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**Title: Association between tunneled pleural catheter use and infection in patients immunosuppressed from antineoplastic therapy: a multicenter study (128/130 characters with spaces)**

**Short title: Tunneled pleural catheter use in immunosuppression (50/50 characters with spaces)**

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## **ABBREVIATIONS LIST**

CI - confidence interval

HR - hazard ratio

IC - immunocompromised

IQR - interquartile range

MPE - malignant pleural effusion

OS - overall survival

PMPE - paramalignant pleural effusion

SHR - subdistribution hazard ratio

TPC - tunneled pleural catheter

## **ABSTRACT**

### **Background**

Patients with malignant/paramalignant pleural effusions (MPE/PMPEs) may have tunneled pleural catheter (TPC) management withheld due to infection concerns from immunosuppression associated with antineoplastic therapy.

### **Research Question**

What is the rate of infections related to TPC use and what is the relationship to antineoplastic therapy, immune system competency and overall survival (OS)?

### **Study Design and Methods**

We performed an international, multi-institutional study of MPE/PMPE patients undergoing TPC management from 2008-2016. Patients were stratified by whether or not they underwent antineoplastic therapy and/or were immunocompromised or not. Cumulative incidence functions and multivariable competing risk regression analyses were performed to identify independent predictors of TPC-related infection. Kaplan-Meier method and multivariable Cox proportional-hazards modeling were performed to examine for independent effects on OS.

### **Results**

A total of 1,408 TPCs were placed in 1,318 patients. Patients had a high frequency of overlap between antineoplastic therapy and an immunocompromised state (75-83%). No difference in the overall (6-7%), deep pleural (3-5%) or superficial (3-4%) TPC-related infection rates between subsets of patients stratified by antineoplastic therapy or immune status was observed. The median time to infection was 41 (interquartile range: 19-87) days following TPC insertion. Multivariable competing risk analyses demonstrated longer TPC duration was associated with a higher risk of TPC-related infection

[subdistribution hazard ratio (95% CI): 1.03 (1.00-1.06),  $p=0.028$ ]. Cox proportional-hazards analysis showed antineoplastic therapy was associated with better OS [hazard ratio (95% CI): 0.84 (0.73-0.97),  $p=0.015$ ].

### **Interpretation**

The risk of TPC-related infection does not appear to be increased by antineoplastic therapy use or an immunocompromised state. The overall rates of infection are low and comparable to immunocompetent patients with no relevant antineoplastic therapy. These results support TPC palliation for MPE/PMPE regardless of plans for antineoplastic therapy.

**Abstract word count: 281/350**

A malignant or paramalignant pleural effusion (MPE/PMPE) is a common complication of advanced malignant disease and conveys a significant burden, not only on the patient's quality of life and independence, but on the healthcare system as well. It is estimated that more than 750,000 patients per year are affected by an MPE/PMPE across the United States and Europe with annual hospital charges exceeding \$5 billion.<sup>1-4</sup> Tunneled pleural catheters (TPCs) are increasingly utilized in the management and palliation of these patients, as they confer treatment advantages over traditional strategies. These advantages include: palliation in a wide range of patients with varying performance status, a shorter hospital stay and lower costs, outpatient management, up to 96% symptomatic improvement, pleurodesis in less than two months with an aggressive drainage schedule or concomitant chemical pleurodesis, and use in patients with non-expandable lung.<sup>5-18</sup>

However, the rate of TPC-related pleural infections has been reported to range from 1-21%.<sup>5-25</sup> In addition, many patients with advanced malignancy may still be undergoing systemic antineoplastic therapy where the resultant immunosuppressive effects may deter clinicians from utilizing TPCs due to the perceived increased risk of pleural infections. While the rates of TPC-related infections specifically in patients on antineoplastic therapy range up to 17%, delaying definitive pleural palliation may result in further progression of symptoms, decreased quality of life and decreased independence.<sup>15,19,25-29</sup>

We thus aimed to assess independent predictors of TPC-related infection over time, specifically in patients on antineoplastic therapy, determine the relationship of such infections to the competency of the immune system, and assess the independent effects on overall survival (OS) in a large, international, multicenter cohort.

