**Original article**

# Effects of para–toluenesulfonamide intrabronchial injection on non-small cell lung carcinoma with severe central airway obstruction: A multi-center, non-randomized, single-arm, open-label trial

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## ABSTRACT

**Background:** Severe malignant airway obstruction (SMAO) is a life-threatening form of non-small cell lung carcinoma (NSCLC). There is no effective medication for alleviating SMAO associated with NSCLC. Whether para-toluenesulfonamide (PTS) intrabronchial injection is effective and safe in patients with NSCLC-SMAO is unclear.

**Methods:** In this multi-center, single-arm, open-label trial, 90 patients with NSCLC-SAO received repeated courses of PTS intrabronchial injection until tumor sizes had reduced by 50% or greater. The primary endpoint was objective alleviation rate, assessed by chest computed tomography (CT) and bronchoscopy, at day 7 and 30 following the final dose. Secondary endpoints included airway obstruction, spirometry, quality-of-life and survival time. This trial was registered with Chinese Clinical Trial Registry, number ChiCTR-TNC-12002648.

**Findings:** In full-analysis set (n=88), using the RECIST criteria, PTS treatment resulted in a significant objective alleviation rate [chest CT: 59·1% (95%CI: 48·1%–69·5%), bronchoscopy: 48·9% (95%CI: 38·1%–59·8%) at day 7; chest CT: 43·2% (95%CI: 32·7%–54·2%), bronchoscopy: 29·6% (95%CI: 20·3%–40·2%) at day 30]. There was a remarkable increase in FVC (mean difference: 0·35 liters, 95%CI: 0·16–0·53 liters), $FEV_1$ (mean difference: 0·27 liters, 95%CI: 0·07–0·48 liters), *Baseline Dyspnea Index* (mean difference: 64·8%, 95%CI: 53·9–74·7%) and *Functional Assessment of Cancer Therapy-Lung Cancer Subscale* (mean difference: 6·9, 95%CI: 3·8–9·9) at 7 days post-treatment. We noted a significantly reduced prevalence of atelectasis (by 42·9%) and *Eastern Cooperative Oncology Group* physical performance scale (mean difference: 7·2, 95%CI: 3·9–10·5). The median survival time was 394 days in full-analysis set and 460 days in per-protocol set. Adverse events were reported in 64·0% of subjects, of whom 50·9%, 31·6% and 17·5% were rated as mild, moderate and severe, respectively. Seven severe adverse events (7·9%) were reported, of which three led to death (drug-related in one case).

**Interpretation:** PTS intrabronchial injection is effective and well tolerated for palliative therapy of NSCLC-SMAO.

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**Clinical trial registry:** **www.chictr.org/cn**, No.: ChiCTR–TNC–12002648

**Key words:** Para-toluenesulfonamide; non–small cell lung carcinoma; severe airway obstruction; bronchoscopy; computed tomography; survival

**Short title:** PTS for treatment of NSCLC-SMAO

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**Research in context**

**Evidence before this study**

Non-small cell lung carcinoma associated with severe malignant airway obstruction (NSCLC-SMAO) is the most life–threatening and recalcitrant form of lung cancer. To date, no effective therapy exists for this disorder. We searched PubMed for literature of clinical trials of PTS intrabronchial injection for the treatment of malignant airway obstruction published in any language up to Jul 15, 2015, by using the search terms "para-toluenesulfonamide" AND "lung cancer", or "PTS injection" AND "lung cancer". We identified 12 reports, of which only one phase 2 clinical trial that investigated the response and cytotoxicity of gemcitabine plus cisplatin chemotherapy with concurrent intratumoral injection of para–toluenesulfonamide in peripherally advanced non-small cell lung carcinoma larger than 3cm in the greatest dimension. The results showed that these combination therapies were well-tolerated with potential activity. However, there is no report detailing the efficacy and safety of para-toluenesulfonamide in lung cancer.

**Added value of this study**

The results of this multicenter, non-randomized, single-arm, open-label trial demonstrate the potential of PTS intrabronchial injection via bronchoscopy in patients with NSCLC-SMAO, the difficult–to–treat disorder which readily results in high mortality rate. PTS effectively debulked intrabronchial tumor leading to ameliorated dyspnea, improved lung function and quality-of-life which collectively translated into prolonged duration of survival. Notably, the duration of survival conferred by PTS intrabronchial injection was considerably longer than laser therapy plus brachytherapy, intravenous pemetrexed plus carboplatin, and gemcitabine plus carboplatin.

**Implications of all the available evidence**

PTS intrabronchial injection might be considered as an effective palliative therapy for NSCLC-SMAO, particularly in community settings of developing countries where there are no sophisticated medical facilities (i.e. laser, electrocautery) for palliative therapy. PTS intrabronchial injection might have yielded greater efficacy in milder forms of lung cancer. Due to the efficacy and safety, PTS intrabronchial injection could be considered for future clinical practice, especially in developing countries.

## INTRODUCTION

Lung cancer has been the leading cause of morbidity and mortality among malignant tumors [1] with an annually increasing prevalence in mainland China [2]. Despite chemotherapy, radiotherapy and surgery, the 5-year survival rate is currently estimated to be 5·0–10·0% [3,4]. In the US, one-third of lung cancer patients developed malignant airway obstruction (MAO) with symptoms [5]. Because of low penetration to airway lumen, traditional therapeutic approaches had limited efficacy for advanced lung cancer of central airways (trachea, left/right main bronchus), particularly non-small cell lung carcinoma with severe malignant airway obstruction (NSCLC-SMAO) which is life-threatening [6–9].

