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# Seizure prevalence, contributing factors, and prognostic factors in patients with leptomeningeal disease

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ABSTRACT

*Background:* To determine seizure prevalence and contributing factors in patients with leptomeningeal disease (LMD).

*Methods:* Authors performed a retrospective review of 79 consecutive patients with a diagnosis of LMD. Associations between categorical variables were assessed using Chi-Square tests or Fisher's Exact tests. Survival was plotted with Kaplan Meier curves. Variables with a log-rank p-value of $< 0.20$ were entered into a Cox Proportional Hazard regression analysis.

*Results:* Seizure prevalence in those with and without brain metastases was 22%. Of those who seized, 65% were admitted for this at least once while only one patient required intubation. Primary malignancy, type or route of chemotherapy administration, form of radiation therapy (craniospinal, focal, or whole brain), surgical treatment, location of LMD, and number of brain metastases did not influence seizure development. Only 13% of patients who never had seizures were on a prophylactic AED (anti-epileptic drug). In patients who had brain metastasis, there was no significant difference in prevalence of seizure before versus after LMD diagnosis suggesting that LMD does not significantly increase the risk of seizure compared to brain metastasis alone. A multivariate analysis revealed that while males trended toward inferior survival, only performance status and treatment with systemic chemotherapy showed a significant association with survival. Median survival time of patients after LMD diagnosis was four months.

*Conclusion:* The prevalence of seizure in LMD patients is 22%. There were no statistically significant predisposing factors to seizure development. ECOG and use of systemic chemotherapy were found to be significant prognostic factors.

## 1. Introduction

Leptomeningeal disease (LMD) is the spread of malignancy to the leptomeninges, or the arachnoid and pia maters [1]. The prevalence of leptomeningeal metastasis varies by tumor type, occurring in 5–8% of solid tumors, 5–15% of hematologic malignancies, and 10–32% in primary central nervous system (CNS) malignancies. The incidence of secondary CNS involvement is increasing due to improved cancer survival rates. The most common cancers of origin are breast, lung, and melanoma [2,3]. Leptomeningeal metastases confer a poor prognosis, with an average survival of two to three months with treatment [1].

Seizures are a well-known complication of CNS malignancy, however, there is little in the literature regarding leptomeningeal disease (LMD) and seizures [4]. The prevalence of seizures is unknown in this specific cohort as is potential efficacy of preventative anti-epileptic drugs (AEDs). Factors that might predispose LMD patients to seize or affect their survival are largely unexplored. Additionally, while many may be tempted to prophylax patients with CNS disease with an AED, these medications are expensive, and side effects include cognitive impairment, dermatologic reactions, liver enzyme elevation, and even myelosuppression. Furthermore, several AEDs directly affect the metabolism of common chemotherapeutic drugs and steroids, often needed in this population.

There have been four prospective studies regarding the use of AED prophylaxis and two meta-analyses on AED seizure prophylaxis for patients with CNS malignancy [5–10]. The consensus from these studies is that AED prophylaxis is generally not recommended and an AED should be started only after a patient's first seizure. However, the majority of this research studied a heterogeneous population of patients with CNS malignancies, including patients with many tumor types and

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none detailed coincident tumor therapies. The four prospective studies all utilized older AEDs which are known to have greater liver enzyme induction, and therefore more medication interactions, which can simultaneously increase or decrease AED and even chemotherapy levels in plasma [11]. Phenytoin was utilized frequently in these studies, and has been proven to have unpredictable efficacy. There are no specific studies evaluating patients with LMD and AED prophylaxis.

There have been several studies that aimed to identify prognostic factors in LMD. Factors that have been associated with a more favorable prognosis include intrathecal/systemic chemotherapy, female sex, longer duration of neurological symptoms, and negative MRI findings [12–16]. Factors that have been associated with a more negative prognosis include brain parenchymal metastasis, progression of systemic disease, cranial nerve deficits, supratentorial involvement, elevated CSF protein, poor performance status, and reduced interval between diagnosis of primary tumor and LMD [12,13,16]. Seizure as a possible prognostic factor has not yet been studied.

