

## Demographics aspects of brain and spine metastatic melanoma. Retrospective analysis in a single third-level center

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### ARTICLE INFO

#### Keywords:

Melanoma metastatic  
Central nervous system  
Brain melanoma metastasis  
Spine melanoma metastasis

### ABSTRACT

**Background:** Melanoma metastases to the CNS rank third in frequency, just after lung and breast metastases. There is controversy regarding the factors predisposing to developing CNS metastases in patients with cutaneous melanoma and their survival with conventional treatments.

**Methods:** We carried out a retrospective analysis in a third-level hospital in Mexico to determine epidemiological aspects of melanoma metastases to the central nervous system, factors related to its appearance, clinical presentation, and survival in three treatment groups: surgery, radiotherapy, and conservative management.

**Results:** We found that the nodular variant has the most significant association with CNS metastases. In addition, the superficial spreading variant has the highest risk of presenting a more substantial number of lesions, up to seven for each case and predominantly in the infratentorial space. On the other hand, we found more remarkable survival in patients treated only with surgery than those treated with radiotherapy or conservatively.

**Conclusions:** This study lays the foundations for future prospective survival analysis of the different current treatment modalities for metastatic melanoma in the brain and spine. It also highlights the clinical risk factors for metastatic brain and spine tumors of melanoma.

### 1. Introduction

Metastatic CNS tumors are the most frequent intracranial solid tumors. Approximately 9%–40% of patients with a solid tumor will develop metastases to the CNS, with survival ranging from three to 27 months, depending on the characteristics and behavior of the primary tumor. On the other hand, according to some reviews, melanoma represents 1.7% of all neoplasms in the body. Melanoma metastases to the CNS rank third in frequency, just after lung and breast metastases, and are also the ones with the worst prognosis, with just six months of survival after diagnosis.<sup>1–4</sup> Some studies have reported an incidence of metastasis to the CNS in patients diagnosed with melanoma of 10%–40%, with higher incidences of up to 90% in post-mortem studies, and in most cases, are multiple lesions that can affect one or more cerebral

lobes and, in a lower percentage of cases, unique circumscribed lesions.<sup>5–7</sup> There is controversy regarding the factors that predispose to developing CNS metastases in patients with cutaneous melanoma and their survival with conventional treatments. We carried out a retrospective analysis in a third-level hospital in Mexico to determine epidemiological aspects of melanoma metastases to the central nervous system, factors related to its appearance, clinical presentation, and survival in three treatment groups: surgery, radiotherapy, and conservative management, this being the first epidemiological study carried out in Mexico with these characteristics.

#### 1.1. Material and methods

A retrospective analysis was carried out in a tertiary-level hospital in

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<https://doi.org/10.1016/j.wnsx.2024.100306>

Received 27 May 2023; Received in revised form 5 October 2023; Accepted 21 February 2024

Available online 25 February 2024

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Mexico. One hundred twenty patients with the diagnosis confirmed by histopathology of malignant cutaneous melanoma with its different histopathological variants were selected. These patients were followed up for 20 years, from 2001 to 2021. Measures of central tendency were analyzed for the variables sex, age, location of metastasis, clinical presentation, and frequency measures for areas in the CNS and histological subtypes of melanomas. Imaging studies determined the most frequent metastasis sites in this follow-up period. Specifically for metastatic lesions to the CNS these were corroborated by simple and contrasted tomography studies or by simple and contrasted magnetic resonance.

The mean in months from the diagnosis of melanoma to the diagnosis of metastasis was determined, as well as the number of lesions and specific location in the CNS. On the other hand, the association was determined using the Chi-square statistical test to determine if there was a correlation between the primary sites of melanoma and its histological variants with the development of metastasis to the central nervous system and its location. In addition, the OR value of the histological subtypes was calculated to determine the risk of presenting lesions in a specific area within the CNS. An analysis of means was also performed with the ANOVA test of one factor to determine if any specific histopathological variant presented a more significant number of metastatic lesions.