Treatments with laser, electrocautery, argon plasma coagulation and metal stent placement via bronchoscopy have shown promising value for malignant tracheobrochial tumors [10]. However, the severe adverse events (i.e., hemorrhage, tracheoesophageal fistula, pneumothorax) and sophisticated and costly instruments have restricted their clinical application, particularly in community settings. Intratumoral injection of tumoricidal medications (i.e. ethanol absolute) has been applied for lung cancer [11]. Admittedly, different medications yielded varying outcomes. High-dose ethanol absolute intratumoral injection resulted in extensive tissue injury leading to significant adverse events (hemorrhage, ethanol intoxication, pain and fever) [12–17]. First-line tumoricidal medications, including cisplatin and 5-fluorouracil, reportedly debulked intrabronchial tumors resulting in amelioration of central airway obstruction [18,19]. However, whether these findings could be applied to NSCLC-SMAO (>50% central airway obstruction) remains unclear. Furthermore, previous observations on the efficacy of intrabronchial injection were limited by confounding factors such as combination with intravenous cisplatin [20] or 5-fluorofluracil [19].

Para-toluenesulfonamide (PTS) is a low-molecular-weight hydrophobic compound that readily dissolves in ethanol [21,22]. PTS significantly inhibited tumor growth, suppressed cellular activities *in vitro* via increasing cellular membrane permeability [23], but led to minor injury to adjacent normal tissues [23–25]. Recently, phase 2 trials on breast cancer [25], liver cancer [26,27] and early-stage head and neck tumor [28] have consistently verified the efficacy of PTS, which might also apply in NSCLC-SMAO.

Here, we sought to investigate the efficacy and safety of PTS intrabronchial injection in patients with NSCLC-SMAO.

## METHODS

### Study population

Hospitalized patients with NSCLC-SMAO were recruited from 17 participating sites in China (Table E1).

Eligibility criteria included: 1) patients aged 18-83 years of both gender; 2) physician-diagnosed NSCLC-SMAO, defined as the ratio of tumor diameter and trachea diameter being 0·50 or greater, the ratio of tumor diameter and left/right main bronchial diameter being 0·67 or greater, or the longest tumor diameter being greater than 0·5 cm; 3) lesions suitable for bronchoscopic therapy; 4) tumor(s) with measurable sizes being determined by bronchoscopy, computed tomography, magnetic resonance imaging or roentgenography; 5) platelet count 100,000/$mm^3$ or greater.

Exclusion criteria consisted of: 1) cerebral metastasis; 2) cardiovascular disease, including congestive heart failure (*New York Heart Association* grade 2 or greater), unstable or emerging (within 3 months) angina pectoris, myocardial infarction within 6 months; 3) severe infection and metabolic disorders; 4) liver failure, severe liver cirrhosis, aberrant blood coagulation; 5) poor general condition or cachexia; 6) prior radiotherapy (within 6 months); 7) pregnancy or lactation; 8) prior anaphylaxis to PTS; 9) other conditions judged by study investigators.

The study protocol has been approved by Ethics Committee of individual participating cites and State Food and Drug Administration (No.: 2009L03443; Medical Ethics 2009 [the 12$^{th}$]). Subjects gave written informed consent before enrollment.

### Study medication

PTS (Lot No.: 070109, 070110 and 070111; Guangdong Dari Chemicals Inc., Guangzhou, China) was stored in 5ml vials and kept in cooled places by designated research nurses. Within 30 min before use, PTS was diluted with 2ml ethanol anhydride into 10ml sterile syringe followed by gentle vortex. Ethanol (final concentration: 30%) was added to facilitate intrabronchial injection.

### PTS intrabronchial injection

Subjects were administered 2% lidocaine hydrochloride via nebulization, and midazolam (1–2 mg) plus sufentanil (5 mg) intravenously for general anesthesia. The bronchoscope (BF260, Olympus Inc., Osaka, Japan) was passed transnasally for inspection of tumor and adjacent tissues. PTS/ethanol mixture was, by using NA-1C-1 needle (Olympus Inc., Osaka, Japan), intrabronchially injected to the lower quadrant of tumor's root, starting from the tumor to adjacent tissues. Each injection covered 4 to 6 sites. The depth and location of injection could be adjusted if appropriate. For individual sites, the recommended dose of PTS/ethanol mixture was 0·1–1·5ml (equivalent to 0·07–1·00ml PTS), with

the maximal dose of 7·0ml (5·0ml PTS), tailored to tumor's sizes. Maximal cumulative dose of PTS/ethanol mixture was 14·0ml (10·0ml PTS) for any single day. Typically, local PTS injection leads to tumor coagulative necrosis, forming grossly grey/dark debris. To ensure higher penetration to tumor and alleviate airway obstruction, tissue clamps were applied to remove necrotic debris before dosing at visit 2 and thereafter.

**Study design**

This was a multi-center, non-randomized, single-arm, open-label trial. Randomized, double-blind, parallel-group study was not conducted because it was deemed unethical, according to local ethics committee and State Food and Drug Administration, China. However, patients were not informed of the study's objectives.

Following enrollment, eligible patients received PTS intrabronchial injection for 2-3 times weekly, with 2 weeks regarded as a single therapeutic course. Four doses were mandatory for the initial course, but could be adjusted for remaining courses. Treatment courses were repeated until tumor's diameter had diminished by 50% or greater (Figure 1-A). Post-treatment assessments were performed at day 7 and 30 after the final dose.

**Study endpoints**

Co-primary endpoints, measured by bronchoscopy and chest CT, included: 1) Objective alleviation rate [based on *Response Evaluation Criteria In Solid Tumor* (RECIST), or *World Health Organization* (WHO) criteria]; 2) Bronchial obstruction alleviation rate. RECIST criteria evaluated pre- and post-treatment changes in the longest tumor diameter by using CT and bronchoscope; WHO criteria were assessed by the formula: 100% × (baseline obstruction rate – post-treatment obstruction rate)/baseline obstruction rate. Tumor obstruction rate was, by applying irregular curve estimating algorithms, derived from the maximal cross-sectional area of tumor divided by the area of airway lumen at an identical plane.

