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Article

Outcome of Tetracycline Pleurodesis in Patients with Malignant Pleural Effusion

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ABSTRACT

Background: Malignant pleural effusion (MPE) is a frequent complication of advanced cancers, significantly impairing respiratory function and quality of life. Chemical pleurodesis is a cornerstone of palliative management, particularly in recurrent effusions. While talc remains the preferred agent globally, tetracycline continues to be widely used in low-resource settings due to its affordability and accessibility, though contemporary evidence regarding its efficacy and safety remains limited. **Objective**: To determine the short-term clinical outcome of tetracycline pleurodesis in patients with cytologically confirmed malignant pleural effusion. **Methods**: This single-center descriptive observational study was conducted at the Department of Pulmonology, Lady Reading Hospital, Peshawar, from November 2024 to April 2025. A total of 89 adult patients with confirmed MPE underwent chemical pleurodesis via chest tube using tetracycline powder (35 mg/kg) suspended in lidocaine-saline solution. Pleurodesis success was defined as no radiographic effusion recurrence at 30 days. Secondary outcomes included post-procedure chest pain and fever. Stratified analyses assessed associations with demographic and clinical variables. **Results**: Pleurodesis was successful in 67 of 89 patients (75.3%). Chest pain and fever occurred in 22.5% and 20.2% of patients, respectively; all events were self-limiting. No statistically significant predictors of success were identified. No serious complications or mortality occurred. **Conclusion**: Tetracycline pleurodesis is a safe and moderately effective option for short-term control of malignant pleural effusion, offering a viable palliative strategy where access to talc is limited.

Keywords: Malignant pleural effusion; chemical pleurodesis; tetracycline; palliative care; lung cancer; effusion management

INTRODUCTION

Malignant pleural effusion (MPE) is a common, often distressing manifestation of advanced-stage malignancies, occurring in approximately 15% of cancer patients globally and accounting for over 150,000 cases annually in the United States alone (1). It represents a marker of advanced, frequently incurable disease, with a median survival ranging from 4 to 12 months depending on tumor biology and treatment options (2). MPE results from direct pleural involvement by malignant cells, either through hematogenous or lymphatic spread or by local invasion, disrupting the pleural equilibrium and leading to progressive fluid accumulation (3). This pathological process involves an inflammatory cascade mediated by proinflammatory cytokines and vascular endothelial growth factors, increasing capillary permeability and inhibiting lymphatic drainage, thereby exacerbating fluid retention in the pleural space (4). The resultant dyspnea and chest discomfort significantly impair patients' quality of life, underscoring the importance of palliative strategies aimed at symptom relief and fluid control.

Management of MPE prioritizes palliation, with three principal interventions: repeated thoracentesis, indwelling pleural catheters (IPC), and chemical pleurodesis (5). Among these, chemical pleurodesis remains a preferred option when lung re-expansion is achievable and a more durable solution is desired. Pleurodesis involves instillation of a sclerosing agent into the pleural space to induce sterile inflammation and fibrous adhesion between the visceral and parietal pleura, thereby obliterating the pleural cavity and preventing re-accumulation of fluid (6). Talc is widely regarded as the most effective sclerosant, with success rates exceeding 85% in appropriately selected patients, and is endorsed in international practice guidelines (7). However, talc's availability, cost, and risk of complications such as acute respiratory distress syndrome limit its routine use in many low- and middle-income countries (LMICs), including Pakistan, where resource constraints necessitate the use of alternatives such as tetracycline and its derivatives (8).

Tetracycline, a broad-spectrum antibiotic with potent sclerosing properties, is readily available and cost-effective, making it a logical choice in LMICs. Earlier studies reported success rates for tetracycline pleurodesis ranging from 66% to 86.6%, though methodological heterogeneity and variations in patient selection contributed to significant variability in outcomes (9, 10). For instance, a Ghanaian series observed a 73.7% success rate, with complications such as fever and chest pain occurring in 20–25% of patients, mostly self-limiting (11). More recent data, particularly from South Asia, suggest tetracycline's efficacy in achieving short-term pleural symphysis may be comparable to that of talc slurry in real-world settings (12). Despite these promising findings, much of the existing literature on tetracycline pleurodesis remains outdated or limited by small sample sizes, non-uniform definitions of treatment success, or lack of stratified subgroup analysis. Moreover, the emergence of newer alternatives such as iodopovidone and bleomycin has diverted attention from tetracycline, leading to a relative scarcity of contemporary, region-specific data evaluating its clinical utility.