## **METHODS**

We performed a retrospective review from 12 sites (Swedish Cancer Institute, Duke University, Johns Hopkins University School of Medicine, MD Anderson Cancer Center, University of North Carolina at Chapel Hill, Medical University of South Carolina, University of Utah, Vanderbilt University, Virginia Commonwealth University, Gloucestershire Royal Hospital, Thoraxklinik Heidelberg, and

University of Oxford). All individual centers secured local ethics committee approval from their respective Institutional Review Boards, and individual consent was waived due to the study's retrospective nature (Swedish Cancer Institute Institutional Review Board study number: SWD5993S-16).

All patients with recurrent MPEs or PMPEs managed with TPC placement between January 1<sup>st</sup> 2008 and April 8<sup>th</sup> 2016 were reviewed. From a total of 1,375 patients there were 57 exclusions: 43 patients with no laboratory data available and 14 where a pleural infection was identified at the time of TPC insertion.

Histocytological proof of malignancy within the pleural space defined an MPE and the presence of a recurrent, large exudative pleural effusion in the context of histologically proven malignancy outside the pleural space defined a PMPE. Antineoplastic therapy was defined by systemic cytotoxic and/or biological therapy. An interruption in antineoplastic therapy as a result of TPC-related infection was defined as a delay in the delivery of active antineoplastic therapy for seven or more days.<sup>30,31</sup> An immunocompromised state was defined by the presence of moderate (absolute neutrophil count  $0.5-1.0 \times 10^9/L$ ) or severe (absolute neutrophil count  $<0.5 \times 10^9/L$ ) neutropenia, as these two categories of immunosuppression confer the highest risk of infection.<sup>32</sup> A TPC-related infection was defined as either an isolated superficial infection (catheter site cellulitis) or a deep pleural infection (purulent pleural fluid and/or a positive fluid gram stain/culture with signs and/or symptoms consistent with pleural infection), requiring systemic antibiotics. TPCs associated with both a concomitant superficial and deep infection were categorized in the deep pleural infection group only.

Descriptive data including patient characteristics, disease and treatment-related factors were summarized by median (IQR, interquartile range) for continuous and count (percentage) for categorical data. Data between groups were compared using the Mann-Whitney U test for continuous variables and the  $\chi^2$  test for categorical variables. Groups were compared using the Yates correction and Fisher's exact test when any of the sub-groups had five or less components. Cumulative incidence functions were used to estimate the cumulative incidence of TPC-related infection over time, and competing risk regression analyses were performed to identify independent predictors of TPC-related infection, taking the

competing risk of death into account. Variables included in the analyses were: age, gender, primary cancer, TPC laterality, antibiotics at the time of insertion, presence of antineoplastic therapy, duration of TPC, concurrent antineoplastic therapy and TPC duration, and immune status. There were 96 patients who were excluded from the competing risk regression analyses due to missing dates of last contact/death and who did not have a TPC-related infection. Overall survival was compared using the Kaplan–Meier method with log-rank test. Multivariable Cox proportional-hazards modeling was performed to examine for independent effects on the risk of death. Disease-specific survival could not be compared due to the low number of events. There were 103 patients who were excluded from the OS analyses due to missing dates of last contact/death. Statistical significance was defined as  $p < 0.05$ . All statistical analyses were performed using R software, version 3.6.0 (R Core Team 2019) and SPSS 24.0 statistical software package (SPSS Inc., Chicago, IL, USA).

## RESULTS

A total of 1,408 TPCs were inserted in 1,318 patients with an MPE or PMPE, of which the characteristics are shown in Table 1. In the 828 (63%) patients who underwent antineoplastic therapy, the median duration of concurrent antineoplastic therapy and TPC drainage was 90 (IQR: 33-230) days. Of the 1,318 patients, 157 (12%) were immunocompromised [76, 6% moderate neutropenia and 81, 6% severe neutropenia].