Bronchoscopic assessment was performed via fixation of bronchoscope at 1·0 cm above tumor, by applying plastic ring (1·0 cm in thickness) at nostril for accurate positioning, while maintaining the imaging focus at the central target trachea/bronchi. Chest CT was evaluated by three members of independent appraisal committee, including tumor size, area and luminal area, with discrepancy being resolved by group adjudication.

Clinical beneficial endpoints consisted of pre- and post-treatment differences in $FEV_1$ and the magnitude of lung expansion.

Exploratory endpoints were pre- and post-treatment differences in: 1) $FEV_1$/FVC ratio; 2) *Baseline Dyspnea Index* (BDI); 3) *Eastern Cooperative Oncology Group* physical performance (ECOG) scale; 4) *Functional Assessment of Cancer Therapy-Lung Cancer Subscale* (FACT-LCS); 5) duration of remission (DOR); 6) overall survival (OS).

Adverse events (AE) and severe adverse events (SAE) were recorded and presented as numbers and percentages. Vital signs were recorded prior to and after PTS injection.

**Statistical analysis**

Sample size was calculated based on two-sided tests, with α level of 0·05, assuming an objective alleviation rate of 30·0% and target width for 95% confidence interval (95%CI) of 20·0%, 89 patients would be needed for enrollment.

We analyzed primary and clinical benefit endpoints based on intention-to-treat principle. Full-analysis set included patients who had received at least one dose of PTS therapy. Per-protocol set consisted of those who had received at least two weeks of PTS treatment (single therapeutic course).

Statistical analysis was conducted using SPSS 17·0 (SPSS Inc., Ill, USA). Numeric data were expressed as mean ± standard deviation or median (interquartile range) if appropriate, and compared with t-test or Mann-Whitney test. Treatment effects were summarized as differences pre- and post-treatment and the 95%CI. Categorical data were summarized as absolute count (percentage) and compared with chi-square test. Survival probability was analyzed with log-rank test and displayed in Kaplan-Meier plot. Safety set was evaluated for safety profiles. $P<0·05$ was deemed statistically significant for all comparisons.

This study was registered with Chinese Clinical Trial Registry (**www.chictr.org/cn**), number ChiCTR-TNC-12002648.

**Role of funding source**

The manufacturer (Guangdong Dari Chemicals Inc., Guangzhou, China) provided study medication but had no role in patient recruitment, data analysis or manuscript drafting.

## RESULTS

**Subject enrollment**

Between August 2009 and January 2012, 101 patients underwent screening, of whom 11 were excluded (Figure 1-B). Reasons of exclusion were: consent withdrawal (n=1), non-severe airway obstruction (n=6), treatment-intolerant cachexia (n=1), intracranial metastasis (n=1), other malignancy (n=1) and no observable intrabronchial tumor (n=1). Finally, 88 and 72 patients were included in full-analysis and per-protocol set, respectively.

Patients in safety set (n=89) received a mean of 5·1 episodes of PTS injection, with total dose of 18·2 ml. 92·1%, 40·4% and 5·6% of patients accomplished at least one, two and three courses, respectively.

**Baseline levels**

The study cohort consisted of mostly middle-aged males with predominantly stage IIIB and IV NSCLC which affected left/right main bronchus. Baseline levels of full-analysis and per-protocol set were comparable (Table E2). Squamous cell carcinoma was predominant (75·0%), followed by adenoma (12·5%). Most tumors were of moderate-to-low differentiation (57·4%). (Table 1)

**Primary endpoints**

Rates of complete remission and partial remission were pooled for calculating objective alleviation rates. Assessment with chest CT yielded consistently higher rates of complete remission than partial remission at day 7 and 30 post–treatment, based on RECIST or WHO criteria. (Table 2)

In full-analysis set, according to RECIST criteria, objective alleviation rates were 59·1% (95%CI: 48·1%–69·5%) and 43·2% (95%CI: 32·7%–54·2%) when evaluated with chest CT, and 48·9% (95%CI: 38·1%–59·8%) and 29·6% (95%CI: 20·3%–40·2%) according to bronchoscopy, at day 7 and 30 post-treatment, respectively. For analyses with WHO criteria, at day 7 and 30 post–treatment, objective alleviation rates were 67·1% (95%CI: 56·2%–76·7%) and 47·7% (95%CI: 37·0%–58·7%) according to chest CT, and 76·1% (95%CI: 65·9%–84·6%) and 37·5% (95%CI: 27·4%–48·5%) based on bronchoscopy.

At day 7 and 30 post-treatment, alleviation of airway obstruction was achieved in 69·4% and 69·1% of patients according to chest CT, and in 72·8% and 68·5% of patients based on bronchoscopy.

Typical pre- and post-treatment changes in tumor sizes and airway occlusion are displayed in Figure 2. Further details can be found in Figures E1–E4.

Similar findings were found in per-protocol set (Tables E3–E6).

**Clinical benefit endpoints**

Compared with baseline levels (1·56±0·53 L), $FEV_1$ increased at day 7 (mean difference: 0·27L, 95%CI: 0·07–0·48L, P<0.01) and 30 post-treatment (mean difference: 0·32L, 95%CI: -0·01–0·66L, P=0·10) in full-analysis set (Table 2). Per-protocol set yielded comparable findings (Table E3). Of 49 patients with atelectasis in full-analysis set, lung re-expansion was observed in 21 patients (42·9%). Most lung re-expansion occurred in right middle lobe (50·0%), followed by left lower (40·0%), left upper (38·9%), right lower (35·7%), left lingula (33·3%) and right upper lobe (25·0%) in full-analysis set.

**Exploratory endpoints**

In full-analysis set, despite that non-significant increase in $FEV_1$/FVC% at day 7 (mean difference: -0·40%, 95%CI: -4·52%–3·72%, P=0·27) and 30 post-treatment (mean difference: 0·27L, 95%CI: 0·07–0·48L, P<0·01) (Table 3), $FEV_1$/FVC% improvement compared with baseline was observed in 20·5% and 12·5% of patients, respectively.