As seizures are a prevalent problem in patients with CNS malignancy, and the incidence of LMD is increasing, the potential threat of seizure from LMD needs to be further explored. This study aims to clarify the risk of seizure from LMD, factors associated with likelihood to seize, and effects on quality of life and survival in this patient population.

## 2. Methods

We completed a retrospective review of 79 patients treated at our institution with a diagnosis of LMD from August 2012 to August 2017. Appropriate IRB approval with a waiver of consent was obtained in accordance with institutional policy. LMD diagnosis was confirmed by evidence of leptomeningeal enhancement on imaging and/or malignant cells in CSF. Seizures were identified by chart review, only witnessed seizure activity was counted. Questionable spells or syncope were not included as seizure. Demographic, treatment and survival data were collected for all patients, as was performance status (ECOG score) at the time of LMD diagnosis. Scores two months or less from the date of LMD diagnosis were included.

Associations between categorical variables were assessed using Chi-Square tests, or Fisher's Exact tests when expected cell sizes were low. Survival, defined as time from LMD diagnosis to death, was plotted with Kaplan Meier curves and differences in survival between levels of a single variable were assessed using log-rank tests; patients who were still alive at the time of last contact were censored. Variables with a log-rank p-value of $< 0.20$ were entered into a Cox Proportional Hazard regression analysis to be able to generate adjusted hazard ratios for survival. All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC). P values $< .05$ were considered significant.

## 3. Results

A total of 79 patients were included in our study. Gender distribution was 68% female and 32% male. Demographic breakdown by race included six African American patients, one Asian patient, three Hispanic/Latino patients, 68 white patients, and one patient with race not specified. Median age at cancer diagnosis was 53.4 years and at LMD diagnosis was 56.6 years. Median time from original cancer diagnosis to LMD diagnosis was 19 months. Median time of follow up from original cancer diagnosis was 25 months. There were 23 patients with isolated LMD and no brain metastasis and two patients had a primary CNS malignancy (i.e. glioblastoma).

The most common primary malignancies were: breast (32%), lung (29%), and melanoma (9%) (Table 1). Molecular subtypes of lung and breast cancer were analyzed for any correlation with seizure. EGFR ($p = 1.0$) and ALK status did not correlate with seizure incidence in the lung cancer group, nor did breast cancer subtype by hormone receptor status and HER2 ($p = .63$). In the lung cancer cohort, eight patients were tested for EGFR (one was positive, seven were negative) and five patients were tested for ALK (all were negative). In the breast cohort, six were triple negative, six were ER/PR+, HER2-, five were ER/PR-, HER2+, and three were ER/PR/HER2+. Sample sizes were too small to determine if molecular subtypes predicted seizure.

**Table 1**
Primary malignancy type and seizure incidence.

| Primary malignancy | Seizure | | |
|---|---|---|---|
| | No | Yes | Total |
| Breast | 20 | 5 | 25 |
| Lung | 20 | 3 | 23 |
| Melanoma | 4 | 3 | 7 |
| Lymphoma | 4 | 2 | 6 |
| Glioblastoma | 5 | 1 | 6 |
| Esophageal | 1 | 1 | 2 |
| CUP | 2 | 0 | 2 |
| Renal | 1 | 1 | 0 |
| Gastric | 1 | 0 | 1 |
| Ovary | 1 | 0 | 1 |
| Sarcoma | 1 | 0 | 1 |
| Submandibular Gland | 1 | 0 | 1 |
| Thyroid | 1 | 0 | 1 |
| Pre-B ALL | 0 | 1 | 1 |
| Total | 62 | 17 | 79 |

Legend: Overall P value $< .52$.

For non-brain primary patients, seizure prevalence in those with LMD alone vs those with LMD and parenchymal brain metastases did not significantly differ at 22% ($p = .96$). Of only 15 patients for whom seizure type was described in the notes, 53% of seizures were generalized and 47% of seizures were partial (including complex and simple partial seizures). Of those who seized, 67% were admitted for this at least once while only one patient required intubation (Fig. 1). For those treated with AEDs, the majority were treated with levetiracetam ($n = 20$) and the most common dose was 500 mg BID with a range of 500–3000 mg daily. This was followed by phenytoin ($n = 3$) with doses ranging from 200 to 400 mg daily. There was one patient each on diazepam (10 mg q8) and lorazepam (0.5 mg QHS).