### *Catheter-Related Infections*

Overall, a TPC-related infection developed in 7% [95% confidence interval (CI): 6-8%, n=89] of patients: deep pleural infection in 4% [95% CI: 3-5%, n=49] and superficial infection in 3% [95% CI: 2-4%, n=40]. The median time to infection from TPC insertion was 41 (IQR: 19-87) days. Of those with infections, 65% (58/89) had antineoplastic therapy, of which 16% (9/58) were immunocompromised (9%, 5/58 moderate neutropenia and 7%, 4/58 severe neutropenia).



The 1,318 patients were stratified into two groups as shown in Table 2: (i) those who underwent antineoplastic therapy versus those who did not, and (ii) those who had an immunocompromised state versus those who did not. Although patients had a significantly higher frequency of overlap between receiving antineoplastic therapy and having an immunocompromised state (75-83%), there was no difference identified in the overall (6-7%), deep pleural (3-5%) or superficial (3-4%) TPC-related infection rates between the stratified groups.

The incidence of TPC-related infections was similar in patients with moderate neutropenia [overall: 7%, 5/76 (deep: 5%, 4/76 and superficial: 1%, 1/76)] versus severe neutropenia [overall: 9%, 7/81 (deep: 5%, 4/81 and superficial: 4%, 3/81)];  $p=0.627$ .

### ***Infection Details, Management and Outcomes***

Details of patients with TPC-related infections, their management and outcomes are shown in Table 3 and are stratified by the type of TPC-related infection. The rates of antineoplastic therapy and an immunocompromised state (including moderate and severe neutropenia) were similar between those with a deep pleural versus superficial TPC-related infection. The median time to infection from TPC insertion, however, was longer in patients who developed a deep pleural infection at 50 (IQR: 23-109) days.

The majority of patients with a deep pleural infection were treated as inpatients with parenteral antibiotics, while patients with a superficial infection were largely treated as outpatients. In those with a deep pleural space infection there was a higher rate of interruption (47%) of antineoplastic therapy (for those still undergoing antineoplastic therapy at the time of infection) as a result of a diagnosis of infection. However, the majority of TPCs (72%, 64/89) were left in situ and there was no difference in the rate of TPC removal between those with deep (24%) versus superficial (33%) infection. Fifteen (31%) of the 49 patients with deep pleural infection received additional management for the infection in the form of intrapleural fibrinolytics, an additional chest tube and/or surgery (Table 3).

For the 64 patients who did not have TPC removal as a result of the infection, the median time the TPC was in situ following the infection was similar in both patients with deep and superficial infections at

almost one month. Three patients developed a second TPC-related infection. Five (0.05%) patients died as a result of infection (all with deep pleural infections), at a median of 11 (IQR, 7-23) days from infection diagnosis. A total of 3 (60%) of these 5 patients had relevant antineoplastic therapy (2 within the month prior to TPC insertion and 1 during TPC drainage); however, all 5 (100%) were not immunocompromised within the month prior to or during TPC management.

### ***Factors Predictive of Infection***

On univariate competing risk regression analyses, longer TPC in situ duration was associated with a higher risk of developing a deep and/or superficial pleural infection [subdistribution hazard ratio (SHR) (95% CI): 1.03 (1.01, 1.06),  $p=0.013$ ]. On multivariable analysis, the outcome was unaltered [SHR (95% CI): 1.03 (1.00, 1.06),  $p=0.028$ ] (Figure 1, e-Table 1). Antineoplastic therapy [SHR (95% CI): 0.82 (0.52, 1.31),  $p=0.410$ ] and immunocompromised state [SHR (95% CI): 1.14 (0.58, 2.24),  $p=0.690$ ] were not significantly associated with risk of TPC-related infection (e-Table 1).

Similar findings were identified when identifying predictors of deep pleural infections alone: longer TPC in situ duration was associated with a higher risk of developing a deep pleural infection [subdistribution hazard ratio (SHR) (95% CI): 1.04 (1.01, 1.07),  $p=0.005$ ]. On multivariable analysis, the outcome was unaltered [SHR (95% CI): 1.04 (1.00, 1.07),  $p=0.035$ ] (e-Table 2). Antineoplastic therapy [SHR (95% CI): 1.11 (0.59, 2.07),  $p=0.750$ ] and immunocompromised state [SHR (95% CI): 1.49 (0.67, 3.33),  $p=0.330$ ] were not significantly associated with risk of a deep TPC-related infection (e-Table 2).

