Supratentorial and infratentorial brain metastases: a single centre, retrospective cohort study

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Abstract

Purpose

15–30% of primary cancers metastasise to the brain. Of these, 10–25% involve the posterior fossa. It remains unclear whether patients undergoing resection for infratentorial brain metastases experience poorer prognosis than those with supratentorial lesions. We aim to compare the post-operative outcomes of these two groups.

Methods

We searched the electronic health records of all patients undergoing brain metastases resection at our regional neurosurgical centre between February 2014 and August 2019. Demographic and clinical data was collected on 85 patients (61 supratentorial, 24 infratentorial metastases). Outcome measures included survival, post-operative complications, and performance status. Patients were followed up until April 21st 2020.

Results

Median post-operative survival of patients with supratentorial metastases was 323 days (95% CI 235–411), compared to 277 days (95% CI 195–359) for those with infratentorial metastases. These two groups experienced comparable survival (log rank = 0.276, $p = 0.60$) in univariate analysis. Infratentorial metastasis location was not significantly prognostic of survival in multivariate analysis of six key clinical and demographic covariates (HR 1.51, 95% CI 0.780–2.92, $p = 0.22$). However, neurological and non-neurological post-operative complications were significantly more common in patients with infratentorial metastases (neurological = 21% v 13%, non-neurological = 25% v 2%, $p = 0.002$).

Conclusions

Infratentorial metastasis location alone was not associated with a significant change in survival in our patient cohort, but was linked to a higher incidence of post-operative complications. Prospective, multi-centre outcomes monitoring following brain metastasis resection is required to overcome the limitations of small sample size and evolving neurosurgical practices.

Declarations

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speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Availability of data and material: The datasets generated during and/or analysed during the current study are not publicly available because they consist of identifiable patient data.

Code availability: All authors ensured that all applications of software and custom code support their published claims and comply with field standards.

Authors' contributions:

MS – data analysis, manuscript preparation

SP – methodology, manuscript preparation

AVG – data collection, data analysis

JE – methodology, manuscript preparation

IL – methodology, manuscript preparation

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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Introduction

The brain is a site of metastasis in an estimated 15-30% of all primary cancers [1]. Approximately 10-25% of brain metastases (BM) involve the posterior fossa [2, 3]. Cerebellar lesions often present differently to supratentorial metastases, commonly with characteristic signs of headache, ataxia, and nausea/vomiting [4]. Additionally, these lesions can rapidly cause obstructive hydrocephalus, brainstem compression, and herniation with acute neurological decline [5]. As a result, previous research has called for infra- and supratentorial metastasis patients to be treated as separate cohorts [6].

While some studies have suggested that posterior fossa metastases are associated with poorer prognosis, the precise relationship between BM location and clinical outcomes remains unclear [4, 6]. The increasing incidence of brain metastases, related to improved neuroimaging and prolonged primary

tumour survival, reinforces the importance of understanding the prognostic value of BM location [7]. Analysing the outcomes of surgical intervention for brain metastases provides valuable clinical insight into possible factors that may aid in management decision-making.

The present study aims to compare the presentation, management, survival, and post-operative complications of patients who underwent surgical resection for supra- and infratentorial BM at a single institution between February 1st 2014 and August 31st 2019.

Methods And Materials

Patient selection

This study was performed under local audit approval. Data on all patients who underwent resection for brain metastases at a regional neurosurgical centre between February 2014 and August 2019 was collected. All patients were followed up until April 21st 2020. Electronic patient records (TrakCare®) were used to collect demographic and clinical data. 85 adult patients (age ≥ 18 years) were included, of which 24 had infratentorial metastases. Two patients from the original dataset were excluded due to obscure metastasis location (pituitary gland and cavernous sinus) that could not be reliably compared to the supra- or infratentorial regions.

Recorded variables

Information on patient characteristics (age, Karnofsky Performance Scale (KPS), comorbidities), clinical presentation, brain tumour size and location, location of primary cancer, surgical management and post-operative outcomes was collected. KPS was assessed by the neurosurgeon accepting the referral at diagnosis and after resection. Presenting symptoms and post-operative complications were categorised as none, neurological, non-neurological or both. Neurological symptoms included focal motor and sensory deficits, as well as other presenting complaints, such as seizures or headaches. Patients rarely presented with non-neurological symptoms. Information on extracranial disease activity and primary cancer pathology was obtained from electronic paper records. The extent of surgical resection (gross total or subtotal resection) was determined by post-operative magnetic resonance imaging (MRI). The primary end points were overall survival (OS), defined as survival since surgery for brain metastasis, post-operative complications and KPS. Additionally, the relationship between extracranial disease activity and OS was assessed.

