CHEST

Thoracic Ultrasound as an Early Predictor of Pleurodesis Success in Malignant Pleural Effusion

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BACKGROUND: Malignant pleural effusion (MPE) is common and imposes a significant burden on patients and health-care providers. Most patients require definitive treatment, usually drainage and chemical pleurodesis, to relieve symptoms and prevent fluid recurrence. Thoracic ultrasound (TUS) can identify the presence of pleural adhesions in other clinical scenarios, and could therefore have a role in predicting long-term pleurodesis success or failure in MPE.

METHODS: Patients undergoing chest tube drainage and talc slurry pleurodesis for symptomatic MPE were recruited to a prospective observational cohort pilot study assessing whether TUS findings pre-talc and post-talc instillation predicted treatment outcome. Participants underwent TUS examination immediately before, and 24 h after talc slurry administration to derive pleural adherence scores for the affected hemithorax. The recorded TUS scans were additionally scored by two independent assessors blinded to the patient's clinical status. The primary outcome was pleurodesis success at 1-month and 3-month follow-up.

RESULTS: Eighteen participants were recruited to the pilot study. Participants who suffered pleurodesis failure had a lower pleural adherence score at 24 h post-talc instillation than those who were successful (difference of 6.27; 95% CI, 3.94-8.59). TUS examination was acceptable to patients, while TUS scoring was highly consistent across all assessors (intraclass correlation coefficient, 0.762; 95% CI, 0.605-0.872).

CONCLUSION: A TUS-derived pleural adherence score may facilitate early prediction of long-term outcomes following chemical pleurodesis, with implications for personalized care and decision making in MPE. Further research is needed to evaluate this novel finding.

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ABBREVIATIONS: MPE = malignant pleural effusion; TUS = thoracic ultrasound; VAS = visual analog scale

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Malignant pleural effusion (MPE) is common,[1,2] and with an aging population and more patients with metastatic cancer surviving long-term,[3,4] the number of cases will continue rising for the foreseeable future. MPE typically carries a limited prognosis,[5] with most patients requiring therapeutic drainage to provide symptomatic relief.[5,6] Many patients with recurrent MPE are managed with chemical pleurodesis, most commonly using sterile talc.[1,5,7] This process generates inflammation, adhesion formation, and pleural space obliteration, with the long-term aim of preventing MPE recurrence.[5,6,8] Randomized trial data[9] report a success rate of around 70% for talc pleurodesis via intercostal chest tube, with no means of predicting which patients will suffer pleurodesis failure.[5] There are few data to guide chest tube removal[5]; a randomized trial[10] reported no difference in pleurodesis success between chest tube removal at 24 and 72 h post-talc, but was underpowered and used only radiological measures of pleurodesis success.

An animal model of chemical pleurodesis demonstrated correlation between thoracic ultrasound (TUS) scoring of lung sliding and the development of a successful pleurodesis.[11] Human studies using TUS to detect pleural adhesions before thoracic surgery[12,13] and following surgical pleurodesis for recurrent pneumothorax[14] have also shown this technique to have potential utility. There are no data relating to TUS in the context of talc pleurodesis for MPE, however.

We hypothesized that TUS could detect the early formation of pleural adhesions following talc pleurodesis for symptomatic MPE, thereby predicting long-term pleurodesis success and facilitating earlier chest tube removal.

Methods

Study Design and Participants

This was a prospective observational cohort pilot study that recruited between May 2015 and April 2017. Adult patients (≥18 years old) undergoing MPE drainage and talc slurry pleurodesis via chest tube (12 Fr per usual local practice) were approached to participate. MPE was defined using widely accepted guidelines and per previous publications.[1,5,9,15,16] Patients were excluded if they were <18 years old, unable to provide informed consent, had an allergy or other contraindication to intrapleural talc, had evidence of unexpandable lung believed by the responsible clinician to represent insufficient pleural apposition that would preclude pleurodesis, and/or had an expected survival of <1 month.

The study was sponsored by the University of Oxford, managed by the University of Oxford Respiratory Trials Unit, and registered with ClinicalTrials.gov (NCT02625675). The protocol and subsequent amendments were approved by the UK National Research Ethics Service (15/LO/0382). Study participants provided informed written consent before recruitment and study-related procedures.

