# The reduction of airway smooth muscle by bronchial thermoplasty stands the test of time



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*To the Editor:*

Bronchial thermoplasty has been proposed to improve asthma control by decreasing the mass of airway smooth muscle (ASM) [1]. Clinical trials with a 5-year follow-up have documented significant improvements of asthma control in terms of severe exacerbations, emergency department visits and quality of life [2–4]. The BT10+ study, a long-term follow-up of 45% of subjects enrolled in these clinical trials, showed that these clinical benefits have persisted with a good safety profile for 10.8–15.6 years (median 12.1 years) [5]. Previously, we showed that the decreased ASM persisted at 34.2 months (range 27–48 months) after bronchial thermoplasty [6]. Similar post-bronchial thermoplasty reduction of ASM has been reported by others [7–9]. Despite studies consistently demonstrating clinical benefits and ASM reduction, a relationship between these elements has not been shown clearly, since only one small study demonstrated a correlation between ASM mass reduction and improvements in asthma questionnaire scores and exacerbation rate [7].

To evaluate whether the reduction of ASM persists longer, 10 subjects who participated in the BT10+ study accepted bronchial biopsies after their BT10+ visit. All patients signed a consent form and the study was approved by our institutional ethical committee (CER 2019–3226). Biopsies were taken from segmental or subsegmental carinas of bronchial thermoplasty-treated lobes and from the untreated right middle lobe (RML). They were processed and analysed as described previously to measure the proportion of the total biopsy area occupied by ASM (% area) using Masson trichrome staining [6]. The analysis of between one and five biopsies (mean: three) were performed blindly by two independent observers with a mean±SEM interobserver variability of 6.3±2.3%. Since no bronchial biopsies were performed previously in the included subjects, we used the clinical and ASM data of 13 bronchial thermoplasty-treated subjects from our asthma clinic with biopsies performed before and ⩾1 year after bronchial thermoplasty as a comparative cohort [10]. Clinical/physiological parameters and ASM % area from both the comparative and BT10+ cohorts were compared using a Kruskal–Wallis ANOVA test with Dunn's multiple comparison correction. Data are presented as median and range.

The clinical follow-up and the bronchial biopsies were performed 13 (12–15) years after bronchial thermoplasty in the BT10+ cohort and 30 (12–48) months after bronchial thermoplasty in the comparative cohort. Both cohorts had few severe exacerbations during the year preceding the follow-up: 0 (0–1) and 0 (0–2) in BT10+ and comparative cohorts, respectively. They were similar in terms of age: 48 (34–70) years and 48 (34–73) years, respectively; male/female ratio: 4/6 and 8/5, respectively; post-bronchodilator forced expiratory volume in 1 s: 2.90 (1.59–3.55) L and 91% predicted (70–116% pred) and 2.75 (1.20–4.59) L, 95% predicted (56–113% pred), respectively; use of oral corticosteroids: none out of 10 and three out of 13, respectively; doses of inhaled corticosteroids: 825 (0–3000) µg and 750 (0–3000) µg fluticasone propionate or equivalent, respectively; doses of long-acting $\beta_2$-agonist: 63 (0–200) µg and 100 (0–200) µg salmeterol or equivalent, respectively; and use of biologics: one out of 10 and three out of 13, respectively. Asthma standardised questionnaires improved in both groups following bronchial thermoplasty, as follows. BT10+ cohort: Asthma Control Questionnaire (ACQ)-7 from 1.29 (0.43–2.71) to 0.79 (0.14–2.00) ($p=0.11$) and Asthma Quality of Life Questionnaire score from 5.36 (3.19–6.88) to 6.20 (4.72–6.94) ($p<0.01$); comparative cohort: Asthma Control Scoring System (a local ACQ equivalent in which a perfect control is measured by a score of 100%) from 78% (25–100%) to 95% (45–100%) ($p<0.01$) [11].