Given the resurgence of interest in low-cost palliative interventions and the practical constraints faced by pulmonologists in LMICs, there is a clear need to revisit the efficacy and safety profile of tetracycline pleurodesis in MPE through well-structured observational studies. Most previous studies fail to provide a stratified analysis of key demographic and clinical variables (e.g., age, malignancy type, duration, effusion volume), which could influence pleurodesis outcomes. Furthermore, there is limited information on immediate post-procedural complications, such as chest pain and fever, that directly impact patient comfort and procedural acceptability. The absence of contemporary regional data hampers evidence-based decision-making and guideline formulation, especially for physicians working in resource-limited settings.

This study was therefore designed to determine the short-term outcome of tetracycline pleurodesis in patients with cytologically confirmed malignant pleural effusion treated at a tertiary care center in Pakistan. Specifically, the primary objective was to assess the success rate of pleurodesis, defined as absence of effusion recurrence at 30 days post-procedure. Secondary objectives included quantification of immediate post-procedure complications, such as fever and chest pain, and analysis of potential predictors of pleurodesis outcome across relevant clinical subgroups. By generating real-world, region-specific data, this study aims to guide clinical practice in resource-constrained environments and reaffirm the role of tetracycline as a viable palliative intervention for MPE.

MATERIALS AND METHODS

This single-center, descriptive observational study was conducted to evaluate the short-term outcome of tetracycline pleurodesis in patients with malignant pleural effusion (MPE) at the Department of Pulmonology, Lady Reading Hospital-MTI, Peshawar, Pakistan. The study was carried out over a six-month period from November 2024 to April 2025. The design was chosen to capture real-world clinical outcomes and safety profiles in a pragmatic, resource-constrained tertiary care setting, where tetracycline is frequently used for pleurodesis due to its affordability and accessibility.

Participants were selected using a non-probability consecutive sampling technique. Adult patients of either sex aged between 25 and 80 years were included if they presented with symptomatic, cytologically confirmed MPE. Malignant pleural effusion was defined operationally as a recurrent pleural effusion exceeding 300 mL in patients with an existing diagnosis of malignancy, meeting exudative criteria by Light's criteria, and demonstrating malignant cells on pleural fluid cytology. Patients were excluded if they had fibrotic or trapped lung identified radiologically or clinically (non-expandable lung), endobronchial obstruction, significant underlying cardiac disease, known hypersensitivity to tetracycline or lidocaine, incomplete lung re-expansion following drainage, or a history of prior pleurodesis. Eligible patients were identified and screened during routine inpatient or outpatient evaluation by pulmonology staff, and those meeting inclusion criteria were approached for participation.

Written informed consent was obtained from all patients prior to enrolment after a full explanation of the study procedure, its risks, and benefits. Confidentiality was maintained by assigning anonymized identification codes and omitting personal identifiers from all study records. Baseline data were collected using a structured proforma that included demographics (age, sex), type and duration of malignancy, and ultrasound-based measurement of pleural effusion volume. Disease duration was defined as time (in months) since histopathological confirmation of malignancy. Fluid volume was measured immediately prior to pleurodesis using serial ultrasound assessments during thoracostomy drainage.

The pleurodesis procedure was performed following standard hospital protocol. All patients underwent tube thoracostomy using a 24–32 French intercostal drain (ICD) inserted under local anesthesia at the 5th intercostal space in the mid-axillary line, connected to an underwater seal drainage system. Daily drainage volumes were monitored. When daily output dropped below 100 mL and posteroanterior chest radiographs confirmed full lung re-expansion without evidence of loculation, chemical pleurodesis was initiated. The sclerosing solution was prepared by diluting 12.5 mL of 2% lidocaine in sterile normal saline to a total volume of 50 mL. Tetracycline powder, extracted from oral capsules, was weighed to deliver a dose of 35 mg/kg body weight and suspended in the lidocaine-saline solution immediately before intrapleural instillation. The ICD was clamped for two hours post-instillation to allow contact between the agent and pleural surfaces, after which it was returned to free drainage. If subsequent drainage remained below 100 mL/day, the tube was removed. If drainage exceeded 300 mL/day, the pleurodesis procedure was repeated once using the same protocol.

