3%) had risk factors, mainly represented by a history of oral corticosteroid use in 13 (43.3%). The
commonest presenting symptoms were cough in 33 patients (91.7%), sputum in 26 (72.2%), haemoptysis in 12 (33.3%), and weight loss in 21 (58.3%). Direct examination of sputum revealed *Aspergillus* hyphae in 18 patients (50%). Sputum cultures were positive in 25 patients (69.4%). *A. fumigatus* precipitins were positive in 29 patients (80.6%). All 36 patients received at least 6 months of antifungal therapy by voriconazole in 31 (86%), itraconazole in 4 (11%) or posaconazole in 1 (3%).

**CT variables at the time of diagnosis**

At time of CPA diagnosis, the most common CT abnormalities were cavities in 32 patients (91.4%), which were unilateral in 21 (65.6%) and predominantly in the upper lobes (Table 2). Cavitation walls were thick in 31 patients (85.1%). Cavities contained fungus balls in 20 patients (55.5%), which were unilateral in 19 (86.4%). Pleural thickening (contiguous to cavities) was identified in 29 patients (81.6%). Additional predominant features in the pericavitary infiltrates were areas of consolidation in 24 patients (66.7%), and tree-in-bud or nodules >5 mm in 16 (44.4%). Other findings included: aerated lobar collapse in 22 patients (62.9%), and bronchiectases in 28 (78.0%). For categorical variables, inter-reader κ-weighted values ranged from 0.64 to 1 and ICC for continuous variables from 0.92 to 0.99 (e-Table 1).

**CT variable changes between time of diagnosis and 6-month CT**

Significant changes in two CT variables were found between M0 and M6 (Table 2). Decreased pleura thickness was the most frequently observed finding (Figure 1). Decreased cavity wall thickness was also observed between M0 and M6 (Figure 1). Other variables did not significantly differ between M0 and M6.
Concordance and association between radiological and clinical response to treatment

Clinical categories of response were established for all 36 patients, of whom seven clinically deteriorated on therapy. Indices of agreement and evolution of each radiological parameter in clinically worsened patients are shown in Table 3. Decreased or stable thickness of the pleura was observed in all patients (36/36), (Figure 2A). Decreased or stable thickness of the cavity wall was observed in 28/29 (96.6%) patients (Figure 2B). The evolution of these two radiological parameters was paralleled by clinical evolution in 29/36 patients (80.6%) and 23/29 (79.3%), respectively for pleura thickness and cavity wall thickness. Improvement of pleura and cavity wall thickness was observed in all clinical responders (respectively 29 and 22 patients, respectively for pleura and cavity wall thickness).

The changes in fungus ball and cavity volumes were not significant over time. Decreased and stable fungus ball volume was observed in 15/20 (75%) patients and an increase in 5/20 (25%) patients with clinically paralleled evolution in 15/20 (75%), (Figures 2C, 3). In 6 patients, the fungus ball had disappeared by M6. All were clinically and radiologically improved at M6 with marked improvement of all other CT variables and a significant association between radiological and clinical evolution (P=0.04).

Concerning cavity volume, 6 (24%) out of the 25 patients who were clinically improved (Figures 1, 2D) presented a paradoxical increase in cavity size. Agreement with clinical evolution was poor, as indicated by the significant negative kappa of -0.24 (95% CI, -0.37, -0.11).

Concerning changes of the pericavitary infiltrates (tree-in-bud, nodules >5mm, lobar collapse, areas of consolidation), agreement was poor for tree-in-bud and nodules as indicated by a significant negative kappa of -0.16 (95% CI, -0.27, -0.05) and -0.13 (95% CI, -0.25, -0.02) respectively. For lobar collapse and areas of consolidation, Cohen’s kappa was non-significant.
No variable associated with favourable clinical evolution was retained in the multivariate logistic regression analysis.

**DISCUSSION**

This is the first study to assess changes over time in CT variables in order to define the CT criteria most relevant to determine therapeutic response in patients with CPA. Pleura and cavity wall thickness were the two variables showing significant changes over time during the 6-month therapy. As regards these two variables, we noted clinically paralleled radiological response in about 80% with a concordance rate of 100% in cases of clinical improvement. Although fungus ball volume variation did not reach significance, there was a strong association between disappearance of the fungus ball and clinical and radiological improvement ($P = 0.04$). The changes in cavity size, nodules >5mm and tree-in-bud were not relevant to assessment of treatment outcome as agreement with clinical evolution was poor.