Finally, we only included three treatment groups for Kaplan-Meier survival curves: surgical treatment, radiotherapy only, and conservative management. We excluded patients with any adjuvant therapy. We performed this analysis, getting four different results: overall survival, survival in patients treated with only radiotherapy, conservative treatment, and patients treated with only surgery.

## 1.2. Results

A total of 120 patients were analyzed, 53 men (44.2%) and 67 women (55.8%), with a mean age at diagnosis of cutaneous melanoma of 61 years (SD + -14.4 years). Of the 120 patients diagnosed with melanoma, 59 patients (49%) had some metastasis during their follow-up, which was a mean of 72 months (SD + - 65 months). Thirty men (56% of all men) and 29 women (43% of all women) presented some metastasis ( $p < 0.05$ ).

Metastases to the CNS occurred in 20% of the cases (12 men and 12 women), 15.8% in the brain, and 4.2% in the spine. The most frequent site of metastasis in the follow-up was lymph nodes at 30.8%, the lung at 20.8%, and in third place, the CNS at 20%. The rest of the metastasis frequencies are presented in Fig. 1.

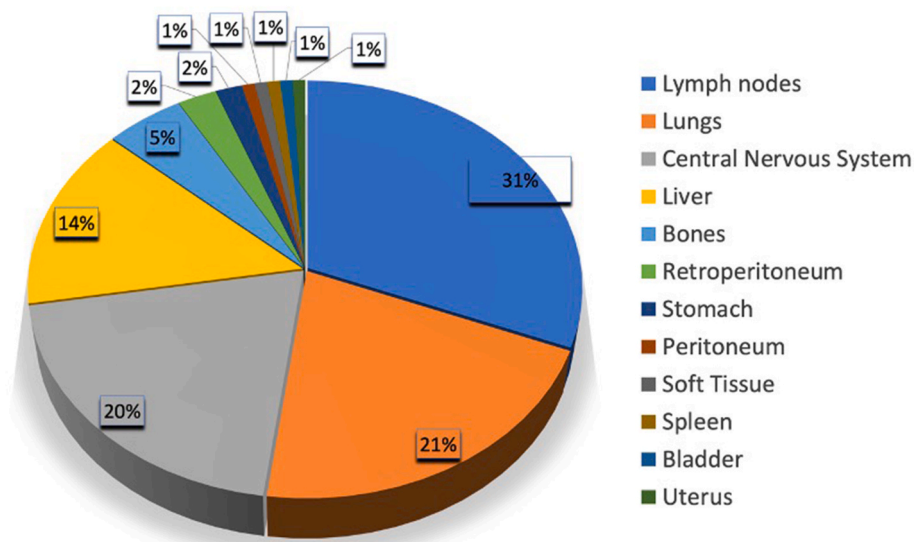


Fig. 1. Graph representing the locations of the most frequent metastases found in cutaneous melanomas during follow-up.

The mean time for metastases to occur from the diagnosis of primary melanoma to the diagnosis of metastases in the CNS group was 43 months. For lymph node metastases, it was 18 months, lung 26 months, liver 32 months, bone 63 months, stomach 32 months, and peritoneum and retroperitoneum 106 and 93 months, all with a  $p$ -value  $< 0.05$ .

Regarding the location by region of the primary melanoma site, it was obtained more frequently in the right foot, with 29 cases (24.2%), followed by the back with 17 patients (14.2%), and in third place, the left foot with 14 patients (11.7%). The rest of the frequencies by location are shown in Fig. 2.

Regarding the histological subtypes of melanomas and their frequency, we obtained that epithelioid, spindle cells and other subtypes melanomas represented 25.8% with 31 registered cases, followed by nodular melanoma with 24.2% of cases (29 cases), superficial spreading melanoma with 23.3% (28 patients), acral melanoma lentiginous with 22.5% (27 patients) and the least frequent, lentigo malign melanoma with 4.2% (5 patients).

The most frequent sites of involvement of metastases to the CNS were in the frontal lobe in 12 patients (50%), followed by the temporal lobe in seven (29.2%), occipital in five (20.8%), and cerebellum in four (16.7%), parietal in four (16.7%), subcortical and brain stem; thoracic spine and lumbosacral spine with three patients respectively (12.5%), frontoparietal in two patients (8.3%) and at the skull base in a single patient (4.2%), not obtaining a record of any case in the cervical spine.