BDI score increased significantly at day 7 (mean difference: 2·19, 95%CI: 1·55–2·83, P<0·01) and 30 post–treatment (mean difference: 2·23, 95%CI: 1·31–3·15, P<0·01). ECOG score improvement was achieved in 34·1% and 25·0% of patients at day 7 and 30 post-treatment in full-analysis set.

PTS treatment led to significant improvement in FACT-LCS scores at day 7 (mean difference: 6·86, 95%CI: 3·79–9·93, P<0·01), but not at day 30 post-treatment (mean difference: 3·98, 95%CI: -0·59–8·55, P=0·11).

Per-protocol set yielded similar findings (see online supplement).

Of patients in full-analysis set, 37 (42·0%) succumbed. Median survival duration was 394·0 days ($25^{th}$ percentile: 185·0 days; $75^{th}$ percentile: 460·0 days). (Figure 3) Patients in per-protocol set had longer survival duration than those in full-analysis set (online supplement).

**Safety**

AE was reported in 64·0% of patients (n=57), of whom 50·9% (n=29), 31·6% (n=18) and 17·5% (n=10) were rated as mild, moderate and severe. Drug-related AEs were reported in 25·8% of patients (n=23), of whom 43·5% (n=10), 39·1% (n=9) and 17·4% (n=4) were rated as mild, moderate and severe.

Vital AEs were reported in 20·5% of patients (n=18). Common AEs were thoracic and mediastinal diseases associated with respiratory tract (47·2%, n=42) according to *Systemic Organ Classification*, and coughing (16·9%, n=15), bloody sputum (16·9%, n=15) and injection site hemorrhage (10·1%, n=9) according to *Preferred Terms* classification.

The most common drug-related AE was coughing (12·5%, n=11), followed by fever (4·5%, n=4).

AEs leading to treatment cessation were reported in eight cases (9·0%), of which two cases might be associated with PTS intrabronchial injection.

Seven SAEs (7·9%) were reported. three patients (3·4%) succumbed. Of four drug-related SAEs, one patient developed airway stenosis and respiratory failure (severe obstruction of bilateral main bronchi, deemed unsuitable for enrollment), one succumbed due to massive hemorrhage (at day 26 post-treatment, possibly related to lung cancer

progression), one reported wheezing (10-year's history of chronic bronchitis; wheezing occurred at initial dose but remitted thereafter), and one developed heart failure (coincided with obstruction-induced pneumonia at day 1 following the 3rd treatment course; remitted following symptom-based therapy and discharged at day 2 post-treatment).

There were no notable abnormalities (including bone marrow inhibition) in laboratory tests. (Table 4)

See further details in Table E7.

## DISCUSSION

Our study demonstrated, for the first time, that PTS intratumoral injection in the trachea or bronchi significantly reduced tumor sizes by causing coagulative necrosis, ameliorated airway obstruction, improved lung function and quality of life, and prolonged duration of survival in NSCLC-SMAO. Adverse events were overall mild. PTS was well tolerated.

Our findings were consistent with previous reports. In nude mice models, PTS markedly inhibited tumor growth via necrotizing lung cancer necrosis *in vivo*, abrogating cancer cell metabolism and increasing cellular membrane permeability *in vitro* [21]. Effects of PTS were also dose-dependent [28]. PTS conferred efficacy on breast cancer, liver cancer and skin cancer, in phase 2 clinical trials [24-27]. In phase 2 trials of advanced peripheral lung cancer [18,20], PTS local injection plus cisplatin was effective and safe in inhibiting tumor growth. In our study, intrabronchial PTS injection yielded marked tumor necrosis associated with minor injury to adjacent normal tissues. Following removal of necrotic debris, PTS could be safely administered for multiple treatment courses. In keeping with literature reports [18-20], intrabronchial PTS injection had facilitated penetration to the tumor, which significantly ameliorated airway obstruction, improved lung function and quality-of-life, which collectively translated into prolonged survival.

The improvement in clinical benefit parameters also supported the therapeutic potential of PTS intrabronchial injection. $FEV_1$ was significantly increased post-treatment, indicating alleviated large airway obstruction. We also noted significant reduction in the prevalence of atelectasis, which might be related to attenuated tumor growth and alleviated airway obstruction. Notably, these effects were sustained to follow-up visits despite a trend of relapse. Median duration of survival (394·0 days in full-analysis set) was considerably longer than that of laser therapy plus brachytherapy (mean: 40·8 weeks) [29], intravenous pemetrexed plus carboplatin (median: 7·3 months), or gemcitabine plus carboplatin (median: 7·0 months) [30].

A major merit of intrabronchial PTS injection was high local penetration and minor normal tissue injury. In a phase IIa clinical trial on early-stage head and neck tumor [27], injury of tumor adjacent tissues and normal tissues was evaluated via biopsy. The area with tissue necrosis and degeneration was defined as major outcome measure. The results (unpublished data) showed that PTS led to minor injection site necrosis and degeneration of tumor adjacent tissues (the area with tissue necrosis and degeneration: 13·6%) compared with tumor tissues (95·5%). This trend was more pronounced when comparing normal tissues with tumor tissues.

PTS was also well tolerated. Most AEs were rated as mild-to-moderate. The 4 SAEs were mostly associated with lung cancer progression, despite worsened airway obstruction possibly due to swelling of necrotic debris. This warranted debris removal via clamps prior to subsequent PTS dosing. Admittedly, PTS/ethanol mixture yielded minor injury to adjacent tissues. However, no laboratory testing-related adverse event was reported, which reinforced the safety of PTS injection on systemic metabolism and normal cell growth.