Study Procedures

Study participants underwent standardized bedside brightness mode TUS assessment immediately before (day 0) and 24 h (day 1) following talc slurry instillation. Lung sliding was scored in nine zones (upper, middle, and lower zones in the anterior, lateral, and posterior chest wall) across the affected hemithorax by the primary TUS operator in real -time as present (= 0), questionable (= 1), or absent (= 2),[11] generating a total pleural adherence score for the hemithorax. Ultrasound video clips were recorded concurrently to facilitate remote scoring by two independent assessors blinded to the original scoring and participants' clinical status. All scorers held Royal College of Radiologists level 1 or 2 TUS accreditation.[17]

Study participants completed a questionnaire relating to their experience of TUS assessment before leaving the hospital. This included a visual analog scale (VAS) score of pain caused by TUS examination (0-100 mm: no pain at 0 mm and worst possible pain at 100 mm), and assessment of willingness to undergo TUS examination again.

Study procedures, including TUS, were performed by a researcher independent of the medical inpatient team. The inpatient team was blind to TUS findings and managed participants according to national guidelines[5] adapted for local practice with respect to timing of talc slurry instillation and subsequent chest tube removal.

Follow-up took place at 1 and 3 months, or until death if sooner. Study participants were assessed for pleurodesis failure, which was objectively defined as fluid recurrence in the ipsilateral hemithorax requiring further therapeutic pleural intervention, with radiological evidence (chest X-ray, CT scan, and/or TUS) of the same fluid recurrence at any point during follow-up. Consistency in the diagnosis of pleurodesis failure was ensured by assessment of participants' data by a researcher and independent chest physician not involved in the participant's clinical care.

Outcomes and Analyses

The primary end point was pleurodesis failure at 1 and 3 months. Secondary end points were patient satisfaction with TUS assessment measured using VAS pain score and a Likert-type scale and the difference between a hypothetical discharge date based on TUS findings and the actual discharge date from hospital based on standard care.

SPSS, version 24, was used for statistical analyses; *t* tests were used for parametric data and Fisher exact test for categorical variables. A *P* value <.05 was considered significant. Interrater reliability was calculated using the intraclass correlation coefficient for continuous variables. Descriptive statistics were used to summarize patient characteristics.

Results

Eighteen participants were recruited; baseline characteristics are in Table 1. Three participants (16.7%) died before the 1-month follow-up; a further six (nine in total, 50.0%) died before the 3-month follow-up.

Primary End Point

Fifteen (83.3%) participants reached the 1-month follow-up and were included in the primary analysis. Four of 15 (26.7%) suffered pleurodesis failure, as defined in the study methodology, by this time point.

TABLE 1] Baseline Characteristics of the Study Population (Total No. = 18 Participants)

Sex	
Male	4 (22.2%)
Female	14 (77.8%)
Age, y	67.6 (9.7)
Primary cancer	
Lung	5 (27.8%)
Gynecological	5 (27.8%)
Breast	4 (22.2%)
Renal	2 (11.1%)
Colorectal	1 (5.6%)
Pleural mesothelioma	1 (5.6%)
Active oncological treatment	
Yes	7 (38.9%)
No	11 (61.1%)
Side of effusion	
Right	8 (44.4%)
Left	10 (55.6%)
LENT score[23]	
Low, 0-1	2 (11.1%)
Moderate, 2-4	14 (77.8%)
High, 5-7	2 (11.1%)
Volume of pleural fluid drained, mL	2,703 (1,062)

Data are presented as either No. (% age) or mean (SD). LENT = pleural fluid lactate dehydrogenase; Eastern cooperative oncology group performance score; serum neutrophil-to-lymphocyte ratio; tumor type.

There was a significant difference between mean total pleural adherence score at day 1 for patients with successful vs failed pleurodesis (Table 2). The area under receiver operating characteristic curves for total pleural adherence scores on days 0 and 1 (Fig 1) were 0.798 (95% CI, 0.671-0.925) and 0.900 (95% CI, 0.812-0.988), respectively. Interrater reliability was good to excellent, with intraclass correlation coefficient (2,1) = 0.762 (95% CI, 0.605-0.872; $P < .001$).

None of the 11 participants with a successful pleurodesis at 1-month follow-up suffered delayed failure, either before death (4/11, 36.4%) or at 3-month follow-up (7/11, 63.6%).

Secondary End points

Fifteen (83.3%) participants completed the questionnaire relating to their satisfaction with TUS. The mean VAS pain score associated with TUS examination was 8.9 mm (SD, 12.9; 95% CI, 1.8-16.1). On a 3-point Likert-type scale (not, slightly, and very time consuming), 10/15 (66.7%) participants did not find TUS examination time consuming, whereas 5 (33.3%) found it slightly time consuming. All 15 participants would have the same TUS examination(s) again if necessary in the future.

