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CLINICAL STUDY

Incidence of seizure in adult patients with intracranial metastatic disease

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Abstract Seizures have considerable impact on a patient's quality of life. While guidelines have been articulated to direct clinicians in their management of patients with IMD who suffer from seizure, there have been few attempts to identify the seizure rate in IMD and to determine which primary cancers may be associated with an increased seizure incidence. To determine the incidence of seizure in patients with IMD. A systematic review on seizure incidence in patients with IMD from the magnetic resonance imaging (MRI) era was performed. Articles published between January 2000 and July 2014 with thirty or more consecutive adult patients were included in this study. Seizure rate was calculated using a pooled data analysis. Differences between observed and expected seizure rates between primary tumour sites were examined using the Chi square statistic and adjusted standardized residuals. The systematic search produced 18 relevant studies, with a total study population of 2012 patients. 14.6% (n = 294) had seizures. There was a significant association between primary tumour site and seizure rates. The seizure rate in patients with primary melanoma tumours was significantly greater than expected ($z = 2.7$; $p = .006$). The seizure rate in patients with primary prostate tumours was significantly lower than expected ($z = -2.6$; $p = .008$). Patients with intracranial metastasis are at significant risk for developing seizure, though at a significantly lower incidence than was estimated by studies performed during the CT era. Seizure rates appear to be greater in certain primary tumours, such as melanoma.

Keywords Metastasis · Intracranial metastatic disease · Seizure · Magnetic resonance imaging · Incidence

Introduction

It is estimated that more twenty percent of patients with cancer will develop a brain metastasis during the course of their disease [1, 2]. Further, the incidence of intracranial metastatic disease (IMD) appears to be increasing, likely as a result of improved imaging techniques that aid in early diagnosis, and the rising use of effective systemic treatment regimens that do not penetrate the blood brain barrier [3–7]. Seizures appear in a significant proportion of patients with IMD, especially in patients who possess multiple metastases [8]. Of patients who do not have seizures as a presenting symptom, some will develop them during the course of the disease [9].

Seizure and the medications that are employed to treat them can present a significant burden for persons with brain tumors, through impairments in neurocognitive functioning, psychological well-being, and the ability to perform daily tasks. Unfortunately, the modern literature does not offer a good estimate of the risk of seizure in patients with IMD. In this study, we sought to characterize the seizure rate in patients with IMD, and to determine if primary cancer type is associated with seizure risk.

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Methods

Search strategy and selection criteria

We performed a systematic review to identify articles from the MRI era that reported seizure rates in patients with brain metastasis from all primary cancers. Articles used for this analysis were identified by searches of PubMed and Embase between January 1, 2000, and July 1, 2014, and references from relevant articles were searched. A Google Scholar search was used to supplement the results. The search terms *brain, metastasis, metastases*, and *seizure* were used. The search was restricted to articles in English. Articles were chosen for full review if the abstract or title reported seizure as a complication of brain metastases. The selected articles were then reviewed to confirm report of seizure rate in patients with brain metastases. Studies on adult patients were selected. Studies reporting data from less than 30 patients were excluded. Eighteen articles were selected for inclusion in the final analysis (Fig. 1).