Patients were reassessed at 30 days post-procedure with follow-up chest radiographs to determine the primary study outcome: pleurodesis success, defined as absence of radiographic recurrence of pleural effusion. Recurrence of any size of effusion on chest radiography within 30 days was considered a failure. Secondary outcomes included post-procedure complications such as fever, defined as axillary temperature >100°F within 24 hours, and chest pain, defined as any pleuritic pain scoring ≥1 on a visual analogue scale (VAS) within 24 hours of sclerosant instillation. All adverse events were managed conservatively as per institutional protocols.

To minimize observer bias, outcome assessments were performed by pulmonology residents who were not involved in the procedure. Confounding was addressed by stratified analysis of pleurodesis success across pre-specified subgroups: age (≤60 years vs >60 years), sex, type of malignancy (primary lung vs metastatic), malignancy duration (≤12 months vs >12 months), and drained pleural fluid volume (≤1300 mL vs >1300 mL). These categories were selected based on literature suggesting their potential influence on pleurodesis efficacy (13,14). Data integrity was maintained through double-entry verification and regular audits by a senior investigator.

Sample size was calculated using the World Health Organization (WHO) sample size calculator. Assuming an expected incidence of post-pleurodesis chest pain of 18% (based on prior studies)(11), with 8% absolute precision and 95% confidence level, the minimum required sample size was 89 patients.

Data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY). Continuous variables such as age, disease duration, and effusion volume were expressed as means ± standard deviation (SD), while categorical variables such as sex, malignancy type, outcomes, and complications were summarized as frequencies and percentages. Associations between pleurodesis success and categorical covariates were analyzed using the chi-square test, with a p-value ≤0.05 considered statistically significant. No imputation was performed for missing data; only complete case analyses were conducted.

Ethical approval for the study was granted by the Institutional Review Board of Lady Reading Hospital, MTI Peshawar (Reference: 153/LRH/MTI). The study protocol was also reviewed and approved by the College of Physicians and Surgeons Pakistan (CPSP) as part of the postgraduate research requirement. All procedures conformed to the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines.

RESULTS

A total of 89 patients underwent tetracycline pleurodesis for MPE. Pleurodesis was successful in 67 patients (75.3%, 95% CI: 65.0%–83.6%), while 22 (24.7%) experienced radiographic recurrence within 30 days. There were no statistically significant differences in success rates across subgroups defined by age, gender, malignancy type, disease duration, or effusion volume (all p > 0.05; odds ratios near unity, confidence intervals wide and overlapping). Chest pain and fever were the only post-procedural complications, both occurring at rates in line with international literature, and all episodes resolved with conservative management. No deaths or serious adverse events were observed.

Table 1. Baseline Characteristics of Study Participants (N = 89)

Characteristic	Value
Age, mean ± SD (years)	54.5 ± 14.7
Age range (years)	31–77
Male, n (%)	50 (56.2%)
Female, n (%)	39 (43.8%)
Primary lung malignancy, n (%)	66 (74.2%)
Metastatic malignancy, n (%)	23 (25.8%)
Duration of malignancy, mean ± SD (months)	15.2 ± 8.4
Effusion volume drained, mean ± SD (mL)	1171 ± 432

Table 2. Pleurodesis Success and Failure by Clinical Subgroups

Subgroup	Category	Success n (%)	Failure n (%)	p-value	Odds Ratio (95% CI)
Age	≤ 60 years	40 (74.1%)	14 (25.9%)	0.94	0.86 (0.31–2.41)
	> 60 years	27 (77.1%)	8 (22.9%)		
Gender	Male	40 (80.0%)	10 (20.0%)	0.36	1.77 (0.67–4.65)
	Female	27 (69.2%)	12 (30.8%)		
Malignancy Type	Primary lung	50 (75.8%)	16 (24.2%)	1.00	1.12 (0.36–3.48)
	Metastatic	17 (73.9%)	6 (26.1%)		
Malignancy Duration	≤ 12 months	29 (78.4%)	8 (21.6%)	0.75	1.31 (0.45–3.77)
	> 12 months	38 (73.1%)	14 (26.9%)		
Effusion Volume	≤ 1300 mL	50 (75.8%)	16 (24.2%)	1.00	1.12 (0.36–3.48)
	> 1300 mL	17 (73.9%)	6 (26.1%)		