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**Airway smooth muscle ablation induced by thermoplasty is maintained for >10 years along with the improvements in asthma control** https://bit.ly/3nGqQSP

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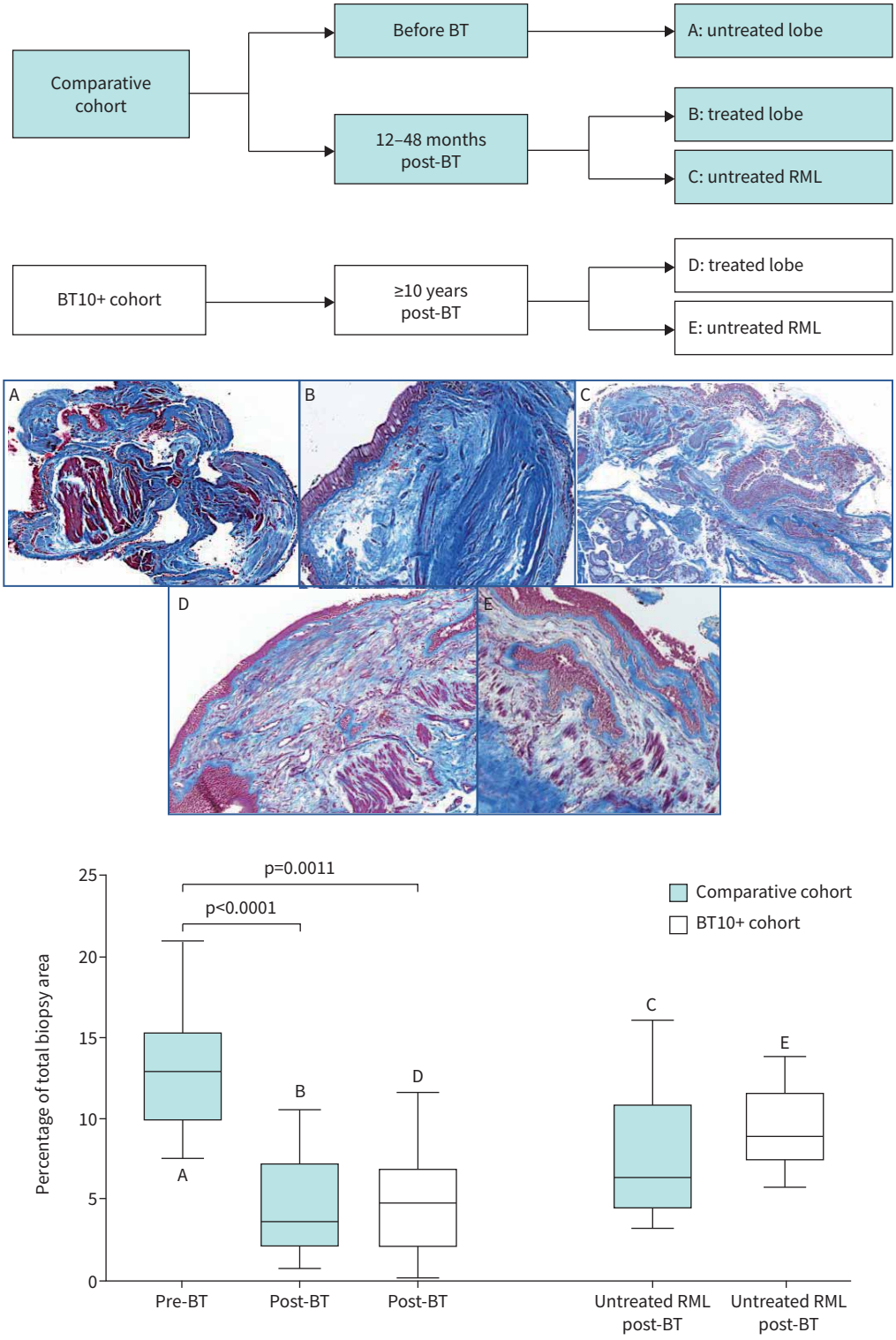


**FIGURE 1** Decrease of airway smooth muscle (ASM) % area induced by bronchial thermoplasty (BT) in both the comparative and BT10+ cohorts. A flowchart displays the study design, and representative photographs of Masson trichrome staining and associated boxplot are shown. Comparative cohort: ASM % area in biopsies collected pre-BT (A) and 12–48 months post-BT in both treated lobes (B) and untreated right middle lobe (RML) (C). BT10+ cohort: ASM % area in biopsies collected 12–15 years post-BT in treated lobes (D) and untreated RML (E).