### ***Overall Survival***

The OS endpoint was calculated from the time of TPC insertion to the time of death from all causes. The overall median survival was 120 (95% CI: 107, 142) days. The median survival for patients with no infection was 109 (95% CI: 98, 129) days, for those with a deep pleural infection was 202 (95% CI: 152, 334) days and for those with a superficial infection was 251 (95% CI: 201, 794) days. Patients

who underwent antineoplastic therapy had improved median OS [147 (95% CI: 128-166) days] compared to those who did not [92 (95% CI: 79-109) days,  $p<0.001$ ] (Figure 2).

Cox proportional-hazards regression analysis demonstrated that antibiotics at the time of TPC insertion [HR (95% CI): 0.81 (0.68, 0.96),  $p=0.013$ ], antineoplastic therapy [HR (95% CI): 0.84 (0.73, 0.97),  $p=0.015$ ], and an immunocompromised state [HR (95% CI): 0.74 (0.60, 0.91),  $p=0.004$ ] were associated with better OS (e-Table 3).

## DISCUSSION

This study has assessed the largest cohort of patients to date with a diagnosis of MPE/PMPE managed with a TPC, and specifically correlates rates of TPC-related infections to antineoplastic therapy use and immune system competency. We identified the overall, deep pleural and superficial TPC-related infection rates in this population to be 7%, 4%, and 3%, respectively. Infection rates were comparable between patients who underwent antineoplastic therapy and those who did not, and between those who were immunocompromised and those who were immunocompetent. While a longer TPC in situ duration was associated with the development of a TPC-related infection, antineoplastic therapy and immune status were not.

Some physicians may hesitate to place a TPC in patients with an MPE undergoing systemic antineoplastic therapy. A study of 23,431 patients diagnosed with an MPE between 2007-2011 identified that only 24% underwent a definitive pleural palliative procedure following effusion recurrence after an initial thoracentesis.<sup>33</sup> Results of our study suggest that moving forward with definitive pleural palliation by TPC is not associated with an increased risk of infection during antineoplastic therapy, as rates are low, comparable to patients not on therapy (3-6%) and well within the ranges previously reported (1-21%).<sup>5-29</sup>

In addition, oncologic treatment and immune status did not appear to have a significant effect on the type of TPC-related infection, as these were similar when comparing patients with deep pleural versus superficial infections. In our population, management of patients with deep infections tended to be more

aggressive than those with superficial infections. More were managed as inpatients, had cultures obtained with identification of organisms, utilized parenteral antibiotics; and more (by nearly seven-fold) experienced an interruption of antineoplastic therapy. However, the rates of TPC removal were similar between deep and superficial infections, with the majority of catheters remaining in situ, allowing for continued palliation without significant consequence. While there is no current standard for TPC-related infection management, our rates for TPC removal are comparable to other results.<sup>6-8,11,13,15,20,22,25,34</sup> In response to this cumulative wealth of data, societal guidelines were recently updated to recommend continuation of infection treatment in patients with a TPC-related infection without TPC removal, unless the infection fails to improve.<sup>34</sup>