Treatment for LMD included: systemic chemotherapy (10 patients), intrathecal (IT) chemotherapy (14 patients), both routes of chemotherapy (5 patients), radiation (42 patients), and best supportive care (8 patients) (Table 2). Types of IT chemotherapy included

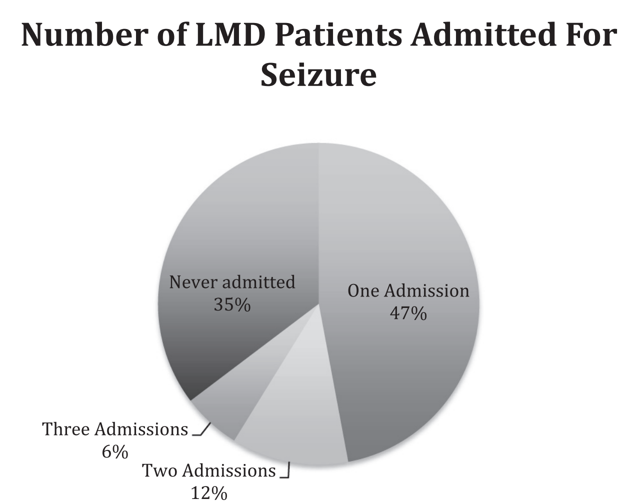


**Fig. 1.** Hospital Admissions of patients with LMD for seizures. Legend: Patient admissions specifically for seizure were counted for each patient, only patients who had seizures were included ($n = 17$). Percentage was calculated and displayed here.

**Table 2**
Treatment and tumor characteristics and seizures.

| | Seizure | | | P-value |
|---|---|---|---|---|
| | No | Yes | Total | |
| Radiation Type for LMD | | | | 0.98 |
| WBRT | 16 | 4 | 20 | |
| RT Focal | 10 | 2 | 12 | |
| CSRT | 8 | 2 | 10 | |
| None | 28 | 9 | 37 | |
| Chemotherapy modality for LMD | | | | 0.33 |
| IT Chemo Alone | 10 | 4 | 14 | |
| Systemic Chemo Alone | 7 | 3 | 10 | |
| Systemic + IT Chemo | 3 | 2 | 5 | |
| None | 42 | 8 | 50 | |
| Treatment involving surgery for Mets | | | | 0.71 |
| No | 53 | 14 | 67 | |
| Yes | 9 | 3 | 12 | |
| Number of brain metastasis/lesions | | | | 0.18 |
| 0 | 18 | 5 | 23 | |
| 1 | 4 | 4 | 8 | |
| 2–3 | 10 | 4 | 14 | |
| ≥4 | 28 | 4 | 32 | |

Legend: WBRT = Whole brain radiation therapy, RT Focal = Radiation therapy focal, CSRT = Craniospinal radiation, IT = Intrathecal.

trastuzumab, cytarabine, methotrexate, and topotecan or a combination of the above with methotrexate being the most popular. Primary malignancy, route (systemic vs IT) agent (for both systemic or IT) of chemotherapy, form of radiation therapy, surgery for brain metastases, and the number of brain metastases were not significantly associated with seizure development.

Location of LMD was also studied in regard to seizure prevalence. There was no significant difference based on LMD location (Table 3). There was a trend toward increased risk to seize in patients with cranial nerve and non-spinal LMD, but this did not meet significance (p = .06).

Only 13% of patients were on primary seizure prophylaxis. In patients who had brain metastases, the distribution of patients who never had a seizure, had seizures prior to their LMD diagnosis, or had seizures after their LMD diagnosis, did not differ between patients who were or were not on an AED at the time of LMD diagnosis (p = .14). Additionally, there was no significant difference in survival time between patients who did or did not seize (p = .68). Median survival time of patients after LMD diagnosis was four months with an IQR of two months to 13 months.

A multivariate analysis using gender, ECOG score, systemic chemotherapy and presence or absence of cerebral LMD revealed that while males trended toward inferior survival, only performance status and treatment with systemic chemotherapy showed a significant association with survival (Table 4).

