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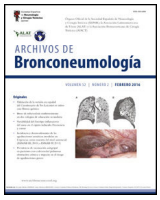

Original Article

Efficacy and Safety of Indwelling Catheter for Malignant Pleural Effusions Related to Timing of Cancer Therapy: A Systematic Review☆

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ABSTRACT

Introduction: To compare the efficacy and safety of indwelling pleural catheters (IPC) in relation with the timing of systemic cancer therapy (SCT) (*i.e.*, before, during, or after SCT) in patients with malignant pleural effusion (MPE).
Methods: Systematic review of randomized controlled trials (RCT), quasi-controlled trials, prospective and retrospective cohorts, and case series of over 20 patients, in which the timing of IPC insertion in relation to that of SCT was provided. Medline (*via* PubMed), Embase, and Cochrane Library were systematically searched from inception to January 2023. The risk of bias was assessed using the Cochrane Risk of Bias (ROB) tool for RCTs and the ROB in non-randomized studies of interventions (ROBINS-I) for non-randomized designs.
Results: Ten studies ($n = 2907$ patients; 3066 IPCs) were included. Using SCT while the IPC was *in situ* decreased overall mortality, increased survival time, and improved quality-adjusted survival. Timing of SCT had no effect on the risk of IPC-related infections (2.85% overall), even in immunocompromised patients with moderate or severe neutropenia (relative risk 0.98 [95%CI: 0.93–1.03] for patients treated with the combination of IPC and SCT). The inconsistency of the results or the lack of analysis of all outcome measures in relation to the SCT/IPC timing precluded drawing solid conclusions about time to IPC removal or need of re-interventions.
Conclusions: Based on observational evidence, the efficacy and safety of IPC for MPE does not seem to vary depending on the IPC insertion timing (before, during, or after SCT). The data most likely support early IPC insertion.

Introduction

Malignant pleural effusion (MPE) is a marker of advanced cancer, which should be treated symptomatically to preserve quality of life. Although some patients are initially asymptomatic and, therefore, do not require invasive procedures,[1,2] most eventually develop dyspnea at exertion or rest, and their treatment should aim to alleviate symptoms in a minimally invasive manner.[1] Traditionally, pleurodesis with talc has been the treatment of choice for MPE patients. Subsequently, indwelling pleural catheter (IPC) emerged as a valuable option for patients with non-expandable lung or failed pleurodesis,[1,3] offering long-term symptom control

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following regular fluid drainage, with the same effectiveness as talc pleurodesis.[4,5]

Advances in pleural palliation have facilitated the widespread adoption of IPCs as a primary intervention in selected patients with symptomatic recurrent MPE.[1,5] IPCs' main advantages over talc slurry pleurodesis *via* chest tube include a shorter hospital stay and fewer requirements for additional pleural interventions; however, the rate of complications may be higher.[2,3] Furthermore, talc may similarly be instilled through a functioning IPC to achieve pleurodesis.[6] According to current guidelines, IPC is a suitable option for both patients with expandable and non-expandable lungs, which can be inserted and managed in the outpatient setting.[1,5,7]

Controversy still exists among oncologists and interventional pulmonologists with respect to the precise timing of the IPC placement, whether it should be placed before or during systemic cancer therapy (SCT) or even wait until SCT completion. Arguments in favor of the first option claim to avoid complications related to pleural effusions, including persistent symptoms, poor quality of life, and development of septations or non-expandable lungs. Arguments in favor of waiting for the oncologic treatment to take effect include: (1) potential risk of IPC infection during administration of some therapies, especially chemotherapy; and (2) potential efficacy of SCT at controlling MPE, thus precluding the need for an IPC. No clear guidelines on this topic exist. Current literature about the timing of IPC insertion in relation to SCT is limited, mainly consisting of small retrospective series or single-arm prospective studies. Moreover, no conclusions can currently be drawn on the usefulness of SCT in MPE control.[4] According to current guidelines, definitive pleural interventions should probably not be deferred until SCT has been completed.[5]

Therefore, our aim was to critically review the existing literature in order to compare the efficacy and safety of IPC insertion for MPE in relation to the timing of SCT, with the IPC being evaluated before, during, or after SCT.

Methods

We performed a systematic review (SR) based on the Cochrane Handbook guidelines of a non-Cochrane review. The PRISMA statement, flow chart, and checklist were being adhered to for the reporting.