We identified that TPC-related infections occurred at a median of 41 days from time of insertion and that median TPC drainage was 55 days. This is consistent with previous literature reporting the vast majority of TPC-related infections occur around six weeks following catheter insertion.<sup>7,11-13,15,19,22,23,25,29</sup> We also identified the TPC in situ duration to be associated with the development of a TPC-related infection. Our data, thus, supports the notion that the majority of TPC-related infections are not due to contamination at insertion, but rather potentially related to prolonged placement and/or access. While infections are low and OS is unchanged by infection, there are strategies to optimize early catheter removal. These include the implementation of rapid pleurodesis protocols to promote early catheter removal, such as an accelerated drainage schedule and/or the addition of chemical pleurodesis.<sup>9,14,16,18,35</sup> The higher rate of pleurodesis and faster time to catheter removal associated with a daily drainage schedule was identified in two recent randomized trials and could potentially prevent delayed infections, without a significant increase in adverse effects.<sup>14,18</sup> The addition of a pleurodesis agent may further accelerate pleurodesis and catheter removal.<sup>9,16</sup> An older prospective study identified a 92% pleurodesis rate at a median of 8 days following concomitant talc poudrage and TPC placement, while a more recent randomized trial identified the outpatient administration of talc through a TPC to have a significantly higher chance of pleurodesis at 35 days compared to placebo.<sup>9,16</sup> While further research on cost implications, practice and resource variation, and patient preference is needed, these treatment strategies

are both outpatient and may maximize in-home days and have the potential to further decrease infection rates.<sup>9,36</sup>

The infection-related mortality rate identified is similar to previous reports and better than pooled analysis, where the rate was as high as 12%.<sup>13,22,25,27,34</sup> Overall, our data supports that patients who underwent antineoplastic therapy had superior OS compared to those who did not. Although this is established in the literature and may represent a selection bias, it is important to highlight that patients should not be denied, or have a delay in antineoplastic therapy initiation, due to a pleural effusion requiring symptom palliation, as antineoplastic therapy clearly can improve survival and TPCs improve symptom palliation without a significant concern for increased infection risk.<sup>28</sup> The finding of an immunocompromised state being associated with better OS is likely tied to these patients receiving antineoplastic therapy and is discussed as above. We also identified that antibiotics at the time of TPC insertion were associated with better OS. This was standard practice for one institution (which constituted 71% of patients who received antibiotics at TPC insertion). Whether clinicians were selective in choosing patients for TPC placement, clinicians were selective in prescribing antibiotics for patients at-high risk for infection, or this was statistical anomaly is uncertain. The role of antibiotics warrants further study.

The major limitation of this study is that immune status could only be defined on quantitative laboratory data from a single point in time versus serial values, as this was a retrospective study and laboratory investigations were not routinely performed in this subset of patients. Thus, some patients with an immunocompromised status may have been missed and the exact relationship between TPC-related infections and immune status could not be determined. However, the impact from antineoplastic therapy tends to be prolonged and we feel that the definition of applicable antineoplastic therapy used in this study (and in previous studies) is clinically relevant.<sup>18,25,26</sup> Another limitation is differing practice patterns across institutions; in particular, referring to follow-up recommendations. Some institutions do not require standard follow-up of patients following TPC insertion and may not manage these patients if admitted to their hospital with TPC-related infections; thus, the rate of TPC-related infections reported here may be artificially low. An additional limitation is the retrospective nature of the study, which is subject to biases

inherent to the design. In particular, selection bias may have contributed to our findings. We acknowledge that patients believed to be more susceptible to a TPC-related infection may not have been offered TPC management, thus resulting in a selected population with a lower pre-test probability of infection. A prospective study of outcomes in TPC management across all centers with a core dataset and pre-hoc definitions of TPC-related infections is needed to definitively determine the risk of antineoplastic-induced immunosuppression.

## **INTERPRETATION**

These results suggest that antineoplastic therapy and immunosuppression are not likely to increase the overall risk of TPC-related infections as the rate remains low and comparable to published rates in patients not undergoing antineoplastic therapy. These results should provide additional data to reassure medical oncologists that the need to initiate and/or continue antineoplastic therapy should not delay definitive pleural palliation with a TPC in patients with MPE/PMPEs.

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Table 1. Clinical characteristics of the patient cohort (n=1,318) and tunneled pleural catheters (n=1,408).