The radiological variables previously used to define response to treatment had been predetermined and differed from one author to another (e-Table 2), thereby explaining the wide variations in response assessment (e-Figure 2). The definition of radiological response given by Agarwal *et al.* in a recent publication was based on criteria different than those used in other definitions. Radiological response was considered present when there was a decrease in the size/number of the fungus balls, attenuation of the pericavitary infiltrates or pleural fibrosis. Response was objectively assessed by measuring the longest diameter of various lesions, and reduction arbitrarily set at 50% was taken as criteria for improvement. Moreover, this work included attenuation of the pericavitary infiltrates, which was not clearly defined. In our study, pericavitary infiltrates included presence of areas of consolidation, lobar collapse or nodules and no significant change over time or concordance with clinical response was observed. Attenuation of pleural fibrosis was not clearly defined as variation of thickness
of the pleura, which significantly changed over time in our study with an elevated concordance rate in cases of favourable clinical and radiological response. Nor were variations in cavity wall thickness considered in the study conducted by Felton et al, in which radiological improvement was imprecisely defined as any improvement in the extent of pericavity and/or pleural thickening or cavity size and/or number and loss of any fungus ball. Increased size or number of cavities was considered as defining deterioration. However, in our study we found a true discordance, as 24% of patients with clinical improvement presented paradoxically increased cavity size with a significant Cohen’s kappa. This is most likely explained by the effect of a pulmonary fibrotic process, responsible for distortion features, traction bronchiectases and parenchymal scarring in the pericavity lung and not related to CPA progression. In the prospective VERTIGO trial, any patient with increased cavity size was considered as a non-responder. However, radiological response assessment was more exhaustive and included a description of each lesion (cavity, mycetoma, nodule, infiltrate, pleural thickening) with quantitative analysis. All three studies considered the variation of fungus ball volume in their definitions of the radiological response to treatment. In the present study, concordance between changes of the fungus ball volume and clinical response was not significant. Nevertheless, in cases of loss of fungus ball, all patients were clinically improved with a marked improvement of all other CT parameters. It is worth noting that the association between spontaneous removal of fungus ball and clinical or radiological improvement had previously been documented. It therefore seems clinically relevant to add fungus ball removal to radiological response assessment.

Efficacy assessment had previously focused on both radiological response and clinical signs. However, assessment of treatment response with clinical parameters such as quality of life and respiratory symptoms has remained indirect and failed to objectively measure the effects of treatment. Similarly, with regard to mycological parameters, the concept of
Aspergillus eradication is probably relevant but remains difficult to apply in a response definition due to a lack of standardization of respiratory processing and to the invasive nature of bronchoscopy. As recently discussed by Hansell and colleagues, the radiologist may be the first to alert clinicians to the possibility of the diagnosis and to appreciate objective evolution under therapy. Focusing on treatment outcome is important, as current treatments used in the management of CPA involve a number of limitations such as side effects, drug interactions, high cost and emergence of resistance. The evaluation of patients treated for CPA with only clinical or mycological parameters should be considered cautiously, as paradoxical clinical and CT evolutions can be observed. Thus a relevant assessment of response to treatment may include the evolution of both clinical and appropriate radiological parameters.

The logistic regression analysis did not retain any radiological variable associated with favourable clinical evolution. These results may be explained by the limited number of patients enrolled in the study, although we report the largest published series so far with a rigorous CT assessment, blinded to the clinical data, of a poorly known pulmonary disease. Furthermore, the comparison between radiological and clinical variables is challenging and due to its somewhat speculative nature, clinical presentation may not be considered as a gold standard but unfortunately, reference to histological data is rarely available.

In summary, since the main aim of CPA treatment is prevention of progressive lung damage, optimally appropriate selection of the variables contributing to assessment of treatment outcome is altogether essential. This study demonstrates that changes in size of cavities are associated with paradoxical clinical and radiological evolutions, suggesting that this is not a relevant criterion for assessing response to treatment. In contrast, decrease in cavity and pleura wall thickness and loss of fungus ball are the most relevant CT criteria in assessment of response to antifungal therapy in patients with CPA.
ACKNOWLEDGMENTS

Guarantor and Author contributions: Author contribution guarantor for the entire manuscript: CG; Conception and design of the work: CG, JC, FL, CBA; Recruited patients (i.e. data collection): CG, JC, CT, AB, CP, BC, VC, BP, PG, GB, FR; Data analysis/interpretation: PI, CG, JC, FL, GB; Revising the manuscript for important intellectual content: CG, JC, FL, JPF, VC, AB; Final approval of the manuscript: all authors.