Search strategy and selection process

Two librarians developed the search strategy using the PRESS guidelines to cross-check results.[8] Medline *via* PubMed (29/01/2023), Embase (29/01/2023), and Cochrane CENTRAL (29/01/2023) were searched from inception using free and MeSH term synonyms of "malignant pleural effusion" and "indwelling pleural catheter" plus filters for SRs, randomized controlled trials (RCTs), and cohorts (see supplementary material for the detailed search strategies).

Studies were eligible if they included adult patients with MPE secondary to any metastatic tumor or primary pleural tumors such as mesotheliomas, irrespective of the SCT (chemotherapy, immunotherapy, molecular targeted therapies, or combinations) instituted, and whether or not the lung was trapped. In addition, to be eligible, the intervention for MPE should be ambulatory, and the outcome should have been recorded considering the time of IPC placement in relation to SCT (before, during, or after SCT). Studies with radiotherapy as the only cancer treatment were excluded, as were those in which the results of treated and untreated arms could not be derived separately. Concerning the type of studies, RCTs, quasi-controlled trials, prospective and retrospective cohorts, and case series involving over 20 patients were all eligible. SRs covering the same topic were screened for additional primary studies that had not yet been included. The lists of references of the included studies were likewise scanned for potential further studies that would have been overlooked.

The studies retrieved by the searches were added to an Endnote 21™ (Clarivate Analytics) library and uploaded to the Rayyan® systematic review software (https://www.rayyan.ai/), where a pair of reviewers performed the study selection independently. First, duplicates were removed, after which the titles and abstracts were screened to discard unrelated studies. All remaining reports were read in full, and data were collected.

Data collection, risk of bias assessment, and synthesis

For each study, the eligibility criteria were checked upfront; if these were not met, the study was added to the list of excluded studies, with a comment specifying the unmet criteria.

Data collected from the primary studies were transcribed by one of the reviewers into an Excel® template, which were agreed *a priori* and cross-checked by the other reviewer. The variables to be collected were related to: (1) *study*: design, year, country, setting (single center or multicenter), follow-up duration; (2) *sample characteristics*: sample size, cancer type, demographic characteristics (age and gender), and performance status (Karnofsky, Eastern Cooperative Oncology Group); (3) *lung and pleural effusion characteristics*: expandable/non-expandable lung, pleural loculations, and fluid data (malignant or non-malignant cells, pH, cellular predominance); (4) *cancer treatment*: use of chemotherapy, immunotherapy, molecular targeted therapy or combinations, and lines of therapy; (5) *IPC*: indication (symptomatic relief, pleurodesis), drainage schedule (on demand, daily), and catheter implantation setting (inpatient or outpatient); (6) *outcomes of interest*: efficacy (symptom improvement, need for further procedures, total number of procedures or re-interventions required, hospital stay, patient survival, degree of auto-pleurodesis achieved [different definitions], and time to catheter removal); safety (intra-pleural infection or empyema, and extra-pleural infection including cellulitis, exit site and tunnel tract infections; symptomatic loculations, metastasis of the tract, pain, bleeding, or other complications such as obstruction).

For each outcome, the definition, effect measure, crude, and adjusted values, as well as covariates were collected, and results were expressed by timing groups. After plotting all the results in tables, the researchers met in order to discuss visualization of results and aggregability of studies.

To assess the risk of bias within the included studies, the Cochrane Risk of Bias (RoB) tool for RCTs and Risk of Bias In Non-randomized Studies of Interventions (RoBINS-I) for non-randomized studies were employed. Studies were assessed by a single reviewer and then cross-checked by another.

Meta-analysis was only planned if the studies were sufficiently homogeneous. A random-effects (DerSimonian and Laird) method for meta-analysis was used. Specifically, a meta-analysis on the risk of IPC-related infections from studies which separated data by groups (with and without SCT while IPC was *in situ*) was performed. Heterogeneity was estimated from an inverse-variance fixed-effect model and presented as I^2. The Stata 12.0 (Stata Statistical Software: Release 12. College Station, TX: StataCorp LLC) metaprop and metan commands were used.

Results

The search identified 971 records, 10 of which were eventually included (see Fig. 1S in the Supplementary material). Seventy stud-

Table 1
Description of the included studies.