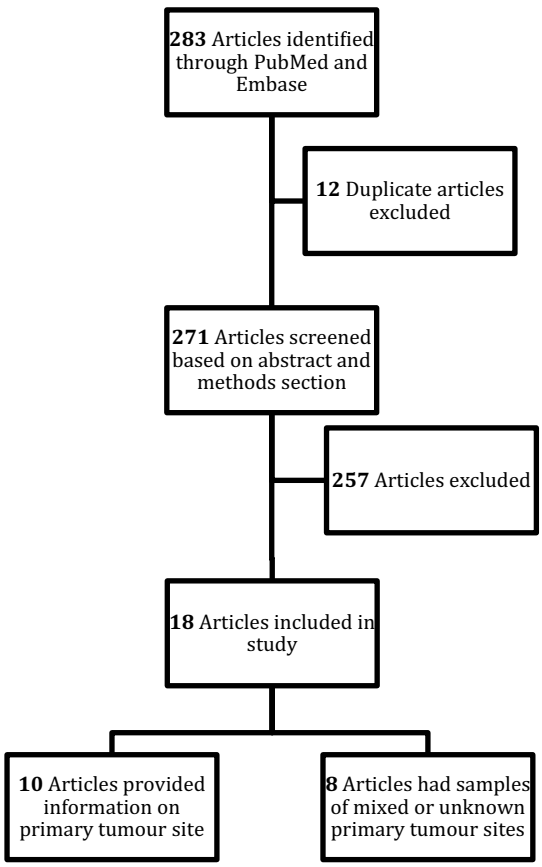

Fig. 1 Flowchart of workflow

Data extraction and analysis

The articles selected for the study were interrogated to identify adult patients with brain metastasis who developed seizure. The data was deconstructed to retrieve the following: patient age, primary cancer, number of patients with brain metastasis, and number of patients who developed seizures. Studies that provided information on the location of the primary tumours were analyzed using the Chi square statistic and adjusted standardized residuals. Cramer's V was calculated to determine the effect size of the Chi square statistic.

Results

Literature search

The systematic search produced 283 studies from which 12 duplicates were removed. The remaining 271 abstracts were screened for inclusion criteria, resulting in exclusion of 257 abstracts. The reference list of the remaining 14 studies were searched and a Google Scholar search was done to supplement the results. An additional 7 studies were added. The 21 full-text studies were examined, and 3 studies were excluded. We excluded two studies in which the brain metastases reported were meningeal carcinomatosis and leptomeningeal metastasis. In a third study, the study population was made up of patients who had been admitted to hospital because of tumor-associated neurological issues. This study was excluded due to a selection bias that we were concerned would artificially magnify the seizure rate.

The final number of studies included in the review was 18 (Fig. 1). Three were prospective studies and fifteen were retrospective studies. Only 10 of the 18 studies provided information on the identity of the primary tumours; only these ten studies were included in the Chi square.

Patient characteristics and incidence of primaries causing IMD

A total of 2012 patients with brain metastasis were identified for study (Table 1). The mean age of the cohort, calculated from 14 studies that provided this demographic information, was 54.4 ± 11.3. The M:F ratio 1.67:1 (1188:713), calculated from data accrued from 16 studies.

Among the 2012 patients included in the study, melanoma was the primary site in 635 (31.56%), lung in 630 (31.31%), genitourinary in 147 (7.31%), breast in 134 (6.66%), colorectal in 84 (4.18%), hepatocellular in 82

Table 1 Study population

	n	Recruitment period	Age	M:F	No. of patients	Primary tumor site	Seizure rate
Goldlust et al. [18]	109	May 2006–Oct 2008	60.5 (SD = 10.3)	72:37	109	Melanoma	36/109 (33.0%)
Miabi [26]	129	Jan 2002–Dec 2007	–	–	129	Mixed	25/129 (19.4%)
Lynam et al. [27]	35	Jan 2005–Dec 2005	71 (SD = 12.5)	20:15	35	Mixed	12/35 (34.3%)
Lee et al. [29]	258	Jan 2008–Dec 2009	59.7 (SD = 8.8)	159:99	258	Lung	32/258 (12.4%)
Srikanth et al. [30]	60	Not reported	–	39:21	60	Mixed	8/60 (13.3%)
Chang et al. [31]	45	Jan 1984–Dec 2000	46.5 (SD = 17)	40:5	45	Hepatocellular	3/45 (6.6%)
Cohen et al. [32]	72	Jan 1975–Apr 2001	50.4 (SD = 12.8)	0:72	72	Ovarian	11/72 (15.3%)
Zacest et al. [33]	147	Jan 1979–Mar 1999	33.2 (SD = 15.5)	101:46	147	Melanoma	20/147 (13.6%)
Tremont-Lukats et al. [16]	103	Jan 1944–Jul 1998	57.3 (SD = 11.5)	103:0	103	Prostate	5/103 (4.9%)
Jena et al. [34]	62	Jan 2003–Dec 2006	57.3 (SD = 11.5)	152:23	62	Lung	8/62 (12.9%)
Paek et al. [35]	208	Mar 1995–Dec 2002	57.8 (SD = 8.06)	103:105	208	Mixed	33/208 (15.8%)
Raizer et al. [36]	355	Jan 1991–Dec 2001	49.8 (SD = 12.7)	217:138	355	Melanoma	39/355 (11.0%)
Mongan et al. [28]	39	Jan 1984–Dec 2006	–	21:18	39	Colorectal	3/39 (7.7%)
Wong et al. [37]	129	Aug 2005–Oct 2007	62.8 (SD = 8.8)	54:75	129	Mixed	14/129 (10.9%)
Shahzadi et al. [38]	50	Jan 2001–Dec 2005	54.3 (SD = 8.5)	29:21	50	Mixed	6/50 (12.0%)
Pokryszko-Dragan et al. [39]	70	Jan 2002–Dec 2005	62.0 (SD = 8.3)	39:31	70	Mixed	21/70 (30%)
Hsiao et al. [40]	36	Jan 1993–Dec 2006	56.0 (SD = 11.6)	39:7	36	Hepatocellular	2/36 (5.5%)
Liigant et al. [41]	105	Jan 1991–Dec 1995		–	105	Mixed	16/105 (15.2%)