<b>PATIENT CHARACTERISTICS</b>	<b>(n=1,318)</b>
Median age at first TPC insertion, years (IQR)	63 (54-72)
Gender, female/male (%)	752/566 (57/43)
ECOG Score (%)	
0-2	736 (76%)
3-4	237 (24%)
Primary cancer (%)	
Lung	471 (36)
Breast	268 (20)
Ovarian	63 (5)
Lymphoma	59 (4)
Mesothelioma	57 (4)
Unknown primary	45 (4)
Other	355 (27)
Underwent antineoplastic therapy (%) <sup>a</sup>	828 (63)
Immunocompromised (%) <sup>b</sup>	157 (12)
Moderate neutropenia	76 (6)
Severe neutropenia	81 (6)
Given antibiotics at time of TPC insertion (%)	287 (22)
TPC removed (%)	565 (43)
<b>TUNNELED PLEURAL CATHETER CHARACTERISTICS</b>	<b>(n=1,408)</b>
Right-sided versus left-sided (%)	802/606 (57/43)
Median time from effusion diagnosis to TPC insertion, days (IQR)	28 (11-74)
Median TPC duration in situ, days (IQR)	55 (26-118)

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; TPC, tunneled pleural catheter.

<sup>a</sup>Antineoplastic (chemotherapy and/or biologic) therapy within one month of TPC insertion, and/or during TPC drainage

<sup>b</sup>Immunocompromised within one month of TPC insertion, and/or during TPC drainage.

Table 2. Patients with tunneled pleural catheter-related infections stratified by antineoplastic therapy and immune status (n=1,318).

	All patients (n=1,318)	Antineoplastic Therapy <sup>a</sup>			Immunocompromised <sup>b</sup>		
		Yes (n=828)	No (n=490)	p Value	Yes (n=157)	No (n=1,161)	p Value
<b>Therapy and Immune Status</b>							
Antineoplastic therapy (%) <sup>a</sup>	828 (63)	828 (100)	0	-	131 (83)	697 (60)	<0.001
Median days therapy + drainage (IQR) <sup>c</sup>	90 (33-230)	90 (33-230)	0	-	114 (41-206)	88 (33-250)	0.594
Immunocompromised (%) <sup>b</sup>	886 (67)	617 (75)	269 (55)	<0.001	157 (100)	0	-
<b>TPC-Related Infections</b>							
Overall infections (%)	89 (7)	58 (7)	31 (6)	0.635	12 (7)	77 (7)	0.635
Deep pleural infections (%)	49 (4)	36 (4)	13 (3)	0.116	8 (5)	41 (4)	0.331
Superficial infections (%)	40 (3)	22 (3)	18 (4)	0.298	4 (3)	36 (3)	0.896
Median days to infection (IQR)	41 (19-87)	55 (23-104)	23 (16-50)	0.231	46 (16-135)	41 (20-86)	0.505
<b>Outcomes</b>							
Median overall survival (95% CI) <sup>d</sup>	(n=1,215) 120 (107, 142)	(n=763) 147 (128, 166)	(n=452) 92 (79, 109)	<0.001	(n=107) 187 (142, 236)	(n=882) 110 (100, 131)	0.001

CI, confidence interval; IC, immunocompromised; IQR, interquartile range.

<sup>a</sup>Antineoplastic (chemotherapy and/or biologic) therapy within one month of TPC insertion, and/or during TPC drainage.

<sup>b</sup>Immunocompromised within one month of TPC insertion, and/or during TPC drainage.

<sup>c</sup>Median duration of concurrent antineoplastic therapy and TPC drainage, days.

<sup>d</sup>Kaplan-Meier method.

Table 3. Characteristics of patients with tunneled pleural catheter-related infections stratified by type of tunneled pleural catheter-related infection (n=89).