Author, year	Country	Design (study time period)	Setting	Follow-up duration	Risk of bias[a]
Akram et al., 2020[11]	Pakistan	Retrospective (2011–2019)	Hospital (n = 1)	Not mentioned	High
Gilbert et al., 2015[12]	USA	Retrospective (2009–2013)	Multicentric (n = 8)	Not mentioned	High
Hak et al., 2016[13]	United Kingdom	Retrospective (2010–2014)	Hospital (n = 1)	6 months	High
Mekhaiel et al., 2013[14]	USA	Retrospective (2005–2011)	Hospital (n = 1)	Not mentioned	High
Mitchell et al., 2018[15]	Canada	Retrospective (2006–2015)	Hospital (n = 1)	Minimum 18 months	High
Morel et al., 2011[16]	United Kingdom	Prospective (2006–2010)	Hospital (n = 1)	Not mentioned	High
Ost et al., 2014[17]	USA	Prospective (2010–2013)	Hospital (n = 1)	Minimum 1 year	Moderate
Porcel et al., 2020[18]	Spain	Retrospective (2014–2019)	Hospital (n = 1)	Median (IQR): 107 (29–357) days	Moderate
Wilshire et al., 2021[19]	International	Retrospective (2008–2016)	Multicentric (n = 12)	Not mentioned	Low
Wang et al., 2023[20]	Canada	Retrospective (2009–2020)	Hospital (n = 1)	Minimum 18 months	High

Abbreviation: IQR, interquartile range.
[a] From the assessment using the Cochrane tools.

ies that were likely to meet the inclusion criteria based on their title or abstract were excluded following detailed reading. A list of the studies that were excluded with sufficient reasons is detailed in the Supplementary material (Tables 1S and 2S). Most studies were excluded because they did not provide enough data to analyze the outcomes by timing of SCT. The reference lists of three SRs with potentially eligible studies were cross-checked,[7,9,10] with no additional studies identified by this or by secondary searches.

In Table 1, the 10 included studies (n = 2907 patients; 3066 IPCs) have been summarized, with their risk of bias being listed.[11–20] No RCT was identified, and there were only two studies with a prospective design.[16,17] The remaining studies exhibited retrospective designs with variable follow-up times (from a median of 107 days to a minimum of 18 months), and two were multicenter in nature.[12,19] Except for the study by Wilshire et al.,[19] the remainder displayed moderate to high risk of bias.

The most common primary tumors were lung (frequency range: 7.3–100%) and breast cancers (12–100%), followed by mesotheliomas, lymphomas or other hematological cancers, ovarian, gastrointestinal, and solid tumors (Table 2). Information about MPE and IPC characteristics was scarce. Loculations were only reported in two studies,[11,20] pleural fluid characteristics in three,[15,18,20] while the percentage of trapped lung ranged from 2% to 42%,[11,12,15,18] with IPC insertion being mainly ambulatory (Table 3). Regarding SCT, different treatments (chemotherapy, radiotherapy, immunotherapy, molecular targeted therapies) with different timings in relation to IPC insertion (before IPC, while IPC was in place, or after IPC removal) were reported. All studies comprised at least one group of patients receiving SCT, but the most common comparison groups were SCT *vs* no SCT whilst IPC was *in situ* (Table 4).

Efficacy and safety outcomes were evaluated, even though they were not always documented in all studies.

Given there were no comparative studies included, it was not possible to assess the efficacy related to symptom improvement or decreased hospitalization days in IPC carriers undergoing SCT. Of the included studies, only three reported re-intervention procedures,[12,17,18] seven patient survival,[11,13,15–19] six indication for catheter removal,[12,15–18,20] and eight time to catheter removal[12–16,18–20] (Table 5).

Safety data were collected by assessing the following information: intra- or extra-pleural infections (all the included studies), symptomatic loculations,[18] metastasis of the tract,[18] and other complications[13,17,18,20] (Table 6).