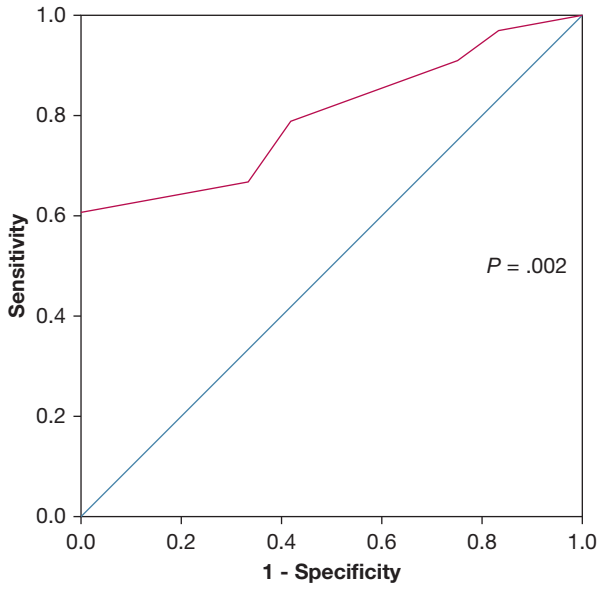
The mean time from chest tube insertion to talc instillation was 4.3 days (SD, 1.53; n = 18 participants). Five of 18 (27.8%) participants suffered a delayed discharge from hospital because of issues unrelated to their pleural disease. As such, time from talc instillation to chest tube removal (actual vs hypothetical based on TUS findings), rather than discharge from hospital, was analyzed. A total pleural adherence score of ≥10 at day 1 (sensitivity 82%, specificity 91% for pleurodesis success; Fig 1) was used as the cutoff for hypothetical chest tube removal.

The mean time from talc instillation to chest tube removal was 2.9 days (SD, 1.1; n = 18 participants). Three of 18 (16.7%) participants had their chest tube removed after 24 hours as part of usual clinical care, compared

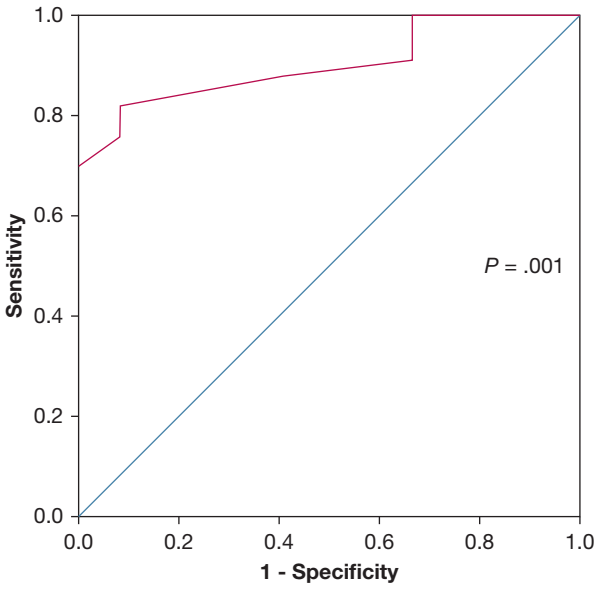
TABLE 2] Total Pleural Adherence Scores (Minimum 0, Maximum 18) on Days 0 (Prepleurodesis) and 1 (24 h Postpleurodesis) for Study Participants (N = 15) With Either Successful or Failed Pleurodesis at Subsequent 1-Mo Follow-Up

	Pleurodesis Success (n = 11 Participants)	Pleurodesis Failure (n = 4 Participants)	*P* Value (Unpaired *t*-test)
Day 0			
Original scorer	10.73 (3.80)	6.50 (1.29)	.0522
Blind scorer 1	8.91 (4.87)	5.00 (2.16)	.1515
Blind scorer 2	10.18 (4.26)	5.00 (3.46)	.0492
Combined scores	9.94 (4.26)	5.50 (2.35)	.0014
Day 1			
Original scorer	13.36 (3.11)	6.75 (2.63)	.0023
Blind scorer 1	11.91 (3.88)	7.00 (3.74)	.0480
Blind scorer 2	13.27 (3.95)	6.00 (2.58)	.0049
Combined scores	12.85 (3.62)	6.58 (2.78)	.0001

Data are presented as mean (SD).