Financial/nonfinancial disclosures:
Cendrine Godet: received consultancy or speaker fees, travel support from Pfizer, Astellas, Gilead, MSD, SOS Oxygene and ISIS Medical.
Anne Bergeron: received advisory board fees from MSD and Pfizer, speaker fees from MSD, Pfizer and Gilead and travel support from Vitalair.
Vincent Cottin: reports personal fees from Actelion, personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from Gilead, personal fees from GSK, personal fees from Intermune / Roche, personal fees from Novartis, personal fees from Roche, personal fees from Sanofi, personal fees from Biogen Idec, outside the submitted work; and Dr Cottin's wife is an employee of Sanofi Pasteur.
Patrick Germaud: received consultancy or speaker fees and travel support from Pfizer and Novartis.
France Roblot: received consultancy or speaker fees and travel support from Astellas, Gilead and Pfizer and is president of French Infectious Diseases Society (SPILF).
Jean-Pierre Frat: reports personal fees from SOS OXYGENE, outside the submitted work.
François Laurent, Pierre Ingrand, Catherine Beigelman-Aubrey, Boubou Camara, Bruno Philippe, Christophe Pison, Cécile Toper, Marie France Carette, Guillaume Béraud, Jacques Cadranel have nothing to disclose.
Role of the sponsors:

This study was funded by grants from Pfizer, Paris, France; ASTELLAS Pharma SAS, France; SOS Oxygène, Nice, France; ISIS Médical, France; AADAIRC, Poitou-Charentes, France. The funder of the study provided access to the Research database, which included collection and management of data. The funder of the study had no role in study design, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Other contributions:

Philippe Gegou from the INTRASENSE technical and computer support team, who enabled us to work on Myrian®, the software suite used for the visualization and post-processing of the medical images.

The authors also wish to thank Jeffrey Arsham, an American medical translator-working at the CHU of Poitiers, for reviewing and editing the original English-language manuscript.

Antoine Khalil, Service de Radiologie, AP-HP, Hôpital Tenon, Paris, France and Gilbert Ferriti, Service de Radiologie, CHU Grenoble, Grenoble, France two radiologists, who assisted us with data collection.

The following investigators participated in the ACHROSCAN study group: François Laurent, CHU Bordeaux, France; Boubou Camara and Christophe Pison, CHU Grenoble, France; Catherine Beigelman-Aubry CHUV Lausanne, Suisse; Vincent Cottin CHU Lyon, France; Patrick Germaud, CHU Nantes, France; Anne Bergeron, APHP Paris, France, Jacques Cadranel, Antoine Khalil and Cécile Toper, APHP, Paris, France; Guillaume Béraud, Pascal Blouin and Cendrine Godet CHU Poitiers, France; Bruno Philippe, CH Pontoise, France.

Cendrine Godet, Jacques Cadranel and Anne Bergeron are members of the GREPI (French Group for Research and Education in Respiratory Infectious Diseases).
Additional information: The e-Appendix and the e-Tables can be found in the “Supplemental Materials” area of the online article.
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Table 1—Characteristics of the 36 patients of the analysis compared to those of the whole study population, and to others included in study database that did not satisfy inclusion criteria (CT follow-up at 6 months)