The total number of metastatic lesions in the CNS recorded by imaging studies was 64 metastatic lesions. Of which 20 presented in the frontal lobe (31.2%), eight in the temporal lobe and cerebellum (12.5%), six in the occipital lobe (9.3%), five in the parietal lobe, thoracic and lumbosacral spine (7.8%), four in subcortical region and brain stem (6.2%), two in the frontoparietal area (3%) and only one in the skull base (1.5%).

The most frequent form of presentation in patients with metastases to the CNS system was pyramidal syndrome in 29%, followed by headache/pain in 25%, intracranial hypertension syndrome in 25%, seizures, and focal involvement in 16%, and cranial nerve involvement in 4%.

For the correlation analysis, we found a positive correlation between the location of the primary melanoma in the right foot and right leg. The left hand presents metastasis to the brain, right foot, and right eye with metastasis to the spine. Regarding the histological subtypes, a correlation was found between the nodular variant and metastatic lesions in the brain. The values of  $X^2$  and their respective  $p$ -values are represented in Tables 1 and 2, and the rest are in Fig. 3.

Eight (28%) lesions for the right foot presented metastasis to the

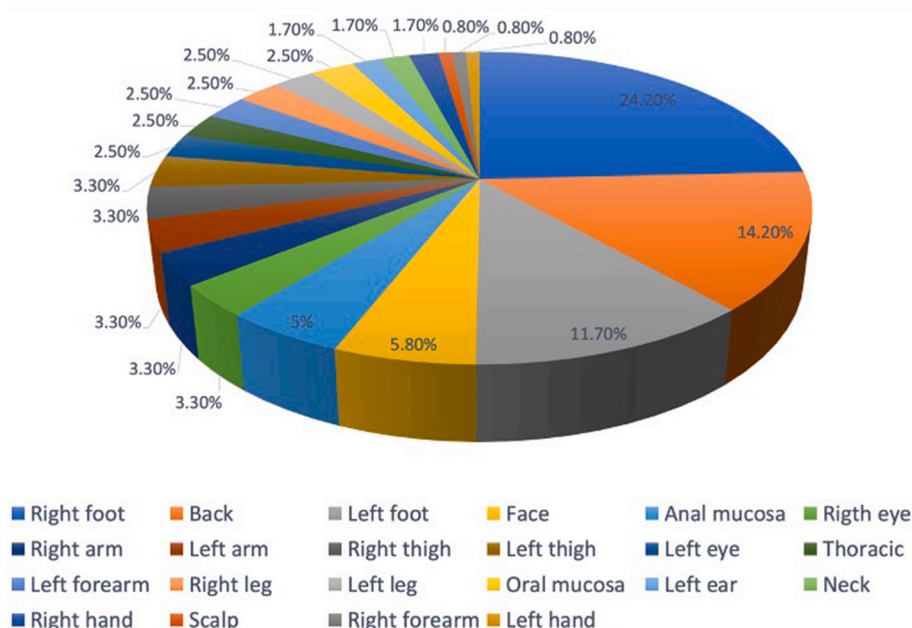


Fig. 2. Graph representing the most frequent sites of cutaneous melanomas on the body.

Table 1

Relationship of the primary site of the cutaneous melanoma with the appearance of metastases to the brain and spine. Chi-square values and their respective p-value.