FACTOR	Deep Pleural Infection (n=49)	Superficial Infection (n=40)	p Value
Therapy and Immune Status			
Antibiotics at time of TPC insertion (%)	14 (29)	4 (10)	0.030
Underwent antineoplastic therapy (%) <sup>a</sup>	36 (73)	22 (55)	0.069
Immunocompromised state (%) <sup>b</sup>	8 (16)	4 (10)	0.385
Moderate neutropenia	4 (8)	1 (3)	0.489
Severe neutropenia	4 (8)	3 (8)	0.780
Infection Details			
Median time to TPC-related infection, days (IQR)	50 (23-109)	34 (15-80)	0.037
Purulent pleural fluid (%)	19 (39)	-	-
Organism identified (%)	40 (82)	5 (13)	0.798
Gram positive	25 (63)	4 (80)	
Gram negative	5 (12)	1 (20)	
Multiple	10 (25)	0	
Infection Management			
Management location (%)			<0.001
Inpatient	43 (88)	9 (23)	
Outpatient	6 (12)	31 (77)	
Antibiotics (%)			<0.001
Parenteral	43 (88)	7 (18)	
Oral	6 (12)	33 (92)	
Interruption of antineoplastic therapy (%) <sup>c</sup>	14/30 (47)	1/14 (7)	0.025
Additional management (%)			
TPC removal	12 (24)	13 (33)	0.403
Fibrinolytics	11 (22)	-	
Additional chest tube	5 (10)	-	
Surgery	2 (4)	-	
Outcomes			
Median time TPC in situ following infection, days (IQR)	28 (11-44)	22 (2-73)	0.747
Additional TPC-related infection (%)			0.858
Deep pleural	0	1 (3)	
Superficial	1 (2)	1 (3)	
Demise from sepsis related to TPC infection (%)	5 (10)	0	0.106

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IQR, interquartile range; TPC, tunneled pleural catheter.

<sup>a</sup>Antineoplastic (chemotherapy and/or biologic) therapy within one month of TPC insertion, and/or during TPC drainage.

<sup>b</sup>Immunocompromised within one month of TPC insertion, and/or during TPC drainage.

<sup>c</sup>Infection resulted in an interruption of antineoplastic therapy (for those still undergoing antineoplastic therapy at the time of infection) for more than 7 days.



## ONLINE ONLY - SUPPLEMENTARY TABLES

*e- Table 1. Independent predictors of incidence of infection using competing risk regression (n=1,222).*

	Univariate analysis		Multivariable analysis	
	SHR (95% CI)	<i>p</i> Value	SHR (95% CI)	<i>p</i> Value
Age, year	0.98 (0.97, 1.00)	<b>0.016</b>	0.98 (0.97, 1.00)	<b>0.010</b>
Gender, male				
Female	Reference		Reference	
Male	0.73 (0.47, 1.12)	0.150	0.82 (0.51, 1.33)	0.420
Primary cancer				
Lung	Reference		Reference	
Breast	1.11 (0.66, 1.87)	0.690	0.85 (0.48, 1.49)	0.560
Other	0.68 (0.42, 1.11)	0.120	0.65 (0.40, 1.07)	0.090
Laterality				
Right	Reference		Reference	
Left	0.85 (0.56, 1.31)	0.460	0.86 (0.56, 1.33)	0.520
Antibiotics at the time of insertion				
No	Reference		Reference	
Yes	1.10 (0.66, 1.85)	0.710	1.17 (0.67, 2.03)	0.580
Antineoplastic therapy <sup>a</sup>				
No	Reference		Reference	
Yes	1.02 (0.66, 1.58)	0.920	0.82 (0.52, 1.31)	0.410
Immunocompromised <sup>b</sup>				
No	Reference		Reference	
Yes	1.18 (0.64, 2.16)	0.600	1.14 (0.58, 2.24)	0.690
Duration of TPC, month	1.03 (1.01, 1.06)	<b>0.013</b>	1.03 (1.00-1.06)	<b>0.028</b>

CI, confidence interval; SHR, Subdistribution hazard ratio for TPC-infection; TPC, tunneled pleural catheter.

<sup>a</sup>Antineoplastic (chemotherapy and/or biologic) therapy within one month of TPC insertion, and/or during TPC drainage.

<sup>b</sup>Immunocompromised within one month of TPC insertion, and/or during TPC drainage.

e- Table 2. Independent predictors of incidence of deep infection using competing risk regression (n=1,182).