(4.08%), ovary in 79 (3.93%), and 72 (3.58%) categorized as others. The primary was unknown in 149 (7.41%) patients.

Seizure rate

294 of the 2012 (14.60%) patients identified had seizures.

The overall seizure rate of the subsample (n = 1226) in which a primary tumour site was reported was 13.0%. 95/161 (15.55%) patients with melanoma had seizures. 40/320 (12.50%) patients with lung cancer had seizure. 5/81 (6.17%) patients with hepatocellular carcinoma had seizure. 11/72 (15.28%) patients with ovarian cancer had seizure. 5/103 (4.85%) patients with prostate cancer had seizure. 3/39 (7.69%) patients with colorectal cancer had seizure.

Difference in seizure rates between different primary cancers

The Chi square analysis was performed to analyze seizure risk in patients with IMD from different primary cancers (Table 2). There was a significant association between primary tumour type and seizure rate ($\chi^2(5) = 14.30$, $p < .05$), though the effect size was small (Cramer's $V = 0.11$). The seizure rate in patients with primary melanoma tumours was significantly greater than expected ($z = 2.7$; $p = .006$), whereas the rate in the primary prostate tumour group was significantly lower than expected ($z = -2.6$; $p = .008$). The number of patients with primary hepatocellular tumours trended towards significance with lower seizure rates than expected ($z = -1.9$; $p = .06$). Seizure rates differed significantly between primary melanoma (combined count = 95), hepatocellular (5), and prostate (5) tumours; between primary lung (40) and prostate (5) tumours; and between prostate (5), lung (40), and ovarian (11) tumours. All other differences were not statistically significant.

Timing of the reporting of seizures

Of the 14 studies, 11 studies reported if the patient had seizures at the time of presentation or after the diagnosis of IMD was made. Among the 1603 patients in this subsample, seizures were reported in 236 patients. 184 of the 236 patients had seizures at the time of presentation, and 52 patients had seizures after the diagnosis of IMD (Table 3).

Table 2 Seizure risk by primary site

Primary tumor site	n	Seizure rate (%)
Melanoma	611	15.6
Ovarian	72	15.3
Lung	320	12.5
Colorectal	39	7.7
Hepatocellular	81	6.2
Prostate	103	4.9

Table 3 Timing of reporting of seizure

	n	Reported at presentation	Reported after diagnosis	Total patients with seizure
Goldlust et al. [18]	109	14	22	36
Miabi [26]	129	25	0	25
Lynam et al. [27]	35	7	5	12
Lee et al. [29]	258	9	23	32
Srikanth et al. [30]	60	8	0	8
Chang et al. [31]	45	1	2	3
Cohen et al. [32]	72	Unknown	Unknown	11
Zacest et al. [33]	147	20	0	20
Tremont-Lukats et al. [16]	103	5	0	5
Jena et al. [34]	62	8	0	8
Paek et al. [35]	208	Unknown	Unknown	33
Raizer et al. [26]	355	39	0	39
Mongan et al. [28]	39	3	0	3
Wong et al. [37]	129	Unknown	Unknown	14
Shahzadi et al. [38]	50	6	0	6
Pokryszko-Dragan et al. [39]	70	21	0	21
Hsiao et al. [40]	36	2	0	2
Liigant et al. [41]	105	16	0	16

Discussion

We performed a systematic review of available literature to determine the seizure rate among patients diagnosed with IMD during the MRI era. A total of 2012 patients from 18 studies were identified for study. Our findings suggest that patients with IMD demonstrate an appreciable seizure rate of 14.6%. There was a significant association between primary tumour type and seizure rates. The seizure rate in patients with primary melanoma was significantly greater than expected. Patients who have prostate cancer with metastatic intracranial disease had a seizure rate significantly lower than expected. Primary hepatocellular tumours trended towards a lower seizure rate than expected. The variability in seizure rates among different primary tumour sites may allow physicians to risk stratify seizure management to optimize the benefit of seizure prophylaxis while minimizing complications and adverse effects associated with prophylaxis.