Primary site of cutaneous melanoma	Chi square value for brain metastasis ( $\chi^2$ )	P Value	Chi square value for spine metastasis ( $\chi^2$ )	P Value
Right forearm	0.19	0.66	0.04	0.83
Left forearm	0.70	0.40	0.13	0.71
Back	0.04	0.82	0.14	0.70
Right leg	5.96	0.01*	0.13	0.71
Left leg	0.57	0.44	0.13	0.71
Right arm	0.77	0.37	0.18	0.67
Left arm	0.26	0.60	0.18	0.67
Right thigh	0.77	0.37	0.18	0.67
Left thigh	0.77	0.37	0.18	0.67
Right foot	3.96	0.04*	3.65	0.05*
Left foot	2.98	0.08	0.68	0.40
Right hand	0.38	0.53	0.08	0.76
Left hand	5.36	0.02*	0.04	0.83
Neck	0.38	0.53	0.08	0.76
Scalp	0.19	0.66	0.04	0.83
Face	0.01	0.90	0.32	0.57
Right eye	0.77	0.37	4.49	0.03*
Left eye	0.57	0.44	0.13	0.71
Anal mucosa	0.00	0.95	0.27	0.60
Oral mucosa	0.57	0.44	0.13	0.71
Thoracic	0.57	0.44	0.13	0.71
Right ear	No data	–	–	–
Left ear	1.78	0.18	0.08	0.76

\*Statistically significant value

brain, while three (10%) to the spine. In lesions on the back of seven primary melanomas in this location, three (18%) presented metastasis to the brain while only one (6%) to the spine. Of the seven lesions on the face, only one (14%) presented lesions to the brain. Of the six lesions in the anal mucosa, one (17%) showed brain lesions. Only one (25%) presented lesions towards the spine from the right eye of four lesions found. Regarding the left arm, of the four lesions, one (25%) presented metastasis to the brain; of the left forearm of three lesions, one (33.6%) presented lesions to the brain. Three lesions were found in the right leg, two of which (67%) showed brain metastasis. In the left ear of the lesions found, one (50%) presented lesions towards the brain, and finally, the

Table 2

Relationship of the main variants of malignant cutaneous melanoma with the appearance of metastasis to the brain and spine. Chi-square values and their respective p-value.

Histpatological Subtype	Chi square value for brain metastasis ( $\chi^2$ )	P Value	Chi square value for spine metastasis ( $\chi^2$ )	P Value
Superficial spreading melanoma	0.06	0.79	1.58	0.20
Nodular melanoma	6.63	0.01*	0.71	0.39
Lentiginous acral melanoma	0.02	0.86	1.51	0.21
Lentigo malignus melanoma	0.98	0.32	0.22	0.63
Others	2.76	0.09	3.17	0.075
Ulcerated	1.58	0.20	1.37	0.24

\*Statistically significant value

only lesion in the left hand showed brain metastasis.

Regarding the risk by histological subtype with presenting metastasis to a specific location within the central nervous system, we found that superficial extension melanomas have an OR of 19 (CI 1.1–314) of presenting lesions to the cerebellum. As well as showing lesions to the brain stem and subcortical region OR 40 (CI 1.7–914), both with p-value <0.05. No statistical significance or risk was found for the rest of the values.

Finally, the histological subtypes that correlate with the most significant number of lesions to the CNS were: for the superficial spreading variant, an average of seven lesions per patient (SD + - 2,  $p < 0.00$ ) was found; for the nodular variant, an average of two lesions per patient (SD + - 0.3,  $p = 0.07$ ) was found, which was below the overall standard of three lesions. For the lentiginous acral variant, an average of two lesions was also found for each case (SD + - 0.5,  $p = 0.44$ ). No patients were found for lentigo malignus that generated metastasis to the CNS, so no data were obtained for this variant. The mean number of lesions for other variants was three (SD + - 0.5,  $p = 0.94$ ). Finally, for the lesions that presented ulceration, the average number of metastatic lesions to the CNS was two lesions (SD of 0.5,  $p = 0.52$ ).

The mortality rate of patients with CNS metastatic lesions was 95%, with only one female survivor up to the time of the study who underwent