**Table 3**
Location of LMD and Seizure.

| | Seizure | | p-value |
|---|---|---|---|
| Location | Yes | No | |
| Cerebellum | | | 1.00 |
| Yes | 3 | 10 | |
| No | 14 | 52 | |
| Cerebral | | | 0.10 |
| Yes | 6 | 10 | |
| No | 11 | 52 | |
| Diffuse | | | 0.10 |
| Yes | 1 | 17 | |
| No | 16 | 45 | |
| Spine | | | 0.06 |
| Yes | 1 | 18 | |
| No | 16 | 44 | |
| Cranial Nerves | | | 0.06 |
| Yes | 4 | 4 | |
| No | 13 | 58 | |
| CSF/Other | | | 1.00 |
| Yes | 2 | 7 | |
| No | 15 | 55 | |

Legend: Location of LMD and number patients with and without seizure. Location was determined by imaging and clinical notes.

**Table 4**
Multivariable analysis of prognostic factors of LMD.

| Variable | | Adjusted Hazard Ratio | 95% Hazard Ratio Confidence Interval | | P-value |
|---|---|---|---|---|---|
| Sex | | | | | 0.06 |
| | Female | 1.00 | Reference | | |
| | Male | 1.96 | 0.97 | 3.98 | |
| ECOG | | | | | 0.01 |
| | 0 | 1.00 | Reference | | |
| | 1 to 2 | 1.65 | 0.69 | 3.99 | |
| | > / = 3 | 5.80 | 1.73 | 19.51 | |
| | N/A | 0.75 | 0.26 | 2.15 | |
| Systemic Chemo | | | | | 0.04 |
| | Yes | 1.00 | Reference | | |
| | No | 2.30 | 1.03 | 5.15 | |
| Cerebral LMD | | | | | 0.12 |
| | No | 1.00 | Reference | | |
| | Yes | 0.53 | 0.23 | 1.19 | |

Legend: Variables were included which had a log-rank p-value of < 0.20. These were entered into a Cox Proportional Hazard regression analysis to be able to generate adjusted hazard ratios for survival.

## 4. Discussion

This study helps to further understand LMD and its relationship to seizures. The current literature supports a 20–40% seizure prevalence for patients with brain metastases–we found the prevalence of seizures to be 22% in patients with LMD both with and without concurrent brain metastases [4]. In patients with brain metastases or primary brain tumors, the development of LMD interestingly did not further increase seizure risk. Additionally, no factors predicted seizure in patients with LMD. No associations were found between seizure and primary malignancy, number of brain lesions, location of LMD, or treatment. When considering a role for primary AED prophylaxis, we could not identify a specific group in which this may be beneficial.

In our cohort, commensurate with the literature which does not support primary prophylaxis outside of the perioperative setting, most patients with LMD were not on primary AED prophylaxis at the time of their diagnosis of meningeal involvement [5–10]. Fifteen percent of patients with LMD who were not on an AED experienced seizure, just under the lower range of expected seizure in patients with brain metastases quoted earlier [4]. It is therefore not surprising that this study did not support a potential benefit for primary AED prophylaxis in LMD.

The location of LMD and its relationship to seizure development was analyzed. Several studies have looked at location of primary/metastatic brain tumors and their relationship to seizure development. Skardelly et al. studied 650 patients who underwent brain tumor surgery and looked at several clinical factors to try to predict preoperative and early postoperative seizures [17]. They found that frontal location of the lesion demonstrated an increased risk for preoperative seizures while diencephalic location was associated with increased risk of surgery-related seizures. Patzold & Haller studied a group of patients with slow growing gliomas with seizures as their only symptom, and all of these were also located in the frontal or centroparietal region [18]. Interestingly, we did not find an increased risk of seizure from LMD located over the cerebral hemispheres, although we did note a trend toward increased risk with both CN involvement and those with any non-spinal disease (p = .06). The fact that statistical significance was not reached could be due to underpowering; multi-institutional studies could help investigate this further.