In a recent prospective trial to determine if perioperative AEDs should be routinely administered to patients with brain tumors who have never had a seizure, Lang and colleagues randomized patients with brain tumors (metastases or gliomas) who did not have seizures and who were undergoing craniotomy for tumor resection to receive either phenytoin for 7 days after tumor resection (prophylaxis group) or no seizure prophylaxis (observation group) [10]. They found the incidence of clinically significant seizure following craniotomy for tumor in patients with no history of seizure to be remarkably low (3%), and likely as a result found no benefit to phenytoin prophylaxis in this population. Their study was motivated by previous reports in which the incidence of seizure in patients with a brain tumor had been estimated to be 30%, and they postulated that many physicians will continue to recommend seizure prophylaxis for patients with a brain tumor for this reason.

Our study suggests that the risk of seizure in patients with IMD is significantly lower than was estimated in historical studies involving this patient population. Seizure rates for patients with IMD had been reported to be 20–48% in studies before 2000. A study by Leroux et al. reported a seizure rate of 36% in patients with ovarian carcinoma as the primary neoplasm. This is considerably higher than the seizure rate for patients with primary ovarian carcinoma found in our study. This trend was also noted in patients with melanoma as the primary. A study by Byrne et al. reported a seizure rate of 48%. This discordance may be attributable to the heightened sensitivity of MRI, which has become the diagnostic modality of choice for IMD [11–17]. It is likely the case that diagnosis with IMD occurs at an earlier time point, resulting in a patient cohort in which the burden of intracranial disease is less, and in whom IMD has been discovered before the onset of significant neurological compromise or disability.

Our data also suggest a higher than expected risk of seizure in patients with IMD secondary to melanoma, compared to a lower than expected risk of seizure in patients with IMD secondary to prostate cancer. We

postulate that differences can be accounted for by differences in hemorrhagic potential, which has previously been shown to correlate with seizure risk [18], and site of metastatic involvement. Prostate cancer, for example, has been shown to only rarely metastasize to the brain parenchyma, and more typically involves the dura mater [19–21]; similarly, one would expect a lower seizure rate in cancer types with a predilection for metastasis to the posterior fossa, such as colorectal cancer [22].

In our study melanoma and lung cancer were the most common primaries reported, in accordance with epidemiologic data on IMD. The paucity of patients with breast cancer and colorectal cancer in our study cohort is surprising, and is likely a function of the selection criteria that we employed to identify patients for this study. In the seminal autopsy study of Posner and Chernik, lung cancer accounted for the most common primary tumor causing IMD, followed by breast cancer, melanoma, and colorectal cancer [23]. More recent studies would suggest that the epidemiology of IMD has remained relatively stable, despite changes related to early screening and changes in disease treatment [24, 25].

There are several limitations to our study. Not all of the studies we identified provided information on when the reported seizures occurred. These data, for example, did not allow us to determine if seizures occurred before patients underwent treatment of their IMD, or if these events occurred prior to placement of an AED. This information would be valuable to understand the risk of seizure throughout the clinical course of patients with IMD. In addition, most of the studies reported on presenting symptoms; therefore, a subgroup of patients who develop seizures later on in the course of their disease may be missed. In our study we could not calculate the risk of developing seizure after diagnosis, as most of the studies did not follow patients throughout their clinical course. Our approach to calculating the overall risk of seizure may also overestimate the risk of seizure in patients with IMD, as patients who have IMD but are asymptomatic would not be captured by the included studies.

Conclusion

Our study demonstrates a seizure rate of 14.6% in patients with IMD. While significantly lower than the reported incidence of seizure-risk from studies pre-dating the MRI era, our study finds that seizure remains a significant risk in patients with IMD.

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