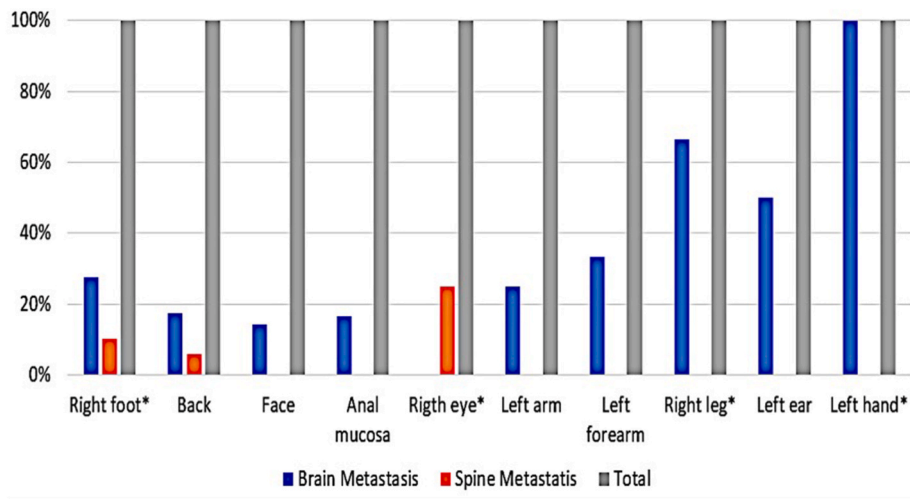


Fig. 3. Relationship of primary melanomas in the body with metastases in the brain and spine. \* Statistically significant value.

surgical treatment for a single left frontal lesion. For the survival analysis, the surviving patients and the patients with spinal involvement were eliminated. Therefore, this comparative analysis was only performed with 18 patients. Nine patients were treated with radiotherapy and four with surgery. The rest (four patients) were not candidates for any treatment of their own decision or clinical condition. The mean overall survival after diagnosis was 6.3 months (SD + -2.4). For the group treated with radiotherapy, it was lower, five months (SD + - 0.9), and for the group treated with surgery, it was 13 months (SD + - 11.3), while for the group treated conservatively, it was three months (SD + -0.8), all with p-value <0.05 (see Fig. 4).

2. Discussion

Although the literature has reported an apparent predisposition for the males in comparison with females in developing CNS metastases in patients with cutaneous melanoma in up to a 2:1 ratio, in our study, we did not find this association since in both groups, in males as in females, there was the same number of cases and the same distribution.<sup>8</sup> The presentation time of melanoma metastases to the CNS from the diagnosis has been reported as a mean of 3.5 years.<sup>9</sup> As we reported in our population, a mean of 3.5 years (43 months) was also found from the diagnosis of primary melanoma, which in all cases was identified. Regarding the location of metastases in the CNS, they have been reported more frequently in the supratentorial space in up to 90% and the