Impact on survival

Survival was expressed as median survival time, 6-month mortality, and mortality with IPC *in situ*. All studies demonstrated a more prolonged survival in those patients in whom the IPC was inserted close to SCT or during SCT.[11,13,15–19]

Akram et al. reported that patients who received chemotherapy before and after IPC insertion exhibited longer median survival in comparison with those who did not receive any oncological treatment (106 *vs* 41 days; p = 0.004).[11] Consequently, the decision regarding institution of the oncological treatment is an essential factor contributing to survival. According to Hak et al. the 6-month mortality was lower in patients with IPC and concomitant SCT than in those without SCT (35% *vs* 59%; p = 0.007).[13] The results of Morel et al. pointed toward the same direction, with lower mortality rates in patients undergoing SCT upon IPC insertion compared with those who did not receive SCT (57% *vs* 68%), although there was no mention of whether this difference was statistically significant.[16] The study by Ost et al. demonstrated an improvement in quality-adjusted survival in patients starting chemo- or radiotherapy immediately after IPC insertion.[17] Mitchell et al. showed that chemotherapy in IPC carriers increased survival time (238 *vs* 114 days),[15] defined as the median time from IPC insertion to death. Finally, Whilshire et al. observed that SCT within a month of IPC insertion or during IPC use was associated with a 16% increase in survival (hazard ratio [HR] = 0.84; p = 0.015).[19]

Conducting a meta-analysis was not considered, given the variability of the outcomes and definition of the interventions.

Indication to remove IPC and duration of IPC insertion

Death and auto-pleurodesis were the most common causes of IPC removal.[12,15–18,20] The rate of spontaneous pleurodesis was high, ranging between 23% and 50% (Table 5). Although using concomitant chemotherapy when the IPC was *in situ* did not impact probability of removal in two studies,[15,18] Wang et al. observed greater rates of spontaneous pleurodesis in patients with lung cancer who were subjected to epidermal growth factor receptor (*EGFR*) therapy while the IPC was *in situ* (adjusted OR = 3.87)[20] (Table 5).

On the other hand, information on the duration of the IPC *in situ* was not fully consistent.[12–16,18–20] Although the variability of the studies does not allow drawing solid conclusions, the results suggested longer catheter duration in patients undergoing SCT, except for the Hak et al. study.[13] However, the differences were only statistically significant in the Mekhaiel et al. study[14] and could be related to longer survival with chemotherapy. Concerning the remaining studies, multivariate analyses either did not reveal differences between patients with or without SCT upon IPC placement[15] or the statistical significance of the comparison was not recorded.[13,16,18,19]

Performing a meta-analysis was not taken into consideration, owing to the difficulty of pooling median times and interquartile ranges, which were the most reported effect measures.

Table 2
Included studies: sample characteristics.

Author, year	No. patients (IPC)	Age, yr[a]		Women *N* (%)		Cancer type			Performance status/risk stratification
						Breast	Lung	Others	
Akram et al., 2020[11]	110 (110)	49 (15)		76 (69%)		53.6%	7.3%	Lymphoma (10.0%) Gastrointestinal (8.2%) Ovarian (7.3%)	Risk stratification (LENT score): - low risk: 40% - moderate risk: 26.4% - high risk: 33.6%
Gilbert et al., 2015[12]	91 (91)	65 (15)		65 (26%)				Lymphoma (62%) Leukemia (21%) Myeloma (13%)	
Hak et al., 2016[13]	104 (104)	ChT on (=43) 64 (15)	ChT off (n = 61) 68 (12)	–		26.0%	32.7%	Mesothelioma (11.5%) Others (29.8%)	
Mekhaiel et al., 2013[14]	243 (262)	69 (59–77)[b]		123 (51)		16%	41%	Lymphoma (7%) Ovarian (7%)	
Mitchell et al., 2018[15]	207 (216)	62 (14)		205 (99)		100%			- ECOG 1: 3.7% - ECOG 2: 24.1% - ECOG 3: 40.3% - ECOG 4: 31.9%
Morel et al., 2011[16]	78 (82)	ChT on 60	ChT off 67	ChT on 12	ChT off 25	27%	16.7%	Mesothelioma (23.1%)	
Ost et al., 2014[17]	266 (266)	60 (12)		166 (62.4)		25.2%	29.7%	Hematologic (12.8%) Other solid tumors (32.3%)	- ECOG 1: 40.2% - ECOG 2: 31.6% - ECOG 3: 23.7% - ECOG 4: 0.7%
Porcel et al., 2020[18]	258 (279)	71 (61–81)[b]		110 (43)		12%	43%	Gastrointestinal (11%) Unknown origin (9%) Hematologic (7%)	- ECOG 0–1: 50% - ECOG 2: 25% - ECOG 3–4: 25% Risk stratification (LENT score): - low risk: 7% - moderate risk: 65% - high risk: 28%
Wilshire et al., 2021[19]	1318 (1408)	63 (54–72)[b]		752 (57)		20%	36%	Ovarian (5%) Lymphoma (4%) Mesothelioma (4%)	- ECOG 0–2: 76% - ECOG 3–4: 24%
Wang et al., 2023[20]	232 (248)	71 (12)		124 (50)			100%		- ECOG 0–2: 71.8% - ECOG 3–4: 28.2%

Abbreviations: ChT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; IPC, indwelling pleural catheter; LENT (L = LDH in pleural fluid; E = ECOG performance status; NLR = neutrophil to lymphocyte ratio; T = tumor type).
In papers without information on the number of IPCs inserted at least the same number of procedures as patients was assumed.

