ORIGINAL ARTICLE

Doxycycline poudrage: An old agent for a new technique

Eman Ahmad Hatata\textsuperscript{a}, Rasha Galal Daabis\textsuperscript{a}, Bassma Mohamed El Sabaa\textsuperscript{b}, Ayman Ibrahim Baess\textsuperscript{a,\ast}, Inas Ahmed Abd El-Rahman\textsuperscript{c}

\textsuperscript{a}Department of Chest Diseases, Alexandria Faculty of Medicine, Egypt
\textsuperscript{b}Department of Pathology, Alexandria Faculty of Medicine, Egypt
\textsuperscript{c}University Students Hospital, Alexandria, Egypt

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KEYWORDS
Medical thoracoscopy; Pleuroscopy; Pleurodesis; Doxycycline poudrage; Malignant pleural effusion

Abstract  Background: Pleurodesis is an, if not the most, important palliative option for management of symptomatic malignant pleural effusion (MPE). Asbestos-free calibrated talc is the most effective agent known for pleurodesis. Unfortunately, this agent is not available in many countries including Egypt. Doxycycline is an old agent used for pleurodesis. No data exists about doxycycline poudrage via thoracoscopy for pleurodesis in malignant pleural effusion.

Objective: To assess the efficacy, safety and outcome of medical thoracoscopic doxycycline poudrage in symptomatic MPE.

Methods: This is a prospective cohort clinical study. Thirty patients with symptomatic MPE were enrolled in March 2013 through March 2014. Medical thoracoscopic pleurodesis was done using oral forms of doxycycline. Patients were followed up for 90 days after the procedure. Efficacy was judged both clinically and radiologically. Procedure-related complications were recorded.

Results: Patients were 20 males and 10 females. Mean age ± SD was 57.67 ± 13.29 years. The most common primary neoplasms were lung cancer and breast cancer (both, \(n = 11\)). After 90 days, 19 out of 22 surviving patients (86.4\%, 95%CI = 59.8–94.8\%) had successful pleurodesis. No procedure-related major complications were recorded. Minor adverse effects included pain (28.6\%), fever (25\%) and wound infection (10.7\%). Survival rate at 90 days was 78.6\%. Mean duration of hospitalization was 1.93 ± 0.92 days.

Conclusion: Doxycycline, as an old agent, when poudraged during medical thoracoscopy proved to be safe and effective agent for pleurodesis in symptomatic malignant pleural effusion.

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\ast Corresponding author at: Chest Department, Secretary Office, Alexandria Faculty of Medicine, Egypt.
E-mail addresses: emanhatata@yahoo.com (E.A. Hatata), rgdaabis@gmail.com (R.G. Daabis), bassma_el_sabaa@yahoo.com (B.M. El Sabaa), ayman.baess@yahoo.com (A.I. Baess), emyasa.rahman@yahoo.com (I.A. Abd El-Rahman).

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Introduction

Malignant pleural effusion (MPE) causes disabling patient morbidity and significant health care burden. The annual incidence of malignant pleural effusion in developed countries has been predicted to be more than 500,000 new cases [1]. Malignancy accounts for 44–77% of all exudative pleural effusions. It develops in nearly half of patients with disseminated malignancy [2]. The presence of a MPE signifies median overall survival of 4–6 months [3]. MPE is not curable and therefore all treatment options are palliative [4]. Pleurodesis and indwelling pleural catheters remain the mainstay treatment options for MPE and recently it has been shown to be equally effective [5]. Pleurodesis through thoracoscopy could be done if the pleura appears abnormal on direct inspection thus offers diagnostic and therapeutic procedures in a single sitting [6]. Talc is considered the best known sclerosing agent especially when used by medical thoracoscopy/pleuroscopy (MT/P). Unfortunately, a serious complication can occur with its use which is acute pneumonitis leading to acute respiratory failure [7]. Graded talc, which is the safest form [8], is not available in many developing countries, including Egypt [9]. Also, injectable tetracyclines' synthesis has been ceased worldwide [10]. Meanwhile, the oral forms of doxycycline are readily available, inexpensive and as effective as its parenteral forms in inducing pleurodesis [11]. Therefore, the aim of this work was to assess the efficacy, safety and outcome of thoracoscopic pleurodesis using doxycycline poudrage in malignant pleural effusion.