The ASM % area in the comparative cohort decreased from 12.91% (7.52–20.90%) to 3.64% (0.75–10.54%) 1 year post-bronchial thermoplasty (figure 1). Comparable ASM % baseline areas and bronchial thermoplasty-induced reductions have been published previously [6, 8, 9, 12]. At long-term follow-up, the BT10+ cohort exhibited an ASM area of 4.83% (0.10–11.56%). This is similar to follow-up data of the comparative cohort post-bronchial thermoplasty and lower than their baseline. Furthermore, the ASM % area in the bronchial thermoplasty-untreated RML was comparable between the BT10+ and the comparative cohorts at follow-up: 8.90% (5.75–13.80%) and 6.26% (3.28–16.04%), respectively. Pretolani *et al.* [13] reported a decrease of ASM % area in the untreated RML 3 months after bronchial thermoplasty varying from 0.05% to 58% (mean 48.7%). They suggested that this may be explained by diffusion of the heat generated in the other two lobes during the bronchial thermoplasty procedure. Goorsenberg *et al.* [12] reported a significant decrease of ASM % area in the untreated RML 6 months after bronchial thermoplasty. They further demonstrated that this decrease was more prominent in segmental than subsegmental airways, supporting the implication of dissipated heat from neighbouring bronchial thermoplasty-treated airways, as the projection of heat across any lung depth follows a gradient that should be exposing proximal airways to more heat than distal airways. Our comparative cohort presented a RML ASM % area decrease of 51.5%. Marked ASM remodelling is characteristic of persistent and severe asthma phenotypes [14]. Higher ASM % area in the untreated RML of the BT10+ cohort similar to post-bronchial thermoplasty values of the comparative cohort suggests that this feature was also characteristic of the BT10+ cohort prior to bronchial thermoplasty. Although we compare ASM data of two different cohorts, a design which is not as robust as longitudinal follow-up, our data strongly suggest similar ASM remodelling profiles between both cohorts post-bronchial thermoplasty in both treated and untreated lobes. Therefore, we believe that our comparative cohort is a suitable control of ASM remodelling prior to bronchial thermoplasty. Furthermore, as for most of previous studies, we found that ASM % area decrease coincides with improvements in asthma control, although we were not able to find a correlation between those two parameters.

Thus, bronchial thermoplasty treatment applied once over three bronchoscopy procedures appears to reverse a cardinal feature of airway remodelling in asthma in a long-lasting fashion. Yet, the link between the observed clinical benefits and this morphological change is still not clear. Other morphological changes have been observed a year or more after bronchial thermoplasty. The persistent reduction of ASM after >10 years reported in the present study suggests that the other improved features may also last for many years, a conjecture that must be confirmed. It is very likely that the observed clinical benefits result from the combination of many observed morphological changes rather than a single one. Moreover, other morphological undescribed changes could also be involved. Since, until now, the bronchial samples used to evaluate the effects of bronchial thermoplasty on asthmatic airways obtained from bronchial spurs were small (1–2 $mm^3$) and rather superficial, their utility for documenting the bronchial thermoplasty-induced changes throughout the whole bronchial wall was limited. In the absence of factors predicting a favourable response to bronchial thermoplasty, arguments supporting a clear positioning of bronchial thermoplasty in the treatment of asthma are missing, an issue that has been recently addressed [15]. Our report is an observational study performed with bronchial biopsies in a limited number of participants ⩾12 years post-bronchial thermoplasty. Nevertheless, it was found that ASM area is reduced in this cohort, as similarly observed at a shorter time after bronchial thermoplasty in a comparative cohort; thus supporting the long-term safety, as well as the long-lasting clinical and matchless morphological benefits of bronchial thermoplasty.

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