[a] Mean (standard deviation) unless otherwise noted.

[b] Median (interquartile range).

Table 3
Characteristics of pleural effusions and indwelling pleural catheters in the included studies, where available.

	Loculations	Fluid characteristics	Trapped lung	Drainage schedule	Insertion setting
Akram et al., 2020[11]	Non-loculated: 60.9% Multiloculated: 39.1%		41.8%		Inpatient: 73.6% Outpatient: 26.4%
Gilbert et al., 2015[12] Hak et al., 2016[13]			16%		Inpatient (71%) Mostly outpatient
Mitchell et al., 2018[15] Morel et al., 2011[16]		Positive cytology: 40.3%	15.7%	Thrice weekly for the first two weeks	Inpatient and outpatient
Ost et al., 2014[17]			2%	• After IPC insertion: daily drainage • Drainage ≤150 mL for three consecutive days: drain every other day • Drainage every other day ≤150 mL on three occasions and steady decline: stop drainage	Inpatient: 30.4 Outpatient: 69.5
Porcel et al., 2020[18]		CRP < 15 mg/L: 53% LDH > 700 U/L: 44%	34%	Three times weekly initially	Inpatient and outpatient
Wang et al., 2023[20]	Loculations needing fibrinolytics: 16.0%	Positive cytology: 72.2%		Home care services three times weekly initially	Inpatient, outpatient or during thoracoscopy

Abbreviations: CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table 4
Characteristics of cancer treatments in the included studies.

Author, year	Cancer treatment	Timing of cancer treatment-IPC insertion (%)	Treatment line
Akram et al., 2020[11]	ChT	- Pre- and post-IPC insertion: 46.4% - None: 53.6%	
Gilbert et al., 2015[12]	ChT Previous HSCT: 18%	- At the time of IPC insertion: 43% - Within the past 6 weeks: 19% - >6 weeks ago: 25% - Unknown: 13%	
Hak et al., 2016[13]	SCT	- Concomitantly: 40% - None: 60%	
Mekhaiel et al., 2013[14]	ChT	- ChT within 6 weeks of IPC insertion or while IPC was *in situ*: 66% - No ChT while IPC *in situ*: 34%	
Mitchell et al., 2018[15]	ChT	- ChT while IPC *in situ*: 48.2% - No ChT while IPC *in situ*: 51.8%	- First: 17.3% - Second: 29.8% - ≥Third: 52.9%
Morel et al., 2011[16]	SCT	- SCT while IPC *in situ*: 28% - No SCT while IPC *in situ*: 72%	Average: 2.5 cycles with IPC *in situ*
Ost et al., 2014[17]	ChT RdT	- Prior RdT: 12.4% - Prior ChT: 75.6% - ChT or RdT after the procedure: 70.7%	
Porcel et al., 2020[18]	ChT	Concomitantly: 63%	
Wilshire et al., 2021[19]	SCT	Within 1 month of IPC insertion and/or during IPC drainage (63%)	
Wang et al., 2023[20]	ChT: 19% EGFR targeted therapy: 15.3% ALK targeted therapy: 3.6% Immunotherapy: 15.7% RdT: 13.3% No medication treatment: 29.8%	While IPC *in situ*	Second line

Abbreviations: ALK, anaplastic lymphoma kinase; ChT, chemotherapy; EGFR, epidermal grow factor receptor; HSCT, hematopoietic stem cell transplantation; IPC, indwelling pleural catheter; RdT, radiotherapy; SCT, systemic cancer therapy.

Re-interventions

Three studies presented data about additional pleural procedures being required. Overall, the frequency of pleural re-interventions was low, but the results were mainly descriptive, without any comparison between patients with or without chemotherapy while the IPC was *in situ*.[12,17,18] Nevertheless, in the study by Gilbert et al.,[12] where all 91 patients included underwent chemotherapy, no additional thoracocentesis was reported, and there was only one placement of a chest tube (1.1%), and 3 thoracoscopic pleurodesis procedures (3.3%) (Table 5).