<table>
<thead>
<tr>
<th></th>
<th>Whole study population (n = 127)</th>
<th>Patients with CT at M0 and M6 (n = 36)</th>
<th>Patients without CT at M6 (n = 91)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr</td>
<td>55 ± 15</td>
<td>58 ± 12</td>
<td>54 ± 15</td>
<td>0.15</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>84 (66.7)</td>
<td>22 (61.1)</td>
<td>62 (68.9)</td>
<td>0.40</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>20.8 ± 4.9</td>
<td>20.9 ± 5</td>
<td>20.7 ± 4.8</td>
<td>0.81</td>
</tr>
<tr>
<td>Underlying condition, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>59 (46.5)</td>
<td>14 (38.9)</td>
<td>45 (49.5)</td>
<td>0.28</td>
</tr>
<tr>
<td>Non-tuberculous mycobacterial disease</td>
<td>14 (11.0)</td>
<td>6 (16.7)</td>
<td>8 (8.8)</td>
<td>0.22</td>
</tr>
<tr>
<td>COPD</td>
<td>47 (37.0)</td>
<td>11 (30.6)</td>
<td>36 (39.6)</td>
<td>0.34</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>15 (11.8)</td>
<td>6 (16.7)</td>
<td>9 (9.9)</td>
<td>0.36</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>12 (9.4)</td>
<td>5 (13.9)</td>
<td>7 (7.7)</td>
<td>0.32</td>
</tr>
<tr>
<td>Post-radiation lung</td>
<td>6 (4.7)</td>
<td>2 (5.6)</td>
<td>4 (4.4)</td>
<td>1</td>
</tr>
<tr>
<td>Diffuse infiltrative disease</td>
<td>5 (3.9)</td>
<td>3 (8.3)</td>
<td>2 (2.2)</td>
<td>0.34</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td>99 (78)</td>
<td>30 (83.3)</td>
<td>69 (75.8)</td>
<td>0.36</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>57 (57.6)</td>
<td>14 (46.7)</td>
<td>43 (62.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>45 (45.5)</td>
<td>13 (43.3)</td>
<td>32 (46.4)</td>
<td>0.78</td>
</tr>
<tr>
<td>Condition</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>1 (1.0)</td>
<td>1 (3.3)</td>
<td>0 (0)</td>
<td>0.28</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (7.1)</td>
<td>2 (6.7)</td>
<td>5 (7.2)</td>
<td>1</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>1 (1.0)</td>
<td>1 (3.3)</td>
<td>0 (0)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Data are presented as % or mean ± SD. Chronic obstructive pulmonary disease (COPD)
<table>
<thead>
<tr>
<th></th>
<th>CT at M0 (n = 36)</th>
<th>CT at M6 (n = 36)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of at least 1 cavity, n (%)</td>
<td>32 (91.4)</td>
<td>27 (81.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Unilateral localisation of cavity, n (%)</td>
<td>21 (65.6)</td>
<td>17 (63.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Number of cavities in the left lung, n (%)</td>
<td></td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>12 (33.3)</td>
<td>12 (36.4)</td>
<td></td>
</tr>
<tr>
<td>[1-5]</td>
<td>24 (66.7)</td>
<td>21 (63.6)</td>
<td></td>
</tr>
<tr>
<td>Number of cavities in the right lung, n (%)</td>
<td></td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>16 (45.7)</td>
<td>17 (51.5)</td>
<td></td>
</tr>
<tr>
<td>[1-5]</td>
<td>18 (51.4)</td>
<td>15 (45.5)</td>
<td></td>
</tr>
<tr>
<td>Average volume of the 6 largest cavities, cm³</td>
<td>42.7 ± 59.3</td>
<td>42.8 ± 65.9</td>
<td>0.28</td>
</tr>
<tr>
<td>Presence of fungus balls, n (%)</td>
<td>20 (55.5)</td>
<td>15 (45.5)</td>
<td>0.10</td>
</tr>
<tr>
<td>Unilateral localisation of fungus balls, n (%)</td>
<td>19 (86.4)</td>
<td>11 (73.3)</td>
<td>0.32</td>
</tr>
<tr>
<td>Average volume of the fungus balls, cm³</td>
<td>13.8 ± 33.2</td>
<td>6.6 ± 9.5</td>
<td>0.27</td>
</tr>
<tr>
<td>Presence of tree-in-bud, n (%)</td>
<td>16 (44.4)</td>
<td>13 (36.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Presence of nodules &gt;5mm, n (%)</td>
<td>16 (44.4)</td>
<td>15 (41.7)</td>
<td>0.56</td>
</tr>
<tr>
<td>Presence of ground glass attenuation, n (%)</td>
<td>9 (25.0)</td>
<td>4 (13.3)</td>
<td>0.32</td>
</tr>
<tr>
<td>Presence of areas of consolidation, n (%)</td>
<td>24 (66.7)</td>
<td>21 (65.6)</td>
<td>1</td>
</tr>
<tr>
<td>Presence of lobar collapse, n (%)</td>
<td>22 (62.9)</td>
<td>20 (55.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Maximum thickness of the pleura, mm</td>
<td>6.6 ± 3.8</td>
<td>5.2 ± 3.1</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>p-value</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>Maximum thickness of the cavity wall, mm</td>
<td>6.2 ± 3.5</td>
<td>4.6 ± 2.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Bhalla Bronchiectasis CT score, points</td>
<td>7.1 ± 3.6</td>
<td>6.4 ± 4.3</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Data are presented as % or mean ± SD
Table 3–Frequencies and percentages of clinical and radiological responses of the study population, together with a measure of agreement (kappa coefficient), test of symmetry (McNemar’s P Value) and Fisher’s exact test P Value testing association between groups