Day 0: ROC area 0.798 (95% CI, 0.671-0.925)



Day 1: ROC area 0.900 (95% CI, 0.812-0.988)

Day 0 ROC curve coordinates		
Successful pleurodesis if pleural adherence score ≥	Sensitivity	1 - Specificity
0	1.000	1.000
1	1.000	1.000
2	1.000	1.000
3	0.970	0.833
4	0.909	0.750
5	0.879	0.667
6	0.818	0.500
7	0.788	0.417
8	0.667	0.333
9	**0.606**	**0.000**
10	0.545	0.000
11	0.515	0.000
12	0.394	0.000

Day 1 ROC curve coordinates		
Successful pleurodesis if pleural adherence score ≥	Sensitivity	1 - Specificity
0	1.000	1.000
1	1.000	1.000
2	1.000	1.000
3	1.000	0.917
4	1.000	0.750
5	1.000	0.750
6	1.000	0.667
7	0.909	0.667
8	0.879	0.417
9	0.848	0.250
10	**0.818**	**0.083**
11	0.758	0.083
12	0.697	0.000

Figure 1 – *ROC curves and coordinates for total pleural adherence score on days 0 and 1 using a combined dataset (original and blind scorers); the proposed score (highlighted) for detecting pleurodesis success using thoracic ultrasound was chosen using a threshold of ≥90% specificity. ROC = receiver operating characteristic.*

with 13/18 (72.2%) participants in the hypothetical TUS-based model ($P = .002$, Fisher exact test).

Discussion

This study shows TUS can detect early pleural adhesion formation following talc pleurodesis for MPE, as manifest in the loss of normal lung sliding artifact. This is consistent with prior data[12,13] demonstrating the same sonographic features in a different setting. The extent of loss of lung sliding on TUS following talc administration appears to predict longer term pleurodesis success. Study participants with a successful pleurodesis at 1 month had a higher mean total pleural adherence score at 24 h post-talc administration compared with those whose pleurodesis failed (difference, 6.27; 95% CI, 3.94-8.59).

TUS examination for this purpose appears acceptable to patients and deliverable at the bedside by physicians, with the potential to enhance decision making around timing of chest tube removal. TUS interpretation appears consistent with excellent interrater reliability across the original bedside operator and two remote blinded observers, meaning the study technique and outcomes can be regarded as robust.

This study establishes proof of concept for TUS as an outcome prediction tool following talc pleurodesis for symptomatic MPE. It is novel in demonstrating the ability of TUS to detect early loss of lung sliding and predict longer term pleurodesis success, whereas prior data in animals[11] and humans[14] were obtained at a delayed interval (2 and 4 weeks postintervention, respectively). TUS assessment delayed by up to a month postintervention would have limited utility in the context of intended definitive treatment for MPE. However, early identification of patients at risk of pleurodesis failure would allow clinicians to consider alternative strategies; for example, planning for indwelling pleural catheter insertion.

An interesting observation was a trend for the total pleural adherence score at day 0 (ie, before talc administration) to predict pleurodesis success (Table 2). Although combined TUS scores reached significance for detecting a difference between the patient groups (pleurodesis success vs failure), this was not the case for individual scorers' data and cannot be considered a reliable finding. Nonetheless, this observation may be linked to the concept of spontaneous (auto-)pleurodesis in MPE; frequently described with indwelling pleural catheters,[15,16] in which up to 50% of patients pleurodese after 12 months without a chemical sclerosant. There are limited data describing autopleurodesis following chest tube drainage of MPE without use of a sclerosant,[8,18-20] although the mechanism is probably similar with the chest tube acting as an inflammatory stimulus, or an unrecognized biochemical or immunological characteristic of the MPE promoting autopleurodesis. Regardless, it may be that TUS can identify patients who will develop autopleurodesis following MPE drainage without the need for talc, saving time and resources.

This study has potential limitations. Participant numbers were small and recruited from a center with expertise in TUS and pleural disease; as such, the findings need validation in a multicenter randomized trial (ISRCTN16441661). One-half of the participants failed to survive to 3-month follow-up; this was not unexpected given the patient population and MPE being a marker of advanced disease.[5] The study methodology was strong, however, including blinded assessors to demonstrate consistency in TUS scoring, which has not been a feature of previous studies.[12,13]

In conclusion, a pleural adherence score obtained using TUS at 24 h post-talc administration in the context of symptomatic MPE predicted longer term pleurodesis success in this pilot study. This has implications for individualized TUS-guided management of patients with MPE, but remains an experimental technique. Further research is needed to evaluate TUS as an outcome prediction tool for patients with MPE undergoing definitive treatment with chemical pleurodesis.

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