Patients and methods

The study was approved by the institutional ethics committee and an informed consent was taken from all patients before participation in the study. The present study prospectively enrolled 30 patients with suspected or established malignant pleural effusion who were admitted to Alexandria Main University Hospital (AMUH) starting on March 2014 through March 2015.

The exclusion criteria in this study were general contraindications to thoracoscopy [12] or local contraindications including trapped lung and previously documented hypersensitivity to doxycycline. There were no explicit exclusion criteria based on performance status or medical condition, but patients had to be judged as capable of undergoing medical thoracoscopy.

All included patients were subjected to the followings: Detailed history taking, full clinical examination, and routine laboratory investigations including: coagulation profile and radiological investigations in the form of chest X-ray and CT chest (ultrasonography of the chest were done when needed). Bronchoscopy was performed only if endobronchial obstruction was suspected. Thoracentesis was performed in all patients and the pleural fluid was sent for biochemical (protein, lactate dehydrogenase (LDH) and glucose), bacteriological and cytological evaluation.

All patients underwent medical thoracoscopy for taking pleural biopsies that were sent for histopathological evaluation in order to confirm malignancy. Pleurodesis was performed via doxycycline poudrage in the pleural space.

The oral doxycycline used was (Vibramycin, 100 mg capsules, Pfizer Egypt, S.A.E Cairo,) and the dose used was 10 mg/kg body weight. The diameter of the particles of vibramycin capsules was measured by electron microscopy (EM) and particle size analyzer (Cilas 1064, Orleans, France) before the beginning of the study to exclude the possibility of systemic side effects (if the mean particle size was <5 μm). As demonstrated in Figs. 1 and 2, the diameter of vibramycin’s particles was 20.04 μm at 90% concentration with the mean particle diameter of 12.20 μm.

**Thoracoscopic doxycycline poudrage technique**

All patients underwent ultrasound-guided medical thoracoscopy with a single port. Rigid thoracoscope (Karl Storz, GmbH & Co., Tuttingen, Germany) was the scope used in the current study using an angled eye-piece, 10 mm in diameter, working length at 27 cm with 6 mm working channel and a metallic trocar with multifunctional valve with insufflation stopcock, 11 mm in diameter and autoclavable. The procedure was performed under moderate sedation and local anesthesia. After systematic exploration of the chest cavity, the pleural fluid was completely removed, mechanical adhesolysis was done (if adhesions were present) and pleural biopsies were taken from the suspected parietal pleural lesions.

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**Figure 1** The electron microscopy photos of vibramycin capsules’ particles.

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The particles of vibramycin capsules were evacuated under complete aseptic technique in the container of the pneumatic atomizer (Powder Blower with Bulb) (Karl Storz, GmbH &. Co., Tuttlingen, Germany). The pneumatic atomizer was introduced into the pleural space through the working channel of rigid thoracoscope and then the powder was insufflated on all pleural surfaces under direct observation to confirm wide distribution of doxycycline.

To evaluate the burden of the lesions inside the pleural cavity, a scoring system was adopted ranging from 1 to 9 [13]. Each parietal pleural surface took a score of (1, 2 or 3) according to their involvement (discrete, diffuse or massive involvement, respectively). The summation of the score for each pleural division constitutes the total thoracoscopy scoring. To quantify the severity of adhesions inside the pleural space, another scoring system was followed [14]. Scoring for adhesions took a score from 0 to 4.

At the end of the procedure, a chest tube was inserted in most cases through the cannula of the trocar [15]. Drains were removed if the chest radiograph confirmed satisfactory lung expansion, and the 24-h drainage was less than 150 ml, with no air leak. All patients were discharged on the same day their chest tube was removed.

**Follow up**

All patients were monitored for procedure-related adverse events. All patients were followed up for three months with focus on re-accumulation of the MPE or the need for further pleural interventions. Follow up was done clinically and radiologically on day 7, 30 and 90 following the procedure. The efficacy of pleurodesis was defined in three levels of response: complete (absence of pleural fluid reaccumulation), partial (residual pleural fluid or reaccumulation, which did not require further intervention or remained asymptomatic), and failed (additional pleural procedures were necessary).