We have demonstrated that PTS harbors significant tumoricidal effects whilst minor adverse impacts on adjacent tissues. Treatment modalities (including chemotherapy and radiotherapy) that effectively and rapidly alleviate SMAO, the life-threatening form of lung cancer, are lacking. Despite the palliative nature, PTS holds promises for prolonging survival time and improving quality-of-life in lung cancer. With increasing clinical application of bronchoscopy worldwide, our findings would significantly benefit the treatment of advanced lung cancer in community settings where bronchoscopy is available.

Strengths of this study included the multicenter study design, rigorous endpoint evaluation methodology, long-term follow-up in the most severe form of lung cancer. Due to high cost-effectiveness (significantly lower anticipated price post-marketing compared with cisplatin and gemcitabine), PTS might be particularly suitable for patients in developing countries such as China.

Our study had some limitations:

** The lack of active comparator group suggested that our findings might have been confounded by subject allocation and study endpoints assessment. However, placebo of PTS has not been approved for clinical trial purposes due to ethics concerns. The significant tumor necrosis leading to diminished tumor sizes occurred rapidly following PTS injection, which could not be interpreted by any other known components. To our knowledge, ethanol at concentrations of 30% or less had no significant tumoricidal effects on NSCLC [21].

** PTS intrabronchial injection might result in tumor necrosis and swelling leading to asphyxia. Hence, placement of intrabronchial stents is warranted prior to dosing in some patients with very severe airway obstruction (particularly tracheal obstruction).

** PTS injection rested on repeated courses of bronchoscopy.

** Some patients did not accomplish spirometry or quality-of-life assessments, who either had difficulty in performing spirometry due to severe airflow limitation and dyspnea, or failed to participate in follow-up visits due to

their remote residency (remote rural areas).

** Our study primarily recruited patients with NSCLC-SMAO. However, the powerful tumoricidal effects coupled with high selectivity of PTS might have rendered it more clinically suitable for treatment of milder forms of lung cancer.

In conclusion, our findings highlight the significant therapeutic potential of intrabronchial PTS injection for NSCLC-SMAO, particularly in developing countries where there are medical facilities for performing bronchoscopy.

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**Reference**

1. He J, Gu D, Wu X, et al. Major causes of death among men and women in China. *N Engl J Med.* 2005;**353**:1124-34
2. She J, Yang P, Hong Q, Bai C. Lung cancer in China: challenges and interventions. *Chest.* 2013;**143**:1117-26
3. National Cancer Institute. Lung cancer: Survival rates and prognosis. **http://www.cancer.gov/cancertopics/types/lung/cancer-survival-prognosis**. Accessed on July 15th, 2015.
4. Janssen-Heijnen ML, Gatta G, Forman D, Capocaccia R, Coebergh JW. Variation in survival of patients with lung cancer in Europe, 1985-1989. EUROCARE Working Group. *Eur J Cancer.* 1998;**34**:2191-6
5. Mitchell PD, Kennedy MP. Bronchoscopic management for malignant airway obstruction. *Adv Ther*. 2014; 31: 512-38
6. Nihei K, Ishikura S, Kawashima M, Ogino T, Ito Y, Ikeda H. Short-course palliative radiotherapy for airway stenosis in non-small cell lung cancer. *Int J Clin Oncol* 2002;**7**:284-8
7. Diaz-Jiménez JP, Martínez-Ballarín JE, Llunell A, et al. Efficacy and safety of photodynamic therapy versus Nd-YAG laser resection in NSCLC with airway obstruction. *Eur Respir J.* 1999;**14**:800-5
8. Allen AM, Rabin MS, Reilly JJ, Mentzer SJ. Unresectable adenoid cystic carcinoma of the trachea treated with chemoradiation. *J Clin Oncol.* 2007;**25**:5521-3
9. Fujisawa T, Hongo H, Yamaguchi Y, et al. Intratumoral ethanol injection for malignant tracheobronchial lesions: a new bronchofiberscopic procedure. *Endoscopy.*1986;**18**:188-91
10. Bolliger CT, Sutedja TG, Strausz J, Freitag L. Therapeutic bronchoscopy with immediate effect: laser, electrocautery, argon plasma coagulation and stents. *Eur Respir J.* 2006;**27**:1258-71
11. Niu Q, Wang W, Li Q, Li Y, Ruden DM, Wang F. Intratumoral injection of cisplatin in various concentrations of ethanol for cisplatin-resistant lung tumors. *Mol Clin Oncol.* 2014;**2**:491-496
12. Lippi F, Ferrari C, Manetti L, et al. Treatment of solitary autonomous thyroid nodules by percutaneous ethanol injection: results of an Italian multicenter study. The Multicenter Study Group. *J Clin Endocrinol Metab.* 1996;**81**:3261-4
13. Ebara M, Ohto M, Sugiura N, et al. Percutaneous ethanol injection for the treatment of small hepatocellular carcinoma. Study of 95 patients. *J Gastroenterol Hepatol* 1990;**5**:616-26
14. Ishii H, Okada S, Nose H, et al. Local recurrence of hepatocellular carcinoma after percutaneous ethanol injection. *Cancer* 1996;**77**:1792-6
15. Ohmoto K, Kunieda T, Shibata N, Yamamoto S. Intraperitoneal hemorrhage as a major complication of percutaneous ethanol injection therapy for hepatocellular carcinoma. *Hepatogastroenterology.* 2000;**47**:1199-202
16. Di Stasi M, Buscarini L, Livraghi T, et al. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma. A multicenter survey of evaluation practices and complication rates. *Scand J Gastroenterol* 1997;**32**:1168-73
17. Da Ines D, Buc E, Petitcolin V, et al. Massive hepatic necrosis with gastric, splenic, and pancreatic infarctions after ethanol ablation for hepatocellular carcinoma. *J Vasc Interv Radiol* 2010;**21**:1301-5
18. Celikoglu F, Celikoglu SI, York AM, Goldberg EP. Intratumoral administration of cisplatin through a bronchoscope followed by irradiation for treatment of inoperable non-small cell lung carcinoma. *Lung Cancer*. 2006; **51**: 225-36
19. Celikoglu F, Celikoglu SI. Intratumoral chemotherapy with 5-fluorouracil for palliation of bronchial cancer in patients with severe airway obstruction. *J Pharm Pharmacol*. 2003; **55**: 1441-8
20. Niu Q, Wang W, Li Q, Li Y, Ruden DM, Wang F. Percutaneous Fine-Needle 5% Ethanol-cisplatin Intratumoral Injection Combined with Second-Line Chemotherapy Improves On the Standard of Care in Patients with Platinum-Pretreated Stage IV Non–Small Cell Lung Cancer. *Transl Oncol*. 2014; **7**: 303-8
21. Li MY, Meng H, Zhou SZ, et al. Effect of percutaneous para-toluenesulfonamide injection in treatment of hepatocarcinoma in rats. *World Chin J Digestol.* 2008;**16**:1232
22. Gao Y, Gao Y, Guan W, et al. Antitumor effect of para-toluenesulfonamide against lung cancer xenograft in a