IPC-related infections

All the included studies presented data on IPC-related infections, whether intrapleural (empyema) or extrapleural (cellulitis, exit site infection or line tract infection). Nevertheless, the direct effect of

Table 5
Outcomes: indwelling pleural catheter efficacy.

Author, year	Pleural re-interventions	Patient survival	Indication for removal	Time to catheter removal
Akram et al., 2020[11]		Median survival ($p = 0.04$): - ChT off: 41 days - ChT pre–post-IPC: 106 days		
Gilbert et al., 2015[12]	$N = 4$ - 3 thoracoscopic pleurodesis - 1 chest tube		- Death: 58% - Autopleurodesis: 23% - Infection: 4% - Patient request: 7%	- Global: 89.9 ± 127.1 days - If spontaneous pleurodesis: 63 ± 48 days ChT did not affect time to removal
Hak et al., 2016[13]		6-Month mortality ($p = 0.007$): - SCT on: 35% - SCT off: 59%		Median (IQR) IPC *in situ*: - SCT on: 28 (14–58) days - SCT off: 69 (47–143) days
Mekhaiel et al., 2013[14]				Median duration (IQR) ($p < 0.01$): - ChT on: 90 (38–162) days - ChT off: 42 (20–116) days
Mitchell et al., 2018[15]		Median time from IPC insertion to death: - ChT on: 238 days - ChT off: 114 days	- Death: 50% - Autopleurodesis: 50% IPC removal (ChT on *vs* off): OR = 1.16 ($p = 0.59$)	Median time to removal (IQR): 53.5 (23–144.5) days No difference in the adjusted analysis between ChT and no-ChT groups
Morel et al., 2011[16]		Mortality with IPC *in situ*: - SCT on: 57% - SCT off: 68%	Autopleurodesis: 35%	Median duration IPC *in situ* (IQR): - SCT on: 84 (11–487) days - SCT off: 66 (6–711) days
Ost et al., 2014[17]	$N = 21$ (14%) - 11 thoracocentesis - 7 IPC reinsertions - 3 chest tubes	Median survival: 171 days ChT or RdT after IPC insertion improved survival (HR 0.17, $p < 0.001$)	- Death or lost to follow-up: 44.3% - Autopleurodesis: 47.7% - Complications or other reasons: 7.9%	
Porcel et al., 2020[18]	$N = 11$ (8%) - 7 IPC reinsertion - 4 thoracocentesis	Median (IQR): 92 (28–293) days	Pleurodesis: 48% Predictor of removal (adjusted) - ECOG 0–2: SHR 2.22 - Expandable lung: SHR = 1.93 - IPC-related symptomatic loculations: SHR = 1.37 ChT did not predict removal	Median (IQR): 50 (27–99) days
Wilshire et al., 2021[19]		Median (IQR): 120 (107–142) days SCT associated with better survival: HR = 0.84 ($p = 0.015$)		Median (IQR): 55 (26–118) days
Wang et al., 2023[20]			Pleurodesis: 42.7% Predictors of removal (adjusted): - ECOG ≤2: OR = 4.82 - EGFR therapy: OR = 3.87	Median time to pleurodesis (IQR): 68 (38–140) days EGFR therapy was associated with earlier pleurodesis: HR = 1.86

Abbreviations: ChT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal grow factor receptor; HR, hazard ratio; IQR, interquartile range; IPC, indwelling pleural catheter; RdT, radiotherapy; SCT, systemic cancer therapy; SHR, sub-hazard ratio.

Table 6
Outcomes: indwelling pleural catheter safety.

Author, year	Infection rate			Infection risk	Infection if neutropenic	Symptomatic loculations	Metastasis of the tract	Other complications
	Overall	Intra-pleural (empyema)	Extra-pleural (skin, cellulitis, tract)					
Akram et al., 2020[11]	25.4% ($n=28$)			No information on relation between infection and timing of ChT[d]				
Gilbert et al., 2015[12]		7.7% ($n=7$)[b]		Timing of ChT related to IPC insertion had no effect on IPC infection risk				
Hak et al., 2016[13]	9.6%	6.7%[c]	2.9%	SCT on: 9.3% SCT off: 4.9% ($p=0.311$)				SCT *vs* non-SCT groups - Pain: 4.7% *vs* 3.3%; $p=0.550$ - Drain blockage: 2.3% *vs* 0%; $p=0.413$
Mekhaiel et al., 2013[14]	6.6% ($n=16$)	3.8%	2.3%	ChT on: 5.2% ChT off: 7.9% ($p=0.42$)	Neutropenia 2/16 (12.5%)			
Mitchell et al., 2018[15]		1.9% ($n=4$)		ChT *vs* no-ChT: RR = 0.57 ($p=0.48$)				
Morel et al., 2011[16]	9%			SCT *vs* no-SCT: 4% *vs* 10%; $p=0.667$	3 patients had neutropenia while IPC *in situ*, but none developed infections			
Ost et al., 2014[17]	5% ($n=13$)	1% ($n=3$)	4% ($n=10$)	ChT or RdT after IPC insertion did not affect any type of complication ($p=0.74$)				Clogged IPC: 3% IPC dislodgment: 1%
Porcel et al., 2020[18]	8.6% ($n=29$)	8% ($n=26$)	3.6% ($n=12$)	Predictors of infection: Pleural fluid CRP < 15 mg/L (OR = 4.42). ChT did not increase the risk of infection		19%	0.3%	- Mild pain with IPC drainage:46% - Mild cough with IPC drainage: 25% - Pain during or after IPC insertion:13% - IPC blockage: 5.4%
Wilshire et al., 2021[19]	7%[a] ($n=89$)	4% ($n=49$)	3% ($n=40$)	SCT was not associated with risk of infection: SHR = 0.82	Immunocompromised (moderate or severe neutropenia): 16% SHR = 1.14; $p=0.690$			
Wang et al., 2023[20]		1.9% ($n=5$)	0.7% ($n=2$)	No information on the relationship between infections and timing of SCT				- Pain necessitating removal: 1.9% ($n=5$) - Leak at catheter site: 1.1% ($n=3$) - Catheter plugged: 1.1% ($n=3$) - Catheter dislodged: 0.7% ($n=2$) - Tumor seeding: 0.7% ($n=2$)

Abbreviations: ChT, chemotherapy; CRP, C-reactive protein; IPC, indwelling pleural catheter; OR, odds ratio; RdT, radiotherapy; SCT, systemic cancer therapy; SHR, sub-hazard ratio.

[a] 16% immunocompromised (9% with moderate neutropenia and 7% with severe neutropenia).

[b] Death-related (septic shock: $n=2$; 28%). Hospital admission required ($n=6$; 86%).

[c] Neutropenic sepsis in 2/43 patients in the chemotherapy on group (4.6%).

[d] Less frequent in those with domiciliary IPC care education (18.2%, $p=0.03$).

SCT and the precise time of infection during treatment were not properly evaluated by all the authors.

The overall infection prevalence was highly variable, which can probably be accounted for by methodological differences among studies. Overall, IPC-related infections ranged from 1.9%[15] to as high as 25.4% in one publication,[11] but in the latter the authors did not specify the infection sites. By infection location, the presence of empyema as a complication of IPC ranged from 1%[17] to 8%,[12] while infections pertaining to the extra-pleural space (cellulitis) exhibited less variation, from 0.7%[14] to 4%.[17] The pooled estimated rate of IPC-related infections was 2.85% (95% confidence interval: 2.24–3.45; I^2 73.39%) (Fig. 2S).

Two of the 10 included studies did not present data on the possible relationship between infection occurrence and SCT timing.[11,20] The Akram et al. study reported a significant reduction ($p = 0.03$) in the infection rate of patients receiving domiciliary care education, but the infection frequency was not analyzed in relation with the chemotherapy timing.[11] Wang et al. reported a prevalence of intrapleural infection of 1.9%, also without information on its possible relationship with SCT timing.[20] The association between complications and SCT timing was analyzed globally, clearly demonstrating that SCT with concurrent or sequential radiotherapy following IPC insertion did not at all increase the overall risk of complications. The association between infection and SCT timing in relation to IPC insertion was analyzed in eight of the 10 studies.[12–19] None of them found a significant increase in infection risk associated with the SCT timing, despite the presence of neutropenia[12–19] (Table 6). A meta-analysis showed that the pooled relative risk (RR) of IPC-related infections while on SCT compared to off-therapy was 0.98 (95% CI: 0.93–1.03; I^2 0.0%) (Fig. 3S).

Other outcomes comprised IPC-related pain and drain blockage, without any effect of SCT timing,[13] in addition to symptomatic loculations, metastasis of the tract, leaks, or tumor seeding which were not analyzed with respect to SCT.[18,20]

Discussion

IPC placement, as an early measure in MPE management, is an adequate option to relief symptoms, maintain quality of life and reduce hospital stays, while potentially reducing the costs related to the latter.[21] However, definitive MPE management is not without complications and the optimal timing of IPC insertion with respect to SCT is still controversial. Some clinicians advocate delaying MPE control, while expecting the response to SCT, whereas others argue that MPE recurrences are the rule, thus resulting in deterioration of the patient's condition and reducing the possibility of further definitive interventions owing to lung entrapment.[22] This systematic review compared the safety and effectiveness of IPCs in relation to the timing of antineoplastic treatment, mainly consisting of chemotherapy (before IPC insertion, while IPC was *in situ*, and after IPC removal).

Results show that IPC carriers undergoing SCT have improved survival, irrespective of the timing of treatment (pre- and post-IPC insertion, concomitant with IPC, after IPC, within 1 month of insertion, or during IPC drainage), although these results could also be due to the better functional status of patients with IPC who are able to receive SCT. Moreover, the rate of auto-pleurodesis reported with targeted therapy to *EGFR* mutations was very high,[20] suggesting that highly effective therapies and overall good disease control increase the probability of spontaneous pleurodesis and early removal of the IPC. In turn, chemotherapy was not a predictor of pleurodesis in the studies included in the current review.[15,18]

Infection is one of the most common complications of IPC, and the prevalence of infections and their relationship with SCT are of paramount importance. Meta-analytical data from this systematic review suggest that SCT timing exerts no effect on the risk of IPC-related complications, including infections, even in immunocompromised patients with treatment-induced neutropenia.

These results are in concordance with the scientific literature. In a longitudinal study involving newly diagnosed MPE due to lung cancer, Chiang et al. demonstrated that early MPE control measures were beneficial at reducing the frequency of further interventions, regardless of the anti-cancer therapies used, including molecular targeted therapy.[21] Other studies have also supported the use of definitive pleural treatments (IPC or pleurodesis) in lung cancer patients with oncogenic mutations, without deferring until the eventual response to targeted therapies become apparent.[23] In a retrospective analysis of MPEs from different tumor types, Holling et al. observed that SCT was not independently associated with MPE resolution, defined by radiologic resolution with removal of drain or catheter and cessation of interventions.[24] Based on these results, the authors stated that all patients with MPE should be offered early definitive pleural interventions, regardless of the oncologic treatment plan,[1,25,26] as an integral part of the early palliative care program.

This systematic review has a few limitations. In general, the quality of the included studies was low to moderate, rendering it necessary to downsize the interpretation of results. First, none of the included studies was a RCT, but rather they were mainly retrospective studies, with only two having a prospective design. Second, most of the studies were conducted at a single center. Therefore, operator-dependent, or other center-related variables may have caused potential selection biases. Other limitations were related to the studies' statistical power that was insufficient to detect differences, along with inadequate handling of potential confounders. Finally, it was not possible to perform a meta-analysis of some outcomes of clinical interest, such as the time to IPC removal according to the simultaneous administration or nor of SCT.

In view of these results, it is crucial to encourage the scientific community to design a proper and pragmatic RCT that evaluates the true influence of diverse SCT on MPE resolution and, therefore, the role of early IPC placement in this setting. International collaboration with prospective standardized databases or registries would allow for more sounded study designs.

In summary, based on observational evidence, it seems that IPC insertion in patients with MPE should not be delayed pending the beneficial effect of SCT, if any, on pleural fluid clearance. In particular, there should be no concern among clinicians about a potential increased risk of IPC infections in patients undergoing SCT compared to those not receiving SCT, as this has not been demonstrated.

Registration and protocol

The review protocol was registered in PROSPERO, prior to the search strategy, under number CRD42022322026.

Availability of data, code, and other materials

The Endnote® libraries and data extraction forms are available upon reasonable request.

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Conflict of interests

All the authors received consultancy fees from SH medical. In addition, JMP received consultancy fees from Becton Dickinson;

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2023.06.007.

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