



# Postoperative course of cerebrospinal fluid diversion in the setting of leptomeningeal disease: a systematic review, meta-analysis, and meta-regression with an illustrative case

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## Abstract

**Background** Management of hydrocephalus symptoms in the setting of leptomeningeal disease (LMD) includes cerebrospinal fluid (CSF) diversion, which can in the form of ventriculoperitoneal shunting (VPS) and lumboperitoneal shunting (LPS). However, the quantifiable postoperative course following this intervention is poorly defined. Correspondingly the aim of our study was to quantitatively define and analyze the pooled metadata regarding this topic.

**Methods** Multiple electronic databases from inception to March 2023 were searched following PRISMA guidelines. Respective cohort-level outcomes were then abstracted and pooled by means of meta-analyses and analyzed by means meta-regression, both utilizing random-effects modeling. Post-hoc bias evaluation was then performed for all outcomes.

**Results** A total of 12 studies were identified for inclusion, describing 503 LMD patients managed by CSF diversion – 442 (88%) by VPS and 61 (12%) by LPS. Median male percentage and age at diversion were 32% and 58 years respectively, with lung and breast cancer the most common primary diagnoses. Meta-analysis demonstrated pooled incidence of symptom resolution in 79% (95% CI 68–88%) of patients after index shunt surgery, and shunt revision required in 10% (95% CI 6–15%) of cases. Pooled overall survival from index shunt surgery was 3.8 mo (95% CI 2.9–4.6 mo) across all studies. Meta-regression demonstrated that studies published later trended towards significantly shorter overall survival from index shunt surgery (co-efficient=-0.38,  $P=0.023$ ), whereas the proportion of VPS to LPS in each study did not impact survival ( $P=0.89$ ). When accounting for these biases, overall survival from index shunt surgery was re-estimated to be shorter 3.1 mo (95% CI 1.7–4.4 mo). We present an illustrative case demonstrating the course of symptom improvement, shunt revision and an overall survival of 2 weeks from index CSF diversion.

**Conclusion** Although CSF diversion in the setting of LMD can improve hydrocephalus symptoms in the majority of patients, there is a non-negligible proportion that will require shunt revision. Postoperatively, the prognosis of LMD remains poor irrespective of shunt type, and despite possible biases within the current literature, the expected median overall survival after index surgery is a matter of months. These findings support CSF diversion as an effective palliative procedure when considering symptoms and quality of life. Further research is required to understand how postoperative expectations can be managed to respect the best wishes of patients, their family, and the treating clinical team.

**Keywords** Shunt · Leptomeningeal disease; carcinomatosis · Ventriculoperitoneal · Lumboperitoneal · VPS · LPS · Survival

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## Introduction

Leptomeningeal disease (LMD, also known as leptomeningeal metastases or carcinomatous meningitis) is a rare but devastating sequela of advanced solid tumors. Prognosis is extremely poor at time of diagnosis, with expected survival of months [1, 2]. LMD is characterized by the simultaneous multifocal tumor involvement of the arachnoid and pia

meninges (leptomeninges) within the craniospinal axis, through which malignant cells spread throughout the subarachnoid space, travel to distant sites, settle, and grow [3]. It is estimated that 5% of patients with metastatic cancer will develop LMD, with the most common being breast and lung cancer primaries [4].

One specific manifestation of LMD is hydrocephalus that presents with clinical symptoms of increased intracranial pressure. This includes headache, nausea, vomiting, gait abnormality and altered mental status [4]. The incidence of hydrocephalus in the setting of LMD is approximately 20%.<sup>5</sup> Cerebrospinal fluid (CSF) diversion is a surgical treatment for elevated intracranial pressure, as it diverts the CSF away from the central nervous system. Diversion can be in the form of a ventriculoperitoneal shunt (VPS), as well as a lumboperitoneal shunt (LPS), both types which have been employed successfully in this setting [6]. To date however, there has been little attempt to quantify the post-operative course of LMD patients following CSF diversion. Correspondingly, the aim of this study was to systemically survey the contemporary metadata and quantify the post-operative course of these patients with respect to symptom improvement, shunt revision and survival from index shunt surgery.