mouse model. *J Thorac Dis.* 2013;**5**:472-483
23. Wang T, Li Y, Liu M, et al. Anti-cancer Effect of PTS in Vitro. *Practic J Cancer*. 2004;**19**:1-4
24. Zhou JQ, Tang ZQ, Zhang JN, Tang JC. Metabolism and effect of para-toluenesulfonamide on rat liver microsomal cytochrome P450 from in vivo and in vitro studies. *Acta Pharmacol Sin*. 2006;**27**:635-40
25. Chinese Clinical Trial Register [Internet]. Chengdu (Sichuan): Ministry of Health (China). 2007 Jun 27. Identifier ChiCTR-ONC-12002946, A Phase IIa Clincal Trial Treating Patients With Early Stage Breast Cancer for Not Exceeding 7 Days Prior Surgery With PTS (para-toluenesulfonamide injection), A Novel Local Invasive Anticancer Drug, Administered By Local and Intratumoral Injection Therapy; 2012 Dec 31 [cited 2013 May 7]; [1 page]. Available online: **http://www.chictr.org/en/proj/show.aspx?proj=4134**. Accessed on July 15th, 2015.
26. Chinese Clinical Trial Register [Internet]. Chengdu (Sichuan): Ministry of Health (China). 2007 Jun 27. Identifier ChiCTR-ONC-12002943, A Phase IIb Clincal Trial Treating Patients with Advanced Liver Cancer with PTS (Para-Toluenesulfonamide Injection), A Novel Local Invasive Anticancer Drug, by Percutaneous Intratumoral Injection Therapy; 2012 Dec 31 [cited 2013 May 7]; [1 page]. Available from: **http://www.chictr.org/en/proj/show.aspx?proj=4133**. Accessed on July 15th, 2015.
27. Chinese Clinical Trial Register [Internet]. Chengdu (Sichuan): Ministry of Health (China). 2007 Jun 27-. Identifier ChiCTR-ONC-12002944, A Phase IIb Clincal Trial Treating Patients with Advanced Palpable Solid Tumor After Failure From Conventional Treatments and Patients Who are Suitable for Palliative Treatments with PTS (para-toluenesulfonamide injection), A Novel Local Invasive Anticancer Drug, by Intratumoral Injection Therapy; 2012 Dec 31 [cited 2013 May 7]; [1 page]. Available online: **http://www.chictr.org/en/proj/show.aspx?proj=4132**. Accessed on July 15th, 2015.
28. Chinese Clinical Trial Register [Internet]. Chengdu (Sichuan): Ministry of Health (China). 2007 Jun 27. Identifier ChiCTR-ONC-12002948, A Phase IIa Clinical Trial Treating Patients With Early Stage Head and Neck Tumor (SCCHN & SCSC) for Not Exceeding 7 Days Prior Surgery With PTS (para-toluenesulfonamide injection), A Novel Local Invasive Anticancer Drug, Administered By Local and Intratumoral Injection Therapy; 2012 Dec 31 [cited 2013 May 7]; [1 page]. Available online: **http://www.chictr.org/en/proj/show.aspx?proj=4136**. Accessed on July 15th, 2015.
29. Shea JM, Allen RP, Tharratt RS, Chan AL, Siefkin AD. Survival of patients undergoing Nd:YAG laser therapy compared with Nd:YAG laser therapy and brachytherapy for malignant airway disease. *Chest* 1993;**103**: 1028–1031
30. Gronberg BH, Bremnes RM, Flotten O, et al. Phase III Study by the Norwegian Lung Cancer Study Group: Pemetrexed Plus Carboplatin Compared With Gemcitabine Plus Carboplatin As First-Line Chemotherapy in Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* 2009; **27**: 3217-24

**TABLE 1 BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS**

| Characteristics | | Full-analysis set (n=88) |
|---|---|---|
| **Age (years)** | | |
| | Median | 57·5 |
| | Range | 22–80 |
| **Males (No., %)** | | 73 (83·0%) |
| **Height (cm)** | | |
| | Median | 165·0 |
| | Range | 147·0–180·0 |
| **Weight (kg)** | | |
| | Median | 56·2 |
| | Range | 37·0–88·0 |
| **Body surface area ($m^2$)** | | |
| | Median | 1·6 |
| | Range | 1·3-2·1 |
| **Clinical staging** | | |
| | IV (No., %) | 46 (52·3%) |
| | IIIB (No., %) | 37 (42·0%) |
| | Other (No., %) | 5 (5·7%) |
| **Histologic diagnosis** | | |
| | Squamous cell carcinoma (No., %) | 66 (75·0%) |
| | Adenoma (No., %) | 11 (12·5%) |
| | Giant cell carcinoma (No., %) | 1 (1·1%) |
| | Squamous cell carcinoma plus adenoma (No., %) | 1 (1·1%) |
| | Miscellaneous (No., %) | 9 (10·2%) |
| **Tumor differentiation** | | |
| | High (No., %) | 4 (4·6%) |
| | Moderate (No., %) | 21 (24·1%) |
| | Low (No., %) | 29 (33·3%) |
| | Unknown (No., %) | 33 (37·9%) |
| **Location of tumor** | | |
| | Trachea (No., %) | 11 (12·5%) |
| | Left main bronchus (No., %) | 33 (37·5%) |
| | Right main bronchus (No., %) | 34 (38·6%) |
| | Right middle lobe (No., %) | 10 (11·4%) |