In regard to prognostic factors for patients with LMD, females tended to have a longer survival although this was not statistically significant in our study (p = .06). Balm & Hammack did find female sex to be an independent positive predictor of survival, while several other studies did not confirm this [12,14–16]. The disease specific graded prognostic assessment (DS-GPA) for brain metastases clearly supports breast cancer patients have a superior survival over other primary malignancies after the development of brain metastases, due to the greater number of effective treatments available for these tumors, so it would not be surprising to see that female patients with breast cancer tend to live longer with LMD as well [19]. Surprisingly, in our sample, this was not the case. Primary malignancy type did not affect survival (p = .62), therefore, it was not included in our multivariate analysis. A separate gender analysis was performed, controlling for primary malignancy, with similar result. Therefore, the trend toward increased risk of death seen in men does not go away after controlling for primary malignancy group. More investigation is needed to determine if primary malignancy plays any role in the gender trend in overall survival for patients with LMD.

Building upon potential effects of gender on LMD, 68% of our patients were female. While in the breast cancer population female predominance is expected (24 F, 1 M), our lung cancer population surprisingly had a predominance of females as well (27 F, 6 M). As patients living longer with cancer are more likely to develop CNS involvement, this may be partly due to the significantly increased survival seen in women with lung cancer in comparison with men, irrespective of stage at diagnosis. This was noted in a population study of over 40,000 lung cancer cases ([20]). Interestingly, many studies of LMD denote percentage of males vs females overall, but not by cancer type. A large cooperative group LMD database would be helpful to ascertain these trends.

Similar to other studies, we found treatment with systemic chemotherapy was protective; controlling for other factors in the model (gender, cerebral LMD, and ECOG score), those who did not receive systemic therapy had more than double the risk of death (p = .04). Oechsle et al. also found that systemic chemotherapy was associated with improved survival. In the largest retrospective study of 155 LMD patients wherein 23% had primary brain tumors, Herrlinger et al. also found systemic chemotherapy to improve survival but only in patients with enhancing LMD on imaging, and only in patients with systemic primary tumors. The same study found that IT chemotherapy was also beneficial in primary systemic solid tumors.

Not surprisingly, performance status was a significant prognostic factor, (p = .007). Specifically, patients with an ECOG of three or higher had 5.80 times the risk of death than patients with an ECOG of zero. Most studies have found performance status to impact survival, [12,14,16] although in the study by Meng et al. it did not retain significance when evaluated in a multivariate analysis. Not surprisingly, our study found that those with better functional status were more likely to receive chemotherapy (p = .06).

Presence of cerebral LMD did not have significant prognostic value in our sample, whereas Balm & Hammack found it to be a negative predictor of survival. Unfortunately, seizure did not meet the requirement to be included in our multivariate analysis (the log-rank p-value was > 0.20).

Our mean survival time is slightly longer than that which is reported in most studies, four months versus two to three months in most of the literature, likely due to the large proportion of breast cancer patients in our patient population, and a more modern cohort [1]. This could also be due to a smaller proportion of our patients (10%) receiving only best supportive care (BSC) compared to the similar aforementioned studies wherein 13%–53% of patients received only BSC [13–16].

Our study does have several limitations, primarily as a retrospective study. We did not obtain CSF on most of those diagnosed with LMD on imaging. Our study is slightly smaller in patient number, but with a more modern and condensed time interval than similar retrospective LMD studies [13–16]. A large LMD database will better power studies such as this one, in this relatively rare disease. We are in the process of joining NeMeRe, a Multi-Institutional Retrospective and Prospective Registry of Neoplastic Meningitis in Adults, and hope to be able to further examine these questions—such as any correlation of seizures with cancer subtype– with a larger cohort available from this multi-institutional endeavor.

## 5. Conclusions

The prevalence of seizure in LMD patients is 22%, similar or less than the risk in patients with parenchymal brain metastases. Specific tumor and treatment characteristics did not correlate with the risk of developing seizures, nor did LMD location. Administration of systemic chemotherapy was associated with improved survival on multivariate analysis. There does not appear to be a benefit to any primary seizure prophylaxis in this population, although prospective large randomized studies would best address that question.

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## Conflict of interests

No conflict of interest for any authors.

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