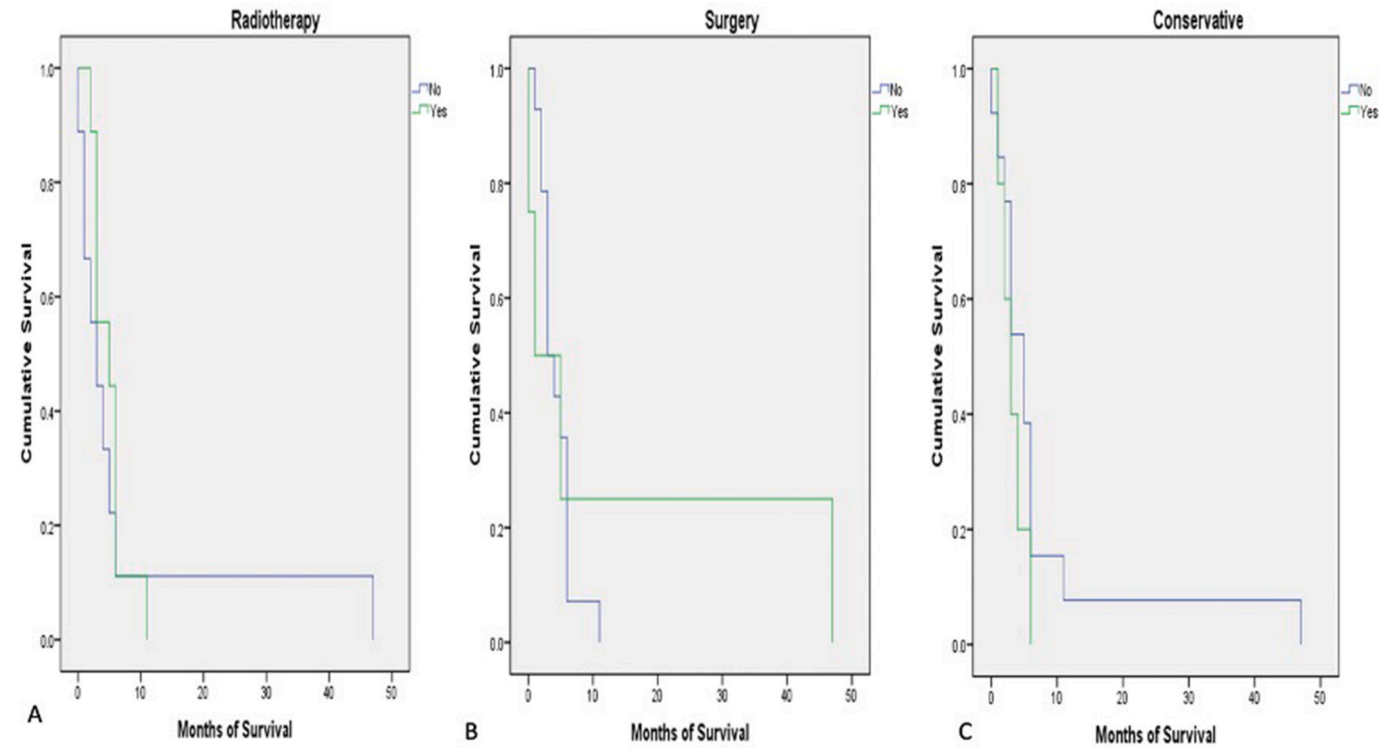


Fig. 4. Kaplan Meyer survival curves, in three management groups. A. Patients treated with radiotherapy. B. Patients treated with surgery. C. Patients managed conservatively.



infratentorial area in 10%.<sup>10–12</sup> Similar locations were reported in our study and our population where the cerebral hemispheres were the most frequently affected, with the frontal lobe being the one with the highest incidence by number of lesions and individual cases. We added the spine to these locations, where practically the places found were at the thoracolumbar level, without having reported any cases with involvement of the cervical spine.

The clinical presentation depends entirely on the site of the metastases, the total number of metastases, the edema of the lesions, the presence of a hemorrhagic event, or if they are associated with intracranial hypertension syndrome. It has been described that the motor deficit occurs more frequently, up to 93%. However, other reports mention that headache is the most frequent symptom in 50%–80%.<sup>10,13</sup> Data like these were found in our description, where motor disturbance and headache/pain were the most frequent forms of presentation, as well as intracranial hypertension syndrome.

Regarding the risk factors identified in previous studies for the incidence of metastases in the CNS, the following have been reported: males, primary lesion in the head or neck, high Breslow index, high serum DHL level, and ulceration of the primary lesion.<sup>14–16</sup> Contrary, we reported the location with the most significant association with metastases was in the right foot and right leg for lesions in the brain and the eye for metastatic lesions to the spine. Similarly, we did not find ulceration presented any risk in the linear regression analysis but a corresponding histopathological result with nodular melanoma. Damsky et al found that the superficial spreading variant had a higher risk of CNS metastasis, data that do not coincide with those reported in our population.<sup>17</sup> However, we found that the superficial spreading variant presented a higher risk of presenting more lesions in the CNS, with an average of up to seven lesions for each case and a clear risk of presenting lesions in the infratentorial space. Another study has reported that the locations with the highest risk of generating CNS metastases five years after diagnosis are those lesions found first on the scalp (12%) and second on the face or neck (6.7 %).<sup>12</sup> Data that do not coincide in our population, in which 28% of the patients with lesions in the right foot presented metastatic lesions to the CNS. This location presented the most significant association with metastatic lesions to the CNS.