**Statistical analysis**

Raw data were transformed into coding sheets using Microsoft Excel 2010 then analyzed using IBM SPSS software.
package (IBM SPSS Statistics for Windows, Version 20.0., IBM Corp., Armonk, NY). Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean and standard deviation, median and inter quartile range (IQR). The significance of the obtained results was judged at the 5% level of significance.

Results

The characteristics of the study population and their primary malignancies as diagnosed by the histopathological examination of their thoracoscopic pleural biopsies are noted in Table 1. The commonest presenting symptom in all studied patients (100%) was dyspnea. Also common was chest pain (73.3%), cough (73.3%) and weight loss (50%) as secondary symptoms. The commonest radiological CT chest findings were pleural nodules and pleural thickening presenting in 63.3% and 60% of our studied patients, respectively. Malignant cells were detected in the pleural fluid of 26.7% of the studied patients.

Intra-thoracoscopic examination of the studied patients revealed that most of the detected pleural lesions were located on the costo-parietal pleura as it was involved in 29 (96.7%) patients followed by the visceral pleura (93.3%) then the diaphragmatic pleura (80%). Pericardial lesions were detected in one patient. Pleural nodules were the commonest lesions detected during the procedure (in 27 (90%) patients). The median thoracoscopic scoring value was 7. Regarding the detected grades of adhesions, grade 1 was detected in 6 (20%) patients, grade 2 in 2 (6.7%) patients and grade 3 in 3 (10%) patients.

As demonstrated in the flow chart in Fig. 3, all eligible patients in the current study were 30 patients, 2 patients were excluded from further analysis either due to the detection of extensive adhesions during thoracoscopy in one patient or trapped lung in follow up chest X-ray in another patient hindering full lung expansion and success of pleurodesis. Furthermore, the 90-day mortality-rate after the procedure was 21.4%. Death of these 6 patients was related to the progression of their malignancy rather than the procedure.

The outcome of thoracoscopic doxycycline poudrage among the studied patients along the follow up period of 3 months is demonstrated in Table 2. The mean duration till chest tube removal after successful pleurodesis which was the same duration of post-procedural hospitalization was 1.93 ± 0.92 days. After exclusion of the 6 patients who died before the completion of their follow up period, the rate of successful pleurodesis was 86.4% with 13.6% of patients having recurrences. The successful pleurodesis rates among all eligible/treated/full lung expansion/alive patients after 90 days of follow up are summarized in Table 3.

The Kaplan-meier curve in Fig. 4 demonstrates the overall survival of the studied patients till 90 days after the procedure. The percentage of overall survival at 90 days after the procedure was 78.6%. The survival of the studied patients was strongly linked to primary tumor type of MPE (p = 0.006) rather than the pleural tumor burden as represented by thoracoscopic scoring (p = 0.1).

No post-procedural major complications were encountered in the current study. There were minor post-procedural complications showed in Table 4. Complications were resolved by follow up only or by other therapeutic measures like non-steroidal anti-inflammatory drugs (NSAIDs), local and systemic antibiotics, higher level chest tube insertion for pneumothorax and modified tunneled pleural catheters TPCs insertion for failed patients.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M: 10; F: 20</td>
</tr>
<tr>
<td>Age in years</td>
<td>Mean (range) 57.67 (37–80)</td>
</tr>
<tr>
<td>History of previous malignancy</td>
<td>n (%)</td>
</tr>
<tr>
<td>Negative</td>
<td>16 (53.3%)</td>
</tr>
<tr>
<td>Positive</td>
<td>14 (46.7%)</td>
</tr>
<tr>
<td>Primary tumor</td>
<td>n (%)</td>
</tr>
<tr>
<td>Lung</td>
<td>11 (36.7%)</td>
</tr>
<tr>
<td>Breast</td>
<td>11 (36.7%)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Uterine cancer</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>1 (3.3%)</td>
</tr>
</tbody>
</table>