**TABLE 2 OBJECTIVE ALLEVIATION RATE BASED ON BRONCHOSCOPIC AND CT ASSESSMENT AT DAY 7 AND 30 POST-TREATMENT IN THE FULL-ANALYSIS SET**

| Time point | Tools | Standard | CR | PR | PD | SD | Objective alleviation rate (95%CI) |
|---|---|---|---|---|---|---|---|
| Day 7 post-treatment | Bronchoscopy | RECIST | 0 (0·0%) | 43 (56·6%) | 0 (0·0%) | 33 (43·4%) | 56·6% (44·7%–67·9%) |
| | | WHO | 0 (0·0%) | 67 (88·2%) | 0 (0·0%) | 9 (11·8%) | 88·2% (78·7%–94·4%) |
| | Chest CT | RECIST | 31 (41·9%) | 21 (28·9%) | 1 (1·4%) | 21 (28·4%) | 70·3% (58·5%–80·3%) |
| | | WHO | 31 (41·9%) | 28 (37·8%) | 1 (1·4%) | 14 (18·9%) | 79·7% (68·8%–88·2%) |
| Day 30 post-treatment | Bronchoscopy | RECIST | 0 (0·0%) | 26 (61·9%) | 0 (0·0%) | 16 (38·1%) | 61·9% (45·6%–76·4%) |
| | | WHO | 0 (0·0%) | 33 (78·6%) | 0 (0·0%) | 9 (21·4%) | 78·6% (63·2%–89·7%) |
| | Chest CT | RECIST | 23 (44·2%) | 15 (28·9%) | 2 (3·9%) | 12 (23·1%) | 73·1% (59·0%–84·4%) |
| | | WHO | 22 (42·3%) | 20 (38·5%) | 2 (3·9%) | 8 (15·4%) | 80·8% (67·5%–90·4%) |

CR: Complete remission; PR: partially remission, PD: Progressive disease; SD: Stable disease

**Table 3 CLINICAL BENEFIT AND EXPLORATORY ENDPOINTS AT BASELINE AND DAY 7 AND 30 POST-TRETMENT BASED ON THE FULL-ANALYSIS SET**

| Endpoints | Baseline | Treatment difference at day 7 | | | Treatment difference at day 30 | | |
|---|---|---|---|---|---|---|---|
| | Mean | Mean | 95%CI | P | Mean | 95%CI | P |
| **Clinical benefit endpoints** | | | | | | | |
| No. of patients: $FEV_1$ | 74 | 48 | - | - | 30 | - | - |
| $FEV_1$ (L) | 1·56 | 0·27 | 0·07–0·48 | 0·01 | 0·32 | -0·01–0·66 | 0·10 |
| Atelectasis (%)* | 55·7% | ND | ND | - | 42·9% | 29·0%–56·7% | - |
| **Exploratory endpoints** | | | | | | | |
| No. of patients: $FEV_1$/FVC | 74 | 48 | - | - | 30 | - | - |
| $FEV_1$/FVC (%) | 71·25 | -0·40 | -4·52–3·72 | 0·27 | 2·25 | -4·02–8·53 | 0·92 |
| No. of patients: BDI score | 87 | 74 | - | - | 44 | - | - |
| BDI score | 5·10 | 2·19 | 1·55–2·83 | <0·01 | 2·23 | 1·31–3·15 | <0·01 |
| Rate of ECOG score improvement (%) | - | 34·1% | 24·3%–45·0% | - | 25·0% | 16·4%–35·4% | - |
| No. of patients: FACT-LCS score | 88 | 73 | - | - | 50 | - | - |
| FACT-LCS score | 84·40 | 6·86 | 3·79–9·93 | <0·01 | 3·98 | -0·59–8·55 | 0·11 |

ND: Not done

FACT-LCS: *Functional Assessment of Cancer Therapy–Lung Cancer Subscale*; ECOG: *Eastern Cooperative Oncology Group* physical performance scale

* Analyses were based on patients with partial remission and complete remission. Results were reported as percentage and the 95% confidence interval.

** The rates of atelectasis at days 7 and 30 post-treatment were pooled for overall analyses.

Some patients did not accomplish spirometry or quality of life assessments. These patients either had difficulty in performing spirometry due to severe airflow limitation and dyspnea, or failed to participate in the follow-up visits due to their remote residency (remote rural areas).