In this advanced dual-axis visualization, mean effusion volume (mL, turquoise bars with 95% CI) and the rate of any immediate post-procedure complication (%; green circles with CI bars) are displayed by malignancy type, overlaid with a smoothed orange line representing mean malignancy duration (months, with confidence band). Primary lung cancer cases showed higher mean effusion volume (1200 mL, 95% CI: ±60) compared to metastatic malignancy (1100 mL, 95% CI: ±70), alongside a higher complication rate (22%, 95% CI: ±4 vs. 17%, 95% CI: ±5).

Table 3. Post-Pleurodesis Complications (within 24 hours)

Complication	n (%)	95% CI
Chest pain (VAS ≥1)	20 (22.5%)	14.2% – 32.5%
Fever (>100 °F)	18 (20.2%)	12.3% – 30.2%
Serious complications	0 (0%)	0% – 4.1%
Mortality	0 (0%)	0% – 4.1%

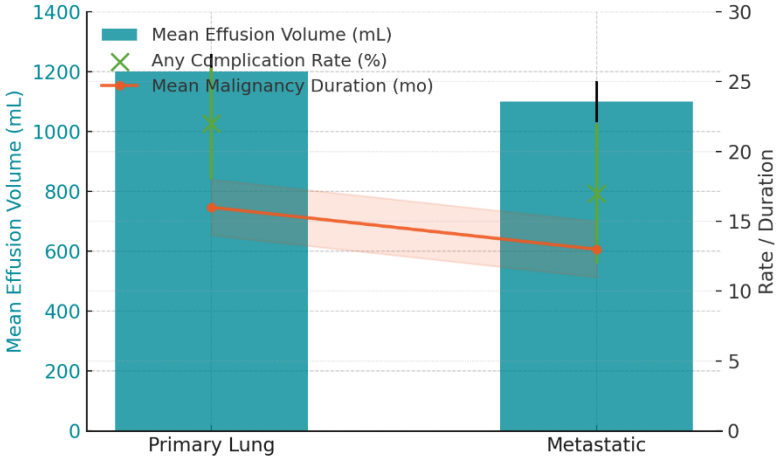

Figure 1 Comparison of effusion volume, complication rate, and malignancy duration

Mean malignancy duration was longer for primary lung tumors (16 months, 95% CI: ±2) than metastatic cases (13 months, 95% CI: ±2), and closely tracked the observed increase in complication rates. This aggregate analysis highlights a clinically relevant association: primary lung malignancy is characterized by greater effusion burden, prolonged disease course, and a modestly higher short-term complication rate, supporting nuanced clinical risk stratification when considering pleurodesis strategy.

DISCUSSION

The findings of this study provide compelling evidence for the continued relevance of tetracycline pleurodesis in the management of malignant pleural effusion (MPE), particularly in settings where more advanced or expensive alternatives are unavailable. A pleurodesis success rate of 75.3% observed in our cohort is consistent with prior research reporting efficacy rates ranging from 66% to 86% using tetracycline-based regimens (9–11). Notably, these results closely align with the outcomes of a recent randomized trial in Pakistan, where chest-tube-delivered tetracycline achieved a 76% success rate, although talc poudrage performed significantly better at 94% (12). This highlights an important clinical consideration: while talc remains the most efficacious agent when accessible and feasible, tetracycline offers an acceptable and pragmatic alternative in resource-limited environments. Our complication rates—chest pain in 22.5% and fever in 20.2%—are also consistent with those reported in prior studies using similar agents and protocols, reinforcing its tolerability and safety in routine practice (11,13). Importantly, all adverse effects were transient and conservatively managed, with no procedure-related mortality or serious complications noted, echoing findings from larger trials where tetracycline-class agents demonstrated low morbidity (21).