	Univariate analysis		Multivariable analysis	
	SHR (95% CI)	p Value	SHR (95% CI)	p Value
Age, year	0.99 (0.97, 1.01)	0.160	0.99 (0.97, 1.01)	0.160
Gender, male				
Female	Reference		Reference	
Male	0.68 (0.38, 1.23)	0.200	0.80 (0.43, 1.51)	0.490
Primary cancer				
Lung	Reference		Reference	
Breast	1.10 (0.57, 2.15)	0.770	0.82 (0.40, 1.67)	0.580
Other	0.48 (0.24, 0.95)	<b>0.036</b>	0.48 (0.24, 0.97)	<b>0.041</b>
Laterality				
Right	Reference		Reference	
Left	0.67 (0.37, 1.22)	0.190	0.69 (0.37, 1.27)	0.230
Antibiotics at the time of insertion				
No	Reference		Reference	
Yes	1.73 (0.93, 3.22)	0.083	1.68 (0.86, 3.28)	0.130
Antineoplastic therapy <sup>a</sup>				
No	Reference		Reference	
Yes	1.51 (0.80, 2.84)	0.210	1.11 (0.59, 2.07)	0.750
Immunocompromised <sup>b</sup>				
No	Reference		Reference	
Yes	1.46 (0.69, 3.11)	0.320	1.49 (0.67, 3.33)	0.330
Duration of TPC, month	1.04 (1.01, 1.07)	<b>0.005</b>	1.04 (1.00-1.07)	<b>0.035</b>

CI, confidence interval; SHR, Subdistribution hazard ratio for TPC-infection; TPC, tunneled pleural catheter.

<sup>a</sup>Antineoplastic (chemotherapy and/or biologic) therapy within one month of TPC insertion, and/or during TPC drainage.

<sup>b</sup>Immunocompromised within one month of TPC insertion, and/or during TPC drainage.

*e-Table 3. Cox proportional-hazards regression analysis for overall survival (n=1,215).*

	Univariate analysis		Multivariable analysis	
	HR* (95% CI)	<i>p</i> Value	HR* (95% CI)	<i>p</i> Value
Age, year	1.00 (1.00, 1.01)	0.388	1.00 (0.99, 1.00)	0.423
Gender, male				
Female	Reference		Reference	
Male	1.27 (1.12, 1.44)	<b>&lt;0.001</b>	1.14 (0.99, 1.31)	0.063
Primary cancer				
Lung	Reference		Reference	
Breast	0.71 (0.60, 0.85)	<b>&lt;0.001</b>	0.76 (0.63, 0.91)	<b>0.003</b>
Other	1.08 (0.94, 1.24)	0.290	1.07 (0.93, 1.23)	0.364
Laterality				
Right	Reference		Reference	
Left	0.98 (0.86, 1.11)	0.703	0.95 (0.83, 1.08)	0.466
Antibiotics at the time of insertion				
No	Reference		Reference	
Yes	0.81 (0.69, 0.95)	<b>0.011</b>	0.81 (0.68, 0.96)	<b>0.013</b>
Antineoplastic therapy <sup>a</sup>				
No	Reference		Reference	
Yes	0.77 (0.67, 0.88)	<b>&lt;0.001</b>	0.84 (0.73, 0.97)	<b>0.015</b>
Immunocompromised <sup>b</sup>				
No	Reference		Reference	
Yes	0.72 (0.59, 0.88)	0.001	0.74 (0.60, 0.91)	0.004

CI, confidence interval; HR, Hazard ratio for death; TPC, tunneled pleural catheter.

<sup>a</sup>Antineoplastic (chemotherapy and/or biologic) therapy within one month of TPC insertion, and/or during TPC drainage.

<sup>b</sup>Immunocompromised within one month of TPC insertion, and/or during TPC drainage.

## FIGURE LEGENDS

**Figure 1.** Cumulative incidence function plot depicting the probability of a TPC-related infection, stratified by whether patients received antineoplastic therapy or not; including the competing risk of death without infection, stratified by whether patients received antineoplastic therapy or not (TPC, tunneled pleural catheter).

**Figure 2.** Kaplan-Meier curve comparing overall survival between patients who underwent antineoplastic therapy versus those who did not.