M = male, F = female, n = number.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>25</td>
<td>89.3</td>
</tr>
<tr>
<td>Complete response</td>
<td>5</td>
<td>17.9</td>
</tr>
<tr>
<td>Partial response</td>
<td>20</td>
<td>71.4</td>
</tr>
<tr>
<td>Failure</td>
<td>3</td>
<td>10.7</td>
</tr>
<tr>
<td>Initial failure</td>
<td>2</td>
<td>7.1</td>
</tr>
<tr>
<td>Recurrence</td>
<td>1</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Table 2 The outcome of thoracoscopic doxycycline poudrage among the studied patients (number of patients = 28).

Figure 3 Flow chart demonstrating the distribution of the studied patients along the follow up period (90 days).
None of the following patients’ parameters have been shown to affect outcome of thoracoscopic doxycycline poudrage; primary tumor type, pleural tumor burden, grades of adhesions, CT chest findings, protein and glucose content of pleural fluid, age and sex of the studied population.

Discussion

Malignant pleural effusion causes significant reduction in the quality of life of patients with advanced malignancy. The median overall survival after its diagnosis is estimated to be around 4–6 months. The management of malignant pleural effusion is usually palliative. Pleurodesis is the most widely acceptable method. A variety of agents could be used to induce pleurodesis. Thoracoscopic talc poudrage is considered the best method of pleurodesis. Graded talc is not available in many developing countries including Egypt. However, oral forms of doxycycline, tetracycline derivative, are available, effective and cheap and could be a good alternative in inducing pleurodesis.

Doxycycline has been used in several studies to induce pleurodesis for palliative management of malignant pleural effusions and for recurrent pneumothoraces [16–18]. This was owed to its similar clinical success rates to tetracycline, although there were no direct studies comparing success rates of both agents, together [19].

According to Teixeira et al. [20], tetracycline derivatives induce pleurodesis by creating an acute pleural injury with subsequent inflammation and fibrosis. Furthermore, the deposition of collagen after instillation of doxycycline or tetracycline might be enhanced by their inhibitory effect on matrix metalloproteinases in the human pleural fluid after instillation of these drugs in vitro and in vivo [21].

Doxycycline use as a sclerosing agent revealed variable success rates ranging from 80 to 92% [22,23]. Unfortunately, the definition of success of pleurodesis as well as the length of follow-up period show notable variation in the literature. This leads to complicated comparative assessment of the different agents used for pleurodesis within studies [24].

The ATS/ERS consensus [2] stated that data from comparative studies of different pleurodesis techniques should be reported with and without inclusion of patients who died within 1 month of pleurodesis. Therefore, the percent of global response (the sum of the complete and partial responses) to thoracoscopic doxycycline poudrage in the present study was 89.3% and at 90 days of follow up it became 86.4% due to exclusion of six patients who died because of the progression of their malignancy.

The observed pleurodesis success rate of thoracoscopic doxycycline poudrage (TDP) in the present study falls within the reported success rates for thoracoscopic talc poudrage, the best sclerosing agent to date, varying between 75% and 95% [25,26] and higher than that reported from the traditional method of doxycycline instillation pleurodesis ranging between 67% and 86% [22,23,27].

The traditional method of doxycycline instillation among studies is tube thoracostomy with tube connected to continuous wall suction [22]. This method was less comfortable requiring patient rotation to disperse the sclerosing agent and limited patient mobility along the whole period of tube drainage [28]. Also, it was time consuming requiring longer hospital stay when compared to the more recent techniques including

### Table 3

Successful pleurodesis rates among all eligible/treated/full lung expansion/alive patients after 90 days of follow up.

<table>
<thead>
<tr>
<th></th>
<th>No. Alive after 90 days without recurrence, No.</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All eligible patients</td>
<td>30</td>
<td>19</td>
<td>63.3</td>
</tr>
<tr>
<td>Eligible, treated</td>
<td>29</td>
<td>19</td>
<td>65.5</td>
</tr>
<tr>
<td>Full lung expansion, treated</td>
<td>28</td>
<td>19</td>
<td>67.9</td>
</tr>
<tr>
<td>Full lung expansion, treated, alive</td>
<td>22</td>
<td>19</td>
<td>86.4</td>
</tr>
</tbody>
</table>

CI = confidence interval.