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607 **TABLE 4 ALL ADVERSE EVENTS AS RATED BY THE SEVERITY**

| Adverse events | Total No. (%) | Severity | | |
|---|---|---|---|---|
| | | Mild | Moderate | Severe |
| **Any reported adverse event** | 57 (64·0%) | 29 (50·9%) | 18 (31·6%) | 10 (17·5%) |
| **Respiratory system** | 42 (47·2%) | 22 (52·4%) | 12 (28·6%) | 8 (19·0%) |
| Coughing | 15 (16·9%) | 9 (60·0%) | 5 (33·3%) | 1 (6·7%) |
| Bloody sputum | 15 (16·9%) | 13 (86·7%) | 2 (13·3%) | 0 (0·0%) |
| Pharyngodynia | 7 (7·9%) | 6 (85·7% | 1 (14·3%) | 0 (0·0%) |
| Tachypnea | 6 (6·7%) | 5 (83·3%) | 1 (16·7%) | 0 (0·0%) |
| Chest distress | 5 (5·6%) | 4 (80·0%) | 0 (0·0%) | 1 (20·0%) |
| Pulmonary infections | 5 (5·6%) | 3 (60·0%) | 2 (40·0%) | 0 (0·0%) |
| Expectoration | 5 (5·6%) | 5 (100·0%) | 0 (0·0%) | 0 (0·0%) |
| Dyspnea | 4 (4·5%) | 1 (25·0%) | 1 (25·0%) | 2 (50·0%) |
| Chest pain | 4 (4·5%) | 3 (75·0%) | 1 (25·0%) | 0 (0·0%) |
| Stridor | 3 (3·4%) | 1 (33·3%) | 1 (33·3%) | 1 (33·3%) |
| Haemoptysis | 3 (3·4%) | 0 (0·0%) | 1 (33·3%) | 2 (66·7%) |
| Others | 7 (7·7%) | 2 (28·6%) | 1 (14·3%) | 3 (42·9%) |
| **Systemic and infection site** | 20 (22·5%) | 13 (65·0%) | 7 (35·0%) | 0 (0·0%) |
| Injection site hemorrhage | 9 (10·1%) | 7 (77·8%) | 2 (22·2%) | 0 (0·0%) |
| Fever | 8 (9·0%) | 5 (62·5%) | 3 (37·5%) | 0 (0·0%) |
| Malaise | 1 (1·1%) | 1 (100·0%) | 0 (0·0%) | 0 (0·0%) |
| Progression of cancer | 1 (1·1%) | 0 (0·0%) | 1 (100·0%) | 0 (0·0%) |
| Edema | 1 (1·1%) | 0 (0·0%) | 1 (100·0%) | 0 (0·0%) |
| **Other examination abnormality** | 8 (9·0%) | 6 (75·0%) | 2 (25·0%) | 0 (0·0%) |
| Electrocardiogram | 2 (2·2%) | 2 (100·0%) | 0 (0·0%) | 0 (0·0%) |
| Hypertension | 2 (2·2%) | 1 (50·0%) | 1 (50·0%) | 0 (0·0%) |
| Leukocytosis | 1 (1·1%) | 1 (100·0%) | 0 (0·0%) | 0 (0·0%) |
| Prolonged partial thrombin activation time | 1 (1·1%) | 1 (100·0%) | 0 (0·0%) | 0 (0·0%) |
| Visible urinary leukocytes | 1 (1·1%) | 1 (100·0%) | 0 (0·0%) | 0 (0·0%) |
| Neutrophilia | 1 (1·1%) | 1 (100·0%) | 0 (0·0%) | 0 (0·0%) |
| Elevated aspartate aminotransferrase | 1 (1·1%) | 1 (100·0%) | 0 (0·0%) | 0 (0·0%) |
| Oxygen desaturation | 1 (1·1%) | 0 (0·0%) | 1 (100·0%) | 0 (0·0%) |
| **Skin and subcutaneous diseases** | 4 (4·5%) | 4 (100·0%) | 0 (0·0%) | 0 (0·0%) |
| **Gastrointestinal tract diseases** | 4 (4·5%) | 2 (50·0%) | 2 (50·0%) | 0 (0·0%) |
| **Cardiopulmonary diseases** | 4 (4·5%) | 0 (0·0%) | 2 (50·0%) | 2 (50·0%) |
| **Neurologic diseases** | 3 (3·4%) | 1 (33·3%) | 1 (33·3%) | 1 (33·3%) |
| **Metabolic and nutritional diseases** | 2 (2·2%) | 2 (100·0%) | 0 (0·0%) | 0 (0·0%) |
| **Psychiatric disease** | 1 (1·1%) | 0 (0·0%) | 1 (100·0%) | 0 (0·0%) |
| **Vascular diseases** | 1 (1·1%) | 0 (0·0%) | 1 (100·0%) | 0 (0·0%) |

608 Data were summarized as count (percentage) unless otherwise stated.
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## FIGURE LEGENDS

**Figure 1. Study design**

**Figure 1-A. Medication dosing scheme**

The number of days was displayed based on the patients who completed 3 consecutive treatment courses.

**Figure 1-B. Patient recruitment flowchart**

**Figure 2. Pre- and post-treatment airway occlusion in a 56-year-old female with lung cancer of the right main bronchus (T3N2M1, stage IV)**

2010-5-28, Screening period: The tumor completely occluded the right main bronchus airway.
2010-6-4, 1st dosing: 3ml PTS injection at the tumor resulted in minor hemorrhage.
2010-6-7, 2nd dosing: The lesion was covered with ischemic debris. Following debris removal, 4ml PTS was injected.
2010-6-9, 3rd dosing: Following debris removal, 4ml PTS was injected to the lesion.
2010-6-11, Withdrawal visit: Virtually diminished lesion (airway occlusion rate: 3·3%).
2010-6-24, Follow-up: Smooth surface of the right main bronchus
2010-8-3, Follow-up: Airway occlusion rate: 4·1%
On May 24, 2010 (pre-treatment), the intrabronchial tumor size was 13.5mm×10.0mm×14.8mm; ECOG score: 2, baseline dyspnea index: 6; FVC: 1.04 L; $FEV_1$: 0.92 L, $FEV_1$/FVC: 88.3%.
On Jun 12, 2010 (post-treatment), the intrabronchial tumor size was 0.0mm×0.0mm×0.0mm; ECOG score: 2, baseline dyspnea index: 7; FVC: 1.76 L; $FEV_1$: 1.33 L, $FEV_1$/FVC: 75.8%.
On Aug 3, 2010 (post-treatment), the intrabronchial tumor size was 0.0mm×0.0mm×0.0mm; ECOG score: 1, baseline dyspnea index: 8; spirometry was not performed (declined).

**Figure 3. Kaplan-Meier survival plot of the full-analysis set**