In the rest of CNS metastases, the main cause of death in up to 90% of cases is extracranial disease (lack of control of the primary disease). This is not the case in melanoma metastases, where the lethality of metastases has been reported in up to 94.5%.<sup>17,18</sup> Similar to our report where we found a 95% lethality, the cause of death being directly related to CNS metastases and there being only one patient up to the follow-up date who was still alive after resection surgery of a single lesion. Overall survival for this type of metastasis has been described as ranging from 4 to 6 months, even being less, up to 3 months in those patients who are not treated and are only offered surveillance.<sup>19,20</sup> The treatment of metastatic melanoma to the CNS has been based on surgery, stereotactic surgery, radiotherapy, or chemotherapy. Survival after surgery was reported in 17 months according to some studies.<sup>21</sup> And although great advances have been made in current treatments and with the implementation of dual therapies, chemotherapy, immunotherapy, or combinations; current survival has been described from 5 to 9 months, very similar to our reported data.<sup>22</sup> According to Thompson et al, in their systematic review they found a difference of 6 months in survival in patients who were treated only with surgery versus those who were treated with radiotherapy alone (10 months versus 4 months respectively).<sup>23</sup> Like our findings where the median survival in patients treated with radiotherapy alone was 5 months and for patients treated with surgery was 13 months.

In the rest of CNS metastases, extracranial disease is the leading cause of death in up to 90% of cases (lack of primary tumor control). This is not the case in melanoma metastases, where the lethality of metastases has been reported in up to 94.5%.<sup>17,18</sup> Similar to our report, we found a 95% lethality, the cause of death being directly related to CNS metastases, and there being only one patient up to the follow-up

date who was still alive after resection surgery of a single lesion. Overall survival for this type of metastasis has been described as ranging from 4 to 6 months, even less, up to 3 months in those patients who are not treated and are only offered surveillance.<sup>19,20</sup> The treatment of metastatic melanoma in the CNS has been based on surgery, stereotactic surgery, radiotherapy, or chemotherapy. Survival after surgery was reported in 17 months, according to some studies.<sup>21</sup> Although significant advances have been made in current treatments and with the implementation of dual therapies, chemotherapy, immunotherapy, or combinations, survival has been described from 5 to 9 months, very similar to our reported data.<sup>22</sup> According to Thompson et al, their systematic review found a difference of 6 months in survival in patients treated only with surgery versus those treated with radiotherapy alone (10 months versus four months, respectively).<sup>23</sup> Like our findings, the median survival in patients treated with radiotherapy alone was five months, and for patients treated with surgery, it was 13 months for metastatic lesions to the CNS.

## 2.1. Conclusions

There are current controversies about the management of metastatic melanoma lesions in the CNS, as well as the factors associated with their development. In our study, we found that the only histopathological variant correlated with the appearance of metastatic lesions to the CNS was nodular, the histopathological variant with the highest risk of presenting a more significant number of lesions to the brain was the superficial spreading variant, data that has not been previously reported up to date in other studies. Regarding survival, there is a more remarkable overall survival in patients treated with surgery only than in patients treated with radiotherapy only or those who are managed conservatively. Our limitation is that this study is a retrospective analysis, uncontrolled, and has the bias of an observational study. Besides, we only analyzed one center Hispanic population, so these results should not be generalized to all communities. However, we laid the basis to enroll patients in a future clinical prospective study.

## Funding sources

This research did not receive any specific grants from funding agencies in the public, commercial, or nonprofit sectors.

## CRedit authorship contribution statement

**Daniel Alejandro Vega-Moreno:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Shunichiro Kuramitsu:** Methodology, Investigation. **Eguchi Kaoru:** Methodology, Investigation. **Kajita Yasukazu:** Project administration, Methodology, Formal analysis. **Ulises García-González:** Validation, Investigation. **Abraham Ibarra-de la Torre:** Validation, Investigation. **Liliana Hernández-Hernández:** Software, Resources, Investigation. **Rosa María Vicuña-González:** Visualization, Software, Resources. **Martha Elena González-Jiménez:** Validation, Supervision, Project administration.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

To Nagoya Medical Center, Japan, to the valuable support and to complete this project. To Central South Hospital, “PEMEX”, Mexico, due to the project administration. Special thanks to Professor Kajita Yasukazu for his kind support and attention.

## Abbreviations

CNS	Central nervous system
OR	Odds ratio
SD	Standard deviation

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