### Table 4

The percentage of occurrence of major and minor complications among the studied patients (n = 28).

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major complications:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death related to the procedure, ARDS, Acute respiratory failure</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Minor complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical emphysema</td>
<td>14</td>
<td>50.0</td>
</tr>
<tr>
<td>Fever &gt; 38 °C</td>
<td>7</td>
<td>25.0</td>
</tr>
<tr>
<td>Wound infection</td>
<td>3</td>
<td>10.7</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1</td>
<td>3.6</td>
</tr>
<tr>
<td>Empyema</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Pain VAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
<td>3.6</td>
</tr>
<tr>
<td>Moderate</td>
<td>4</td>
<td>14.3</td>
</tr>
<tr>
<td>High</td>
<td>15</td>
<td>53.6</td>
</tr>
<tr>
<td>Very high</td>
<td>8</td>
<td>28.6</td>
</tr>
</tbody>
</table>

ARDS: Acute respiratory distress syndrome, VAS: visual analogue score.
thoracoscopic insufflation and small-bore catheters. The mean duration of tube drainage after thoracostomy and doxycycline instillation as demonstrated by Mohamed and Hassan [29], and Putnam et al. [30], was 4.2 ± 2.6 days and 6.5 days, respectively.

It is greatly interesting to note that pleurodesis has been accomplished within 2 days of (TDP) in most of the studied patients (88%) in the current study. This means that the previously discussed problems [27,31] when using doxycycline as a sclerosing agent have been bypassed by this new method. As it showed less recurrence rate, less need for repeated dosing and shorter duration of chest tube retain in place. These disadvantages were greatly increasing the cost of the traditional method of doxycycline pleurodesis [32].

In comparison with the relatively more recent method of doxycycline instillation, the study of Seaton et al. [33] has reported the highest 30-days success-rate of small bore catheter pleurodesis which was 95%. This was very close to our success rate after the same period (92.5%). However, the diagnosis of malignant pleural effusion (which determines operability in lung cancer patients) [34] was confirmed only in 71.4% of the studied patients in the latter study due to the previously mentioned limited diagnostic yield of cytological examination of pleural fluid [35]. Also, it is worth noting that the mean duration of tube drainage after sclerotherapy in that study was 5 days ranging from 2 days to 10 days while in ours the mean duration was 2 days ranging from 1 day to 5 days as a maximum.

On the other hand, it is widely known that the dilemma of undiagnosed exudative effusions with negative pleural fluid cytology and suspected malignancy could not be actually worked out without the help of medical thoracoscopy [12]. This was one of the great advantages of this method of pleurodesis. Near half (46.6%) of our studied patients had undiagnosed recurrent exudative pleural effusion. They had no history of previous malignancy and negative cytological examination for malignant cells after thoracentesis.

Those patients have been enrolled in our study due to their highly suspicious clinical and radiological history [36] to get benefit from the high diagnostic and therapeutic efficacy of medical thoracoscopy (achieving diagnosis and management of pleural effusion in the same session) [37,38]. Afterwards, the malignant etiology of their effusion has been confirmed by histo-pathological examination of their thoracoscopic biopsies. And those who had negative pleural biopsy for malignancy were excluded from the study.

It is also worth noting that despite the presence of malignant cells in the pleural fluid samples, medical thoracoscopy is still indicated for determination of the extent and stage (operability) of primary tumor [39,40] and obtaining tissues for further workup (e.g., in cases of breast cancer metastases or lymphoma) [41,42].

Although talc is considered the best known sclerosing agent [7,8], there were serious concerns about the safety of talc with reports of acute respiratory distress syndrome ARDS following its administration. De Campos et al. [7] in the review for their 15 years of experience with thoracoscopic talc poudrage showed major morbidity in the form of empyema in 4%, re-expansion pulmonary edema in 2.2%, and respiratory failure 1.3% of their patients. Nevertheless, in the systematic review by Tan et al. [25] for the evidence on the effectiveness of management of MPE, 36 cases of pneumonitis have been reported following talc pleurodesis. Moreover, treatment-related mortality occurred in 3.7% of patients receiving talc insufflation and 2.9% of patients receiving talc slurry in the study of Dresler et al. [43].

However, when graded talc was used and small particles were avoided, this complication has been omitted [25]. In consistent with this, Maskell et al. [44] and Rossi et al. [45] have suggested that ARDS after talc pleurodesis is mainly related to the particle size of the talc used. Unfortunately, graded talc is not available in many developing countries, including Egypt due to the stringent requirements needed for its manufacture [10].

Therefore, the size of the particles of doxycycline capsules (vibramycin®, 100 mg capsule, Pfizer) has been measured at the beginning of the study to assess the probability of systemic inflammation after its insufflation. The mean particle diameter was 12.20 μm. This means it is larger than the injurious size (5–10 μm) [46] that would cause systemic inflammation. Thus, according to doxycycline particles’ size, it is safe to be insufflated into the pleural space. So, the availability, accessibility and feasibility of thoracoscopic doxycycline poudrage made the procedure a good and effective alternative for pleurodesis in malignant pleural effusion.

Comparing our results with that of iodo-povidone, another available and inexpensive sclerosing agent, Banawan et al. [47] have demonstrated success rates of 73.3% and 86.7% following wide bore and thoracoscopic instillation of iodopovidone. In agreement with this, Agarwal et al. [48] in the systematic review for assessment of efficacy and safety of iodopovidone showed pooled success rate of 88.7%. However, they also reported that iodine can cause severe allergic reactions, especially in patients with allergic diathesis and also may precipitate thyrotoxicosis in subclinical hyperthyroidism cases as it has been shown in the same study [48].

To date and to our knowledge, the study of Elnady and Sakr [49] is the first and the only study evaluating the efficacy of thoracoscopic doxycycline poudrage in inducing pleurodesis in MPE. In consistency with our study, success was achieved in 25 patients of 27 studied patients (92.6%) after 30 days of follow up and the mean duration of tube drainage was 1.52 days, versus 89.3% success rate and 1.93 ± 0.92 days for duration of tube drainage in our study. Differences between Elnady study and our study are in the study design being (retrospective vs. prospective) and the total follow up period after the procedure (30 days only vs. 30 & 90 days).

Many studies reported serious respiratory complications after talc pleurodesis even with low dose of 2 g and with different techniques of application [19]. None of these major complications has occurred after thoracoscopic doxycycline poudrage as it has been demonstrated by Elnady and Sakr [49] and also in our series.

Notably, minor complications have been encountered in the current study. The most frequent ones were post-procedural pain and fever. Pain and fever were the most reported complications following the use of different sclerosing agents as well as with variable methods of administration as demonstrated in the five English speaking countries’ survey done by Lee et al. [19]. In agreement with this, Shouman et al. [11] and Bakr et al. [50] showed that post-pleurodesis chest pain and fever were the commonest problems encountered in their studies occurring in all of their studied groups following the use of different sclerosing agents but with variable percent of incidence.
Considering the 90-day survival rate among the studied patients and in agreement with Kolschmann et al. [51], survival outcome in the present study was strongly linked to the primary tumor type. This was demonstrated by the higher 90-day survival rate among patients with breast cancer than in those with lung cancer and any other type of primary cancer (p = 0.006). Meanwhile, the pleural tumor burden (thoracoscopic scoring) did not predict survival outcome in the current study. This was explained in the literature [20] by the differences in tumor aggression among different types of metastases and the different degrees of response to chemotherapy. This was obviously demonstrated in breast cancer patients in whom pleural tumor burden was larger but their response to chemotherapy is greater than any other tumor type [13,52].

The current study provides a circumstantial evidence for that medical thoracoscopy can be valuable in magnification of panoramic view of the pleura as well as allows adequate biopsy specimens access for histologic examination and also gives the option for therapeutic procedures to be performed like pleurodesis. Thoracoscopic doxycycline pleurodesis is highly effective and safe in the longer term management of patients with MPE.

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