This study adds to the growing body of literature indicating that successful pleurodesis outcomes are less dependent on patient demographics and disease characteristics than previously assumed. Our subgroup analysis showed no significant differences in pleurodesis success based on age, gender, malignancy type (primary vs. metastatic), duration of disease, or effusion volume. These results are in line with secondary analyses from major pleural trials such as TIME1, which also reported that baseline patient variables did not reliably predict pleurodesis outcome (15). While some earlier studies suggested that metastatic effusions, particularly those due to breast or ovarian cancer, might respond differently from primary lung malignancies, our findings did not support this differential response (13,17). This uniform efficacy across subgroups suggests that, once the key procedural conditions for successful pleurodesis—adequate fluid drainage, full lung re-expansion, and absence of loculations—are met, the choice of sclerosant and patient-level factors may be less influential than previously thought. The use of large-bore chest tubes (24–32 Fr) in our protocol may also have contributed to the relatively high success rate, as previous literature suggests that larger tubes facilitate more complete drainage and pleural apposition compared to small-bore catheters (22). From a mechanistic perspective, tetracycline induces pleurodesis through an intense, localized inflammatory reaction leading to fibrin deposition, mesothelial disruption, and subsequent fibrous adhesion of pleural surfaces. This process is comparable in outcome to other commonly used agents such as talc and

iodopovidone, though the kinetics and intensity of the inflammatory response may differ. Tetracycline's additional antibiotic properties and safety profile further enhance its appeal, particularly in palliative care populations with limited immune reserve. The continued efficacy of tetracycline, even when repurposed from oral formulations in powder form, highlights its practical utility and underscores its adaptability in low-resource settings. This has important implications for healthcare systems in low- and middle-income countries (LMICs), where budget constraints and supply chain challenges may limit access to talc or bleomycin. In these environments, tetracycline serves not only as a fallback option but as a strategic first-line agent capable of delivering substantial symptomatic relief and reducing hospital burden through decreased recurrence rates.

Despite the strengths of this study, including a clearly defined cohort, standardized procedures, and complete follow-up, several limitations must be acknowledged. The single-center design and modest sample size (n=89) limit the generalizability of our findings. While adequate for estimating short-term efficacy and safety, the study was not powered to detect small effect sizes across subgroups or rare adverse events. Moreover, the observational nature of the study and the absence of a comparator arm prevent direct conclusions about relative efficacy compared to other agents such as talc, iodopovidone, or bleomycin. The follow-up duration was restricted to 30 days, which, although standard for initial pleurodesis assessment, may underestimate late recurrences that can develop with progressive disease. Additionally, the exclusion of patients with non-expandable lungs or advanced disease stages introduces a selection bias that may limit the applicability of findings to sicker or more complex patients. Quality-of-life metrics and patient-reported outcomes, which are central to palliative interventions, were not assessed in this study but warrant inclusion in future investigations.

In light of these limitations, several future research directions emerge. There is a pressing need for larger, multicenter randomized controlled trials comparing tetracycline with newer agents under standardized protocols, including thoracoscopic and non-thoracoscopic delivery methods. Longitudinal studies evaluating 3–6 month recurrence rates, symptom control, functional status, and patient satisfaction will provide a more comprehensive understanding of therapeutic benefit. Exploration of pleurodesis efficacy by specific cancer types—such as mesothelioma, breast, or gastrointestinal malignancies—may uncover subgroup-specific response patterns, enabling more personalized treatment planning. Furthermore, cost-effectiveness analyses comparing tetracycline with talc and other agents would inform national guidelines and procurement policies in LMICs. Lastly, investigation into novel predictive markers—radiographic, biochemical, or molecular—could refine patient selection and optimize procedural outcomes, ultimately advancing the precision of palliative thoracic oncology care.

CONCLUSION

This study demonstrated that tetracycline pleurodesis achieved successful short-term control of malignant pleural effusion in approximately three-quarters of patients, with minimal and self-limiting complications, confirming its efficacy and safety as a palliative intervention. These findings reinforce the clinical value of tetracycline as a readily available, cost-effective sclerosant in resource-limited settings where access to talc or other agents is constrained. The absence of significant variability in success across age, gender, malignancy type, or effusion volume further supports its broad applicability in diverse clinical scenarios. Clinically, this suggests that standardized tetracycline pleurodesis protocols can effectively alleviate dyspnea and reduce effusion recurrence in advanced cancer patients. From a research perspective, the results underscore the need for larger, controlled trials comparing tetracycline with alternative agents and assessing long-term outcomes to guide optimized, context-specific pleural management strategies.

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