## Methods

### Search strategy

Our search strategy was designed using the Population, Intervention, Comparison, Outcome, Study type (PICOS) question format: *How do patients with LMD (Population) that undergo CSF diversion in the form of VPS or LPS (Intervention, no comparator) perform in terms of overall survival, symptomatic relief and shunt revision (Outcome) based on cohort studies (Study Type)?* We conducted the review in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and recommendations [7]. Electronic searches were performed using Ovid Embase, PubMed, SCOPUS, and the Cochrane databases, from inception to February 2023. Database searches were completed using the string “((cerebrospinal fluid) OR ventriculoperitoneal) AND (shunt OR diversion) AND (leptomeningeal)”. These results were then screened against the criteria of our PICOS question.

### Selection criteria

All retrieved articles were screened against predetermined selection criteria independently by two investigators (V.M.L. and H.A.) for identification of relevant studies, as

per the PRISMA guidelines. Any differences were resolved by consensus discussion with senior author. Inclusion criteria for all articles were (1) patients with LMD, (2) who underwent CSF diversion in either form of VPS or LPS, with (3) median overall survival reported and (4) aged  $\leq 18$  years old. Concurrent Ommaya reservoir placement was not a contraindication to inclusion, neither was the use of post-procedural therapies including immunotherapy. Exclusion criteria were (1) heterogeneous cohorts in which outcomes of LMD patients with and without CSF diversion could not be separated, and (2) cohorts with 3 or less patients (including case reports). Where duplicate studies with overlapping cohorts were reported from individual institutions, only the most complete report was included to avoid any overlapping bias in analysis. Studies were limited to English language publications; database studies, review articles, conference abstracts or presentations, and editorials or expert opinions were excluded to reduce publication bias.

### Statistical techniques

Our primary summary outcomes were pooled survival from shunt surgery, and then incidence of symptom resolution and shunt revision. All outcomes were reported with 95% confidence interval (CI), and obtained by meta-analysis of non-integer proportions where applicable. All pertinent metadata were handled as previously described, [8] utilizing a random-effects (RE) model in all cases. Statistical tests were 2-sided, and significance was defined using the alpha threshold of 0.05. All analyses were conducted using STATA 14.1 (StataCorp, College Station, Texas).

### Bias and certainty, and quality assessments

Publication bias was assessed through the generation of a funnel plot, and small study biases were assessed by Egger's linear regression test and Begg's correlation tests [9, 10]. A trim-and-fill method was prespecified for recalculation of pooled effect size if bias was suspected, irrespective of sample size [11]. To evaluate the certainty of the pooled results based on the characteristics of included studies, the strength of evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria [12]. Each included article was also appraised using the Newcastle-Ottawa Scale (NOS) to determine the quality of the original study design to answer the PICOS question of the current study [13].

## Results

### Search strategy

The search strategy identified a total of 656 studies for review (Fig. 1). After removal of 175 duplicate studies, inclusion and exclusion criteria were applied to titles and abstracts of the 481 articles. This yielded 20 studies that underwent full-text analysis. A total of 12 studies<sup>5,14–24</sup> satisfied all selection criteria, which were published between 2011 and 2022 and all single-institution retrospective cohort experiences with the one [24] exception involving two institutions.

### Demographic and clinical parameters

In total, there were 503 LMD patients managed by CSF diversion described by all studies, with cohorts ranging from  $n=4$  to  $n=190$  (Table 1). In terms of diversion type, there were 442 (88%) cases by VPS and 61 (12%) cases by LPS. Median male percentage and age at diversion were 32% (range, 0–45%) and 58 years (range, 49–65 years) respectively. In terms of LMD primary, the most common were lung and breast cancer, with median cohort proportions of 41% (range, 0–100%) and 33% (range, 0–100%) respectively across all studies. In terms of CSF diversion valve, nine studies reported valve type, with 5 studies [19–22, 24] utilizing programmable shunts only, 1 study [23] utilizing

non-programmable shunts only, and 3 studies [5, 14, 18] using both types of shunts at the surgeon's discretion.