<table>
<thead>
<tr>
<th></th>
<th>R(+) C(+)</th>
<th>R(-) C(-)</th>
<th>coefficient†</th>
<th>McNemar’s P Value</th>
<th>Odds Ratio (95% CI)</th>
<th>Fisher’s P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural wall thickening</td>
<td>29 (80.5%)</td>
<td>0 (0.0%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(n=36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavity wall thickening</td>
<td>22 (75.8%)</td>
<td>1 (3.4%)</td>
<td>0.20</td>
<td>0.03</td>
<td>-</td>
<td>0.24</td>
</tr>
<tr>
<td>(n=29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of fungus ball</td>
<td>13 (65.0%)</td>
<td>2 (10.0%)</td>
<td>0.29</td>
<td>1.00</td>
<td>4.33</td>
<td>0.25</td>
</tr>
<tr>
<td>(n=20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.19, 0.77)</td>
<td>(0.20, 77.97)</td>
</tr>
<tr>
<td>Volume of cavities</td>
<td>19 (61.3%)</td>
<td>0 (0.0%)</td>
<td>0.24†</td>
<td>1.00</td>
<td>0</td>
<td>0.31</td>
</tr>
<tr>
<td>(n=31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.37, 0.11)</td>
<td>(0, 2.68)</td>
</tr>
<tr>
<td>Tree-in-bud</td>
<td>25 (69.4%)</td>
<td>0 (0.0%)</td>
<td>0.16†</td>
<td>0.55</td>
<td>0</td>
<td>0.56</td>
</tr>
<tr>
<td>(n=36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.27, 0.05)</td>
<td>(0, 4.80)</td>
</tr>
<tr>
<td>Nodules &gt;5 mm</td>
<td>26 (72.2%)</td>
<td>0 (0.0%)</td>
<td>0.13†</td>
<td>0.34</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>(n=36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.25, 0.02)</td>
<td>(0, 7.44)</td>
</tr>
<tr>
<td>Lobar collapse</td>
<td>28 (77.8%)</td>
<td>0 (0.0%)</td>
<td>0.05</td>
<td>0.07</td>
<td>0</td>
<td>1.00</td>
</tr>
</tbody>
</table>
(n=36)  

Areas of consolidation  

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 (78.1)</td>
<td>0 (0.0)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>0.12</td>
<td>0.06</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>(0.14, 0.04)</td>
<td>(0.16, 0.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0, 78.71)</td>
</tr>
</tbody>
</table>

Definitions of abbreviations: CI = confidence interval; C(+) = patients clinically stable or improved; C(-) = patients clinically worsened; R(+) = patients radiologically stable or improved; R(-) = patients radiologically deteriorated

* kappa value <0.00 = poor, 0.00-0.20 = slight, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = substantial and 0.81-100 = almost perfect

† In case of loss of fungus ball, all patients (6/6) were clinically and radiologically improved at M6 with a marked improvement of all other CT parameters and with a significant association between radiological and clinical evolution (Fisher’s P-value = 0.04)

‡ Discordance between variation in size of cavities, tree-in-bud, nodules >5mm and clinical evolution

For pleural and cavity wall thickening, changes were defined as follows: deteriorated, a change > than 20% (with a minimum of 2 mm); stable or improved, a change ≤ 20% (with a minimum of 2 mm). For volume of fungus ball or cavities, changes were defined as follows: deteriorated, a change >30% change in volume; stable or improved, a change ≤30% change in volume. The severity of tree-in-bud, nodules, areas of consolidation and collapse items was designated with scores detailed in the online supplement. Significance of changes for each score was defined as at least >1 change in the delta score. Deteriorated was defined as follows: a change >1 change in delta score; stable or improved, a change <1 change in delta score.
**Figure Legends:**

**FIGURE 1.** Representative examples of CT changes in a patient with CPA at the time of diagnosis, lung window (A) and soft tissue window (B) and at 6 months (C). An increase in size of the cavity of the left apex and a decrease in size of the cavity wall and pleura thickness were observed.

**FIGURE 2.** Individual changes in pleura thickness (A), cavity wall thickness (B), fungus ball volume in mm$^3$ (C) and volume of the cavities (D). Each vertical bar represents individual patients. Y-axis represents evolution over time between M0 and M6. Decreases in pleural (A) and cavity wall thickening (B) were the most frequently observed. A paradoxical increase in size of cavities was observed in 6 subjects (D).

**FIGURE 3.** Representative examples of CT changes in patients with CPA at time of diagnosis (A) and at 6 months (B). CT showing a decrease in size of both the left upper lobe fungus ball and the cavity. No change was found in the right apex in which bronchiectases within a right upper lobe atelectasis was observed.
Figure 1:
Figure 2:

A Individual changes in pleural thickness

B Individual changes in cavity wall thickness

C Individual changes of fungus ball volume

D Individual changes in volume of the cavities
Figure 3: