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Title	Clinical predictors of successful and earlier pleurodesis of tunneled pleural catheters in malignant pleural effusions: a cohort study
Authors	Pen Li MD, Alison Graver MD, Sarah Hosseini MD, Sunita Mulpuru MD MSc, Lorraine Cake BScN, Lynn Kachuik BScN MSc, Tinghua Zhang MSc, Kayvan Amjadi MD
Reviewer 1	Ashley Gillson
Institution	Department of Medicine, Division of Pulmonary Medicine Faculty, University of Alberta, Edmonton, Alta.
General comments (author response in bold)	No concerns, good study **Thank you**
Reviewer 2	Lama Sakr
Institution	Sir Mortimer B Davis Jewish General Hospital, Pulmonary Division, Montreal, Que.
General comments (author response in bold)	This is an interesting question, which you have explored in a very large cohort. I would like to address the following questions. Do you have any data on serum inflammatory markers such as CRP, WBC and LDH? If so, is there any association between serum levels of these inflammatory markers and rate of pleurodesis or time delay in pleurodesis? **Thank you for the suggestion. We did not record data on serum inflammatory markers, as they were not routinely taken at the time of pleural catheter insertion. In a literature search, there is one small study looking at serum CRP predicting TALC pleurodesis (ANZ J Surg. 2007 Apr;77(4):253-5.) but none for tunneled pleural catheters. This may be an area of future research. A comment to this effect has been added to page 9 (limitations paragraph).** Can you comment whether use of intra-pleural fibrinolytics may have had an effect on the rate and time to pleurodesis? **Thank you for the question. In our analysis we did not find use of TPA to be related to be significantly related to rate and time to pleurodesis. A statement of this was added to page 7, complications paragraph.** Do you have data with regard to the use of chest radiation and whether this could have had an effect on the rate or time to pleurodesis? **Thank you for the question. We did not collect data on use of chest radiation on rate and time to pleurodesis. This is a complicated question to answer, as timing of radiation may also affect the result if there is a true signal. Also, in general, all patients are stage 4 malignancies, and generally don't receive radiotherapy as part of their main therapy. We added this as a limitation to our study (page 9, limitations paragraph)** Do you have any data on the use of systemic corticosteroids, as these are often administered as anti-emetics, in the symptomatic treatment of pulmonary lymphangitic disease, as appetite stimulants, in the palliation of vasogenic cerebral edema, or as treatment of chemotherapy or immunotherapy related toxicity? Could the use of systemic steroids reduce the rate of pleurodesis, given their anti-inflammatory effect? **Thank you for the question. This is an interesting question. We did not collect data on steroids on effect of pleurodesis. This poses an interesting question that may be answered in an alternate study looking at steroids at or around the time of pleural catheter insertion. We added a statement to the limitations section (page 9) of our retrospective study in this regard.** Any thoughts on why ECOG PS was a predictor of higher pleurodesis rate? Could ECOG PS correlate with the use of chemotherapy or other systemic treatments that could increase success of pleurodesis? **Thank you for the question. We suspect that ECOG may have higher pleurodesis rates for at least 2 reasons. The first is the use of systemic chemotherapy, and the second may be simply the patients have an opportunity to achieve pleurodesis before dying from their cancer. A statement explaining this was added to page 8, paragraph 3.** Is there any value in using pleural ultrasound for detection of lung sliding, as a way of differentiating successful pleurodesis caused by local inflammatory process- in which case no lung sliding is detected, versus treatment response to systemic anti-neoplastic treatments-where we would expect lung sliding to be present? **Thank you for the question. This is a very interesting question and method to assess for pleurodesis. Clinically, this may not be a significant differentiation because in our cohort, the recurrence rate is very low, only 3%. A statement to commenting this has been added to page 9, limitations paragraph.** **Perhaps lung sliding can be used as a tool to assess likelihood of recurrence. Although this is not the topic of our study, it is a great idea for future research.** Can you comment on the potential instillation of talc into the tunneled pleural catheter in patients who are likely to have a delayed pleurodesis? **Thank you for the question. A statement in the interpretation reads "MT may also be combined with talc pleurodesis11 if**

	earlier pleurodesis is desired, or delayed catheter removal is expected." And in the conclusion reads "In patients expected to have lower probability of pleurodesis or who are expected to keep their TPC for a longer duration, such as in breast cancer patients, chemical pleurodesis could be considered. We recommend individual consideration of each case." As in our statement, we feel that ideally the decision to use pleurodesis or not is up to the clinician and patient as pleurodesis can be painful.
Reviewer 3	Alain Tremblay Dr. Tremblay
Institution	Health Sciences Centre, University of Calgary, Calgary, Alta.
General comments (author response in bold)	The authors present a larger retrospective series of patients with malignant pleural effusions treated with tunnelled pleural catheter, and identify factor associated with pleurodesis frequency and time. Other studies have investigated this issue, and found similar results altough some of the findings were novel, partly based on the practice pattern of the center. While of interest to physicians treating this patient population, I wonder if these findings will be relevant for a general medical audience. In addition, few of the factors are "actionable" as they are a result of the patients' diagnosis and clinical presentation. As such, it is not clear that this would change practice patterns. **Thank you for your comment. We are aware of one other smaller study specifically interested in assessing predictors of pleurodesis of TPCs in malignancy. We do feel that our data adds to decision making and may potentially change practice patterns. For example, perhaps breast cancer patients with delayed pleurodesis of their TPC, would benefit more from chemical pleurodesis. This is noted on page 9, conclusions.** Other comments: The authors should be cautious about using the term pleurodesis. Some patients may have catheter removal without actual pleurodesis (e.g. following response to chemotherapy). **Thank you for the comment. We do believe our clinical definition of pleurodesis is reflective, as mentioned in a response above, our recurrence rate is very low, only 3%. A statement explaining this is on page 9, limitations paragraph.** I am not sure the data presented is a good argument to do thoracoscopies in patients with advanced malignancy and exudative effusions but negative cytology. It is known that pleural fluid cytology is not highly sensitive for malignancy, but unless exclusion of malignant effusion is required in order to pursue curative intent treatment for the primary cancer, thoracoscopic diagnosis is not required and palliative treatment should proceed accordingly. **Thank you for the comment. In our manuscript we recommend that if tissue is required in cancer management, that medical thoracoscopy can be considered to both acquire tissue and treat dyspnea, as it seems to be associated with earlier pleurodesis. Each case should be considered individually, which we have highlighted in our conclusion.**