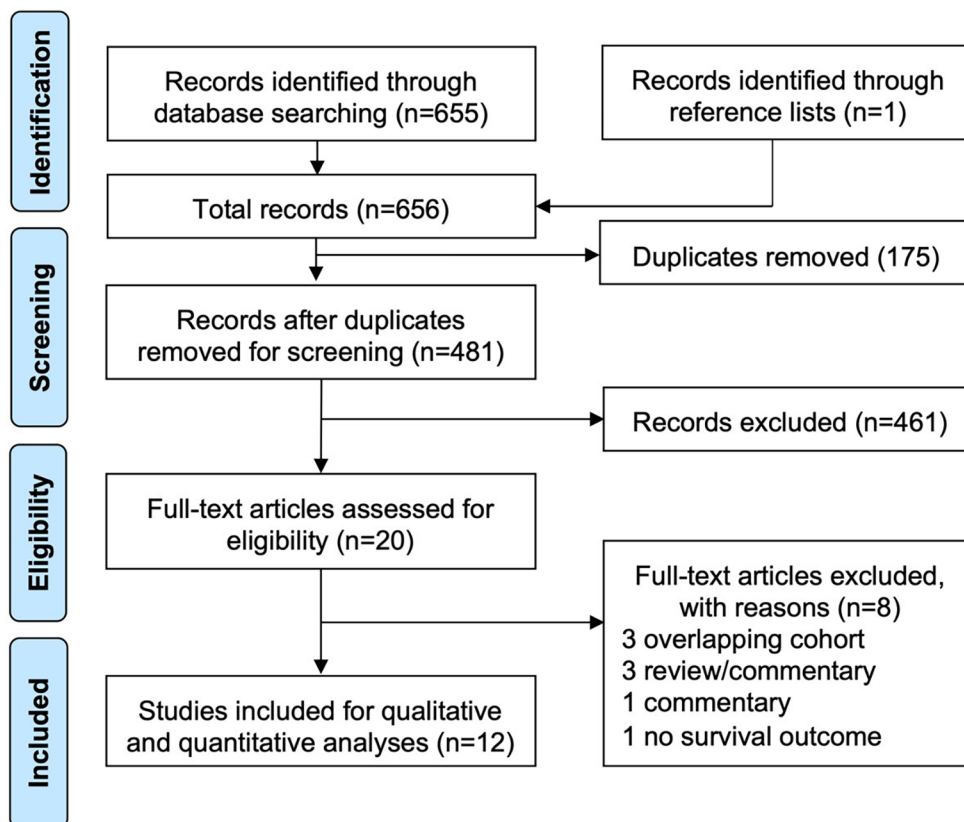
### Symptoms and improvement

Although all studies reported hydrocephalic symptoms as indication for CSF diversion, only 7 studies [14–17, 21, 23, 24] reported symptom breakdown. Amongst specific symptoms when reported by at least three separate studies, the most common symptom was headache in 50% (194/385 in 7 studies [14–17, 21, 23, 24]), followed by nausea and vomiting in 30% (95/318 in 5 studies [14, 15, 17, 21, 23]), then gait abnormality in 23% (55/241 in 3 studies [14, 15, 21]) and altered mental status in 21% (67/325 in 5 studies [14–17, 21]). A total of 8 studies<sup>15,17–19,21–24</sup> reported symptom response to CSF diversion. Pooled estimate by meta-analysis indicated a weighted incidence of 79% (95% CI, 68–88%;  $I^2=78\%$ ;  $P\text{-heterogeneity}<0.01$ ) (Fig. 2A).

### Shunt revision

A total of 10 studies<sup>14–16,18–24</sup> described incidence of shunt revision in 12/426 (3%) total patients. Pooled estimate by meta-analysis indicated a weighted incidence of 10% (95% CI, 6–15%;  $I^2=30\%$ ;  $P\text{-heterogeneity}=0.17$ ) (Fig. 2B). Of these, 9 studies<sup>14,15,18–24</sup> reported a pooled weighted

**Fig. 1** PRISMA search results for all included studies



**Table 1** Design, demographics and clinical features of all included studies. All categorical data expressed as n (% total of study cohort), and all continuous data expressed as median (range). R, retrospective; OCS, observational cohort study; LMD, leptomeningeal disease; CSF, cerebrospinal fluid; VPS, ventriculoperitoneal shunt; LPS, lumboperitoneal shunt

Study	Design*	Period	Location	Size	Males	Median age (yr)	LMD primary		CSF diversion	
							Breast	Lung	VPS	LPS
Su et al. 2022	R OCS (1)	2017–2020	Taipei, Taiwan	40	18 (45%)	59 (42–75)	0	40 (100%)	33 (83%)	7 (17%)
Bander et al. 2021	R OCS (1)	2010–2019	New York, USA	190	61 (32%)	57 (20–82)	65 (34%)	77 (41%)	189 (99%)	1 (1%)
Kim et al. 2021	R OCS (1)	2001–2017	Seoul, South Korea	70	0	49 (30–69)	70 (100%)	0	70 (100%)	0
Yoshioka et al. 2021	R OCS (1)	2010–2019	Osaka, Japan	14	3 (21%)	65 (36–76)	6 (43%)	8 (57%)	5 (36%)	9 (64%)
Kim et al. 2019	R OCS (1)	2002–2017	Goyang, South Korea	70	30 (42%)	53 (41–81)	6 (9%)	45 (64%)	51 (73%)	19 (27%)
Mitsuyu et al. 2019	R OCS (1)	2008–2017	Shizuoka, Japan	31	11 (35%)	59 (NR)	0	31 (100%)	13 (42%)	18 (58%)
Burger et al. 2018	R OCS (1)	2008–2017	Frankfurt, Germany	6	2 (33%)	58 (33–70)	2 (33%)	2 (33%)	6 (100%)	0
Murakami et al. 2018	R OCS (1)	2007–2016	Fukushima, Japan	11	2 (19%)	58 (17–73)	4 (36%)	4 (36%)	8 (73%)	3 (27%)
Yamashiro et al. 2017	R OCS (1)	NR	Kumamoto, Japan	4	1 (25%)	62 (53–68)	0	4 (100%)	0	4 (100%)
Jung et al. 2014	R OCS (1)	2005–2012	Gwangju, South Korea	7	4 (57%)	60 (37–80)	1 (14%)	4 (57%)	7 (100%)	0
Gonda et al. 2012	R OCS (1)	2005–2010	Boston, USA	36	16 (44%)	59 (31–78)	9 (25%)	13 (36%)	36 (100%)	0
Lin et al. 2011	R OCS (2)	2005–2009	Boston, USA	24	7 (29%)	57 (23–75)	9 (38%)	4 (17%)	24 (24%)	0
			Total/Median	503	155 (31%)	58	172 (35%)	232 (47%)	442 (88%)	61 (12%)

\*parentheses represents number of institutions involved

incidence for shunt infection of 2% (95% CI, 0–6%;  $I^2=47%$ ; P-heterogeneity = 0.06).

### Survival from index shunt surgery

All studies reported median survival of all 503 LMD patients after index shunt surgery. Pooled estimate by meta-analysis indicated a weighted survival time of 3.8 mo (95% CI, 2.9–4.6 mo;  $I^2=73%$ ; P-heterogeneity < 0.01) (Supplementary Fig. 1).

### Meta-regression

A meta-regression approach was utilized for each reported outcome of this study, evaluating the statistical impact of the following variables: year of publication, proportion of VPS to LPS within the cohort; cohort size, proportion of males within cohort, median age at CSF diversion, presenting symptoms of headache, nausea and vomiting, and gait issues, and proportion of lung and breast cancer primary of the LMD. This approach demonstrated a significant relationship between year of publication and reported survival from index shunt surgery (slope  $-0.38$ ;  $P=0.023$ ; 95% CI  $-0.68$  to  $-0.06$ ) (Supplementary Fig. 2). There was no significant relationship between proportion of VPS to

LPS on reported survival from index shunt surgery (slope  $0.32$ ,  $P=0.89$ ). There were no statistically significant relationships observed in our meta-regression analysis for the remaining variables.

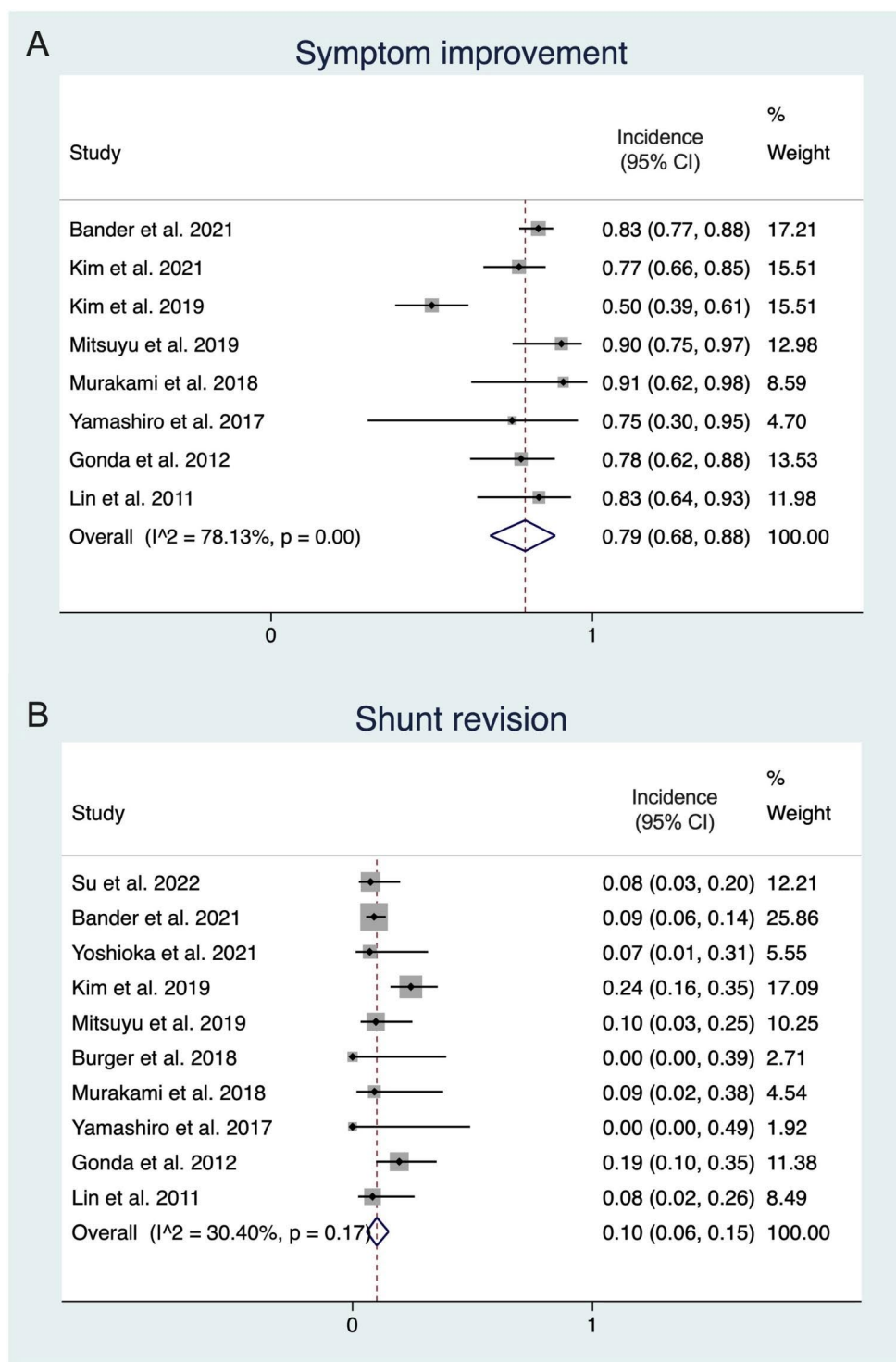
### Bias assessment

Bias in reporting outcomes were evaluated subjectively and objectively. The funnel plot for survival from index shunt surgery was asymmetric demonstrating likely publication bias, and tested positive for small-study bias by Egger's test ( $P<0.01$ ) but not Begg's test ( $P=0.73$ ) (Supplementary Fig. 2). A trim-and-fill approach demonstrated 5 studies needing to be imputed to alleviate this bias and generated a revised weighted survival time of 3.1 mo (95% CI 1.7–4.4 mo) from index shunt surgery. Funnel plots and small-study tests for the remaining outcomes were negative for biases.

### Certainty assessment

GRADE assessment evaluated the certainty of the overall quantitative results of our study (Table 2). All outcomes were deemed to be of very low certainty, primarily due to the heterogeneity in the clinical features of LMD and its associated hydrocephalus between studies.

**Fig. 2** Pooled incidence of (A) symptom improvement and (B) shunt revision after index shunt surgery for CSF diversion in LMD patients by means of random-effects model



**Quality assessment**

The Newcastle-Ottawa Scale was used to determine the quality of the original study design to answer our PICOS question (Supplementary Table 1). There were 4/12 (33%) studies [14, 17, 18, 24] rated high quality with respect to our study question. The remaining 8/12 (67%) studies were of

moderate quality with respect to our study question, primarily due to unclear follow-up duration.

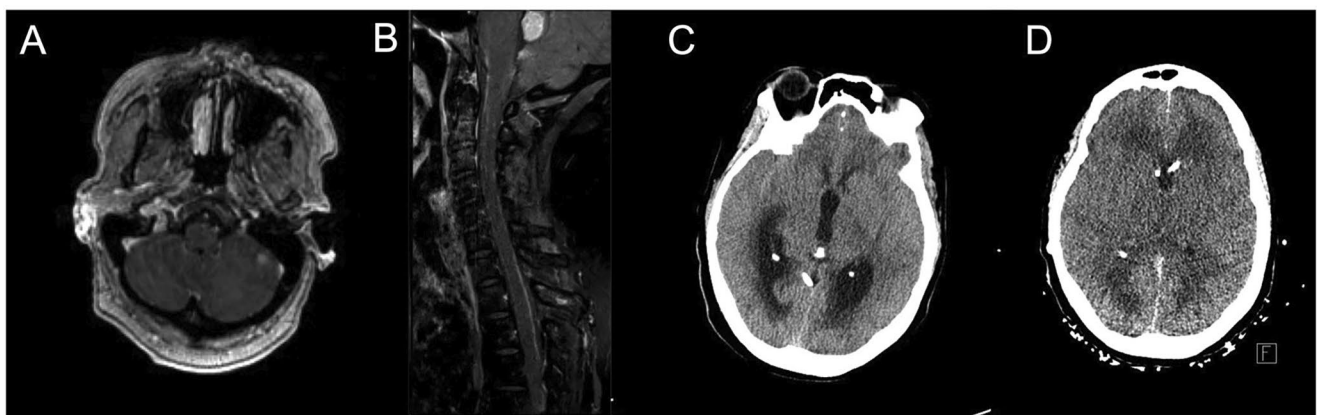
**Illustrative case**

A 54-year-old female with one-year history of breast cancer status post successful mastectomy and subsequent adjuvant

**Table 2** GRADE assessment for reported outcomes. GRADE, Grading of Recommendations, Assessment, Development and Evaluations

Outcome	Estimate (95% CI)	No. of cohorts	Certainty assessment					Effect size	Overall Quality	Certainty
			Type of Evidence	Quality	Consistency	Directness	Effect size			
Symptom improvement (%)	79% (68–88%)	8	+2	-2	-1	-1	+2	0	Very low	
Revision surgery (%)	10% (6–15%)	10	+2	-2	0	-1	+1	0	Very low	
Survival from shunt (mo)	3.7 mo (2.9–4.6 mo)	12	+2	-2	-1	-1	+2	0	Very low	

The overall quality score is determined based on the sum of the included domains. Type of evidence is based on design of the included studies (range, +2 to +4). The study quality reflects the blinding and allocation, follow-up and withdrawals, sparsity of data, and methodological concerns (range, -3 to 0). Consistency is graded based on heterogeneity of included population and study end points with respect to one another (range, -1 to +1). Directness is graded based on generalizability of included results (range, -2 to 0). Effect size is graded based on the number of percent deciles the pooled 95% CI overlap with at either 0% or 100% (range, 0 to +2). The overall quality of results for each outcome can be considered high ( $\geq 4$  points), moderate (3 points), low (2 points) or very low ( $\leq 1$  point)



**Fig. 3** An illustrative case. (A) axial T1-sequence with contrast MRI brain showed left enhancing cerebellar lesion and thick nodular enhancement in the bilateral internal auditory canals, as well as involvement of the cisternal segments trigeminal nerves. (B) sagittal T1-sequence with contrast MRI cervical spine showed both an enhancing fourth ventricular lesion and diffuse thick enhancement along the

lower cervical spine. (C) CT head demonstrated ventriculomegaly most pronounced in third ventricle and bilateral temporal horns 10 days after initial admission to hospital. (D) After loss of neurologic exam head two weeks after index shunt surgery, CT head after contralateral EVD placement demonstrated collapse of the ventricular system and loss of gray-white matter differentiation

chemoradiation and immunotherapy presented with new onset lower extremity weakness. Imaging demonstrated new lesions within the central nervous system indicating leptomeningeal perineural invasion and LMD (Fig. 3). Patient was admitted for medical management. Ten days later, patient was found to demonstrate altered mental status, endorsing headache with mild aphasia and cranial nerve VI and XII palsies. CT head demonstrated enlarged ventricular system, and an emergent EVD was placed, with restoration of mental status seen shortly after. A permanent VPS was placed four days later for CSF diversion without complication. However, one week after VPS placement, the patient was found obtunded with bilaterally enlarged pupils, and was taken emergently to the operating room for shunt revision which demonstrated a shunt valve with proteinaceous material causing failure. Valve obstruction to cellular debris has been reported in the literature previously [25]. The valve

was replaced without issue and postoperatively the patient regained her mental status and her pupils normalized. Three days later however, the patient was found to be in respiratory distress requiring emergent intubation followed by loss of her entire neurologic exam. Bedside attempts to draw CSF from the VPS valve were not successful, and an emergent contralateral EVD was placed without restoration of neurologic exam. CT head demonstrated at this time collapse of the ventricular system and loss of gray-white matter differentiation. The poor prognosis was discussed with family, and ultimately care was withdrawn. Overall survival was 2 weeks after index shunt surgery.

## Discussion

The postoperative course of CSF diversion in the setting of LMD patients with hydrocephalus symptoms is not well understood. Our analysis of the most contemporary meta-data demonstrates that headaches, nausea and vomiting are the most common symptomatic indications for diversion, of which 4-in-5 patients will experience symptom improvement after diversion and only 1-in-10 patients will require shunt revision. Survival from index shunt surgery was estimated to be 3.8 months, however our bias and meta-regression analyses indicate this value is skewed. Re-estimates accounting for this suggest a shorter survival of 3.1 months. None of these outcomes were affected by the choice of diversion between VPS versus LPS based on our meta-regression modeling.

Broadly, CSF diversion alleviates the burden of increased intracranial pressure. Therefore, it is encouraging that our study showed the majority of LMD patients who present with hydrocephalic symptoms experience improvement after shunting. This improvement appears universal based on the included studies irrespective of shunt type, with symptom relief reported to be independent of LMD primary, [15] as well as the genetics within primary subtypes [17]. There was however a non-negligible rate of shunt revision. In the general adult shunt population, the incidence of revision shunt surgery for both VPS and LPS ranges from approximately 5–25% [26–28]. It is within this range that our pooled estimate of shunt revision was, which suggests that in the setting of LMD there is no specific indication that a surgeon should be more or less suspicious of shunt failure.

Hydrocephalus is a known contributor to the progressive neurologic dysfunction that precedes death in LMD [29]. Thus it is intuitive that multiple included studies [5, 14, 18, 24] were able to demonstrate the use of CSF diversion leads to statistically longer overall survival from index diagnosis of hydrocephalus symptoms in LMD patients than those without CSF diversion. Yet as our meta-regression showed, there is no clear evidence that a survival difference exists between diversion type. This was the conclusion of Mitsuyu et al. [19], who reported overall survivals from index shunt surgery of 3.9 versus 3.5 months ( $P=0.88$ ) between LMD patients managed by VPS versus LPS respectively. This distinction of indifference is important for surgeons to be aware of as to not falsely influence CSF diversion type selection when evaluating LMD patients.

The choice between CSF diversion type for LMD patients has no definitive published selection guidelines. It can be argued its choice is both patient- and surgeon-dependent. As in our case example (Fig. 3), ventricular CSF outflow obstruction caused by mass lesions in the setting of LMD would favor a more proximal diversion by means of a VPS

than a LPS to alleviate the hydrocephalus. This is more likely to apply to cases with advanced intracranial metastatic disease. Yet, in the broader management paradigm of LMD, LPS can afford greater access to the thecal sac and wider subarachnoid distribution for intrathecal therapy than VPS [30]. There is also a suspicion that VPS can provide a direct conduit for intracranial LMD to spread into the peritoneum if not present already, which can increase then increase the oncologic burden on patients. This suspicion however has yet to be confirmed in large cohort studies [23].

Our meta-regression demonstrated that later years of publication were significantly associated with shorter overall survival from index shunt surgery. This has not been posited before, and likely this is multifactorial in nature secondary to the complexity of LMD and its treatment. The number of LMD patients eligible for treatment has increased over time with improved access to care and new therapy options, leading to more progressed disease with poorer prognosis being more treatable in later studies than earlier studies. This is exemplified by the fact that the latest study we included was by Su et al. [14] published in 2022 which included multiple different immunotherapy treatments in their pre-diversion management, compared to the earliest study we included by Lin et al. [24] published in 2011 which did not have any adjuvant therapy used outside standard chemotherapy and radiation therapy. The inclusion of more palliative cases, cases in which prolonging survival was not the primary intention of treatment, in later studies is a possible driver for our meta-regression finding.

Currently the literature is limited in its data about nature of death in the setting of LMD [31]. Whether or not death was a result of natural progression, elective withdrawal of care, or LMD treatment complication can greatly reshape the conversation about overall survival following index shunt surgery.

Quality of life data is crucial in understanding how CSF diversion fits in the LMD management paradigm, however data remains very limited. For example, successful discharge from hospital is one component that drives improved quality of life. Yet only 2 studies [15, 24] reported length of stay after CSF diversion procedure, ranging on average from 2 to 7 days. Further detail as to if these stay metrics are prolonged due to LMD-related comorbidities versus time to access adjuvant care is not reported. Another example of this type of data is duration of symptomatic relief, as this is one of the primary indications for CSF diversion in this setting. However, no included study quantified this outcome further than the one by Lin et al. [24] where they found that improvement was sustained at 6-month follow-up period for 10/24 (42%) of their patients. More quantitative outcome of data such as these will greatly enhance the discussion

regarding how CSF diversion can be optimally utilized in this unique setting.

### Strengths and limitations

This study incorporated the most contemporary metadata available, and employed only a RE model to generate the reported pooled estimates accounting for the statistical heterogeneity seen in the outcomes. By applying meta-regression techniques, we were able to identify these biases within the literature regarding overall survival from index shunt surgery, and still demonstrate a medial expected survival within the third postoperative month.

There are limitations to our study. The first is given the lack of consensual indications for CSF diversion between studies and practice, it is likely that not all patients treated within one cohort would have satisfied criteria for treatment of the others. Similarly, the selection and use of VPS versus LPS was study dependent. Further, it is unclear if any utilized antibiotic-impregnated catheters in this setting which may impacted these revision and infection results further [32]. This clinical heterogeneity limits the generalizability of our results, summarized by the significant P-heterogeneity seen in our pooled outcomes. The second limitation is that the absence of individual patient-level data, the provided cohort-level data precludes more granular analyses. For example, the nature of LMD, not all patients were treated with CSF diversion at the same time of their disease course. As such, the optimal timing for diversion cannot be determined based on our study. Another example is if particular hydrocephalus presentations, such as symptoms compatible with more niche diagnoses such as normal pressure hydrocephalus, respond better to CSF diversion than others. More individual patient-level data is needed. Finally, the indications for CSF diversion, as well as patient and family preferences, cannot be affirmed retrospectively in the included studies. Quality of life metrics in the future will be needed to quantitate the utility of CSF diversion in the setting of this dismal diagnosis.

### Conclusion

CSF diversion by means of either VPS or LPS confers the majority of LMD patients symptomatic relief when presenting with symptoms of hydrocephalus. There is a low incidence of shunt revision, and survival at this stage is typically within months after the index shunt surgery. We showed that based on the current metadata, CSF diversion choice by either VPS or LPS does not significantly impact prognosis of LMD. The utility of this from a palliative medicine perspective is not well understood. Understanding more about

how improved comfort measures can benefit patients, families and clinical teams will be better inform the appropriate indications and expectations for CSF diversion in the future.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s11060-023-04334-2>.

**Author contributions** VML: Methodology, Software, Visualization, Investigation, Writing- Reviewing and Editing. All authors: Conceptualization, Data curation, Writing- Original draft preparation, Writing- Reviewing and Editing.

### Declarations

**Conflicts of interest** The authors declare no competing interests.

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