Statistical analysis

Data analysis was conducted in SPSS (Version 24.0. Armonk, NY: IBM Corp). The log rank test was used for univariate survival analyses, which are visualised in Kaplan-Meier plots. A Cox proportional hazards model was used to assess the effects of individual variables on survival while controlling for certain covariates. Patients in these analyses were censored if they were alive at the date of last follow-up (21/04/2020). The chi-square and Fisher's exact tests were used to assess the significance of

relationships between categorical variables. Fisher's exact test was used in the presence of one cell in the contingency table with an expected frequency of <5. T-tests were used to assess the significance of differences in continuous variables across groups. The alpha level that defined statistical significance was set at 0.05.

Results

Descriptive statistics

85 patients were included. 54 (60%) were female and 31 (40%) were male, with a mean age of 60.5 (9.84) years at time of BM diagnosis. 61 (72%) patients were diagnosed with supratentorial metastasis, while 24 (28%) patients were diagnosed with infratentorial lesions. Supratentorial metastases were most often located in the frontal (n = 25, 41%), parietal (n = 13, 21%) or occipital lobe (n = 9, 15%). Of those with an infratentorial location, 23 (96%) metastases were found in the cerebellum and 1 (4%) was found at the cerebellopontine angle. The most commonly identified primaries were lung (n = 46), breast (n = 7) and colorectal (n = 6). The most common comorbidity was hypertension (n = 18, 21%) and 31 (36%) patients were either current or former smokers. 19 (22%) patients had no recorded comorbidities. For patients with necessary data available (n = 73, 86%), the median time from the BM diagnosing scan to surgery was 28 days (range = 0-893). 99% (n = 83/84) of patients survived longer than 30 days, 90% (n = 76/84) survived longer than 90 days and 77% (n = 65/84) survived longer than 120 days. No patients were censored prior to 120 days following surgery. Table I provides an overview of the patient data analysed in the present study.

Exploratory analyses

A chi-square test showed a significant relationship between sex and brain metastasis location, χ^2 (1, N = 85) = 4.68, p = 0.03, with infratentorial tumours presenting more commonly than expected in males. There was no significant association between surgical approach (gross total versus subtotal resection) and brain metastasis location, χ^2 (1, N = 85) = 0.578, p = 0.45. Adjuvant therapy use (none, SRT, or WBRT) was not related to region of brain metastasis, as evidenced by Fisher's exact test (p = 0.88).

Infratentorial location and OS

Necessary data for survival analysis was available for 99% (n = 84/85) of patients. By the end of the follow up period, 19/84 (23%) of patients were still alive and therefore censored. This censorship level was comparable between supratentorial (23%) and infratentorial (22%) patients. Supratentorial patients had mean OS of 575 days (95% CI 403-747), compared to 561 days (95% CI 270-853) for infratentorial metastases. The median OS was 323 days (95% CI 235-411) for supratentorial metastases and 277 days (95% CI 195-359) for infratentorial metastases. In univariate analysis, posterior fossa location was not associated with a significant change in overall survival (log rank test = 0.276, p = 0.60). A log rank test was used despite the crossing of the Kaplan-Meier survival curves. This is because any deviations from proportional hazards are believed to be a coincidence of random sampling, rather than evidence that

patients in one group were more likely to die early and patients in the other group were more likely to die late. This approach has been validated elsewhere [8]. The comparison of survival between supra- and infratentorial patients is shown in figure I.

Infratentorial location and post-operative complications

The most common neurological post-operative complication was a speech deficit (n = 3, 4%). Wound infection was the most common non-neurological post-operative complication (n = 4, 5%). A significant association between infratentorial location and post-operative deficits was found using Fisher's exact test (p = 0.002). Patients undergoing resection for supratentorial metastases experienced neurological deficits in 13% (n = 8/61) of cases and non-neurological complications 2% of the time (n = 1/61). This was in comparison to posterior fossa lesions, where neurological complications occurred in 21% (n = 5/24) of cases and non-neurological events occurred in 25% (n = 6/24). Supratentorial patients more frequently experienced no post-operative complications (82% v 54%).

Infratentorial location and KPS

KPS was assessed at time of BM diagnosis in 64 patients and post-operatively in 63 patients. At diagnosis, mean KPS was 87.8 (11.8) amongst supratentorial patients and 90.0 (8.45) for patients with infratentorial metastases. Following resection, supratentorial patients had a mean KPS of 86.1 (13.0), compared to infratentorial patients with 89.3 (16.4). Using two-tailed independent samples t-tests, posterior fossa location was not associated with a significant difference in KPS at diagnosis, $t(62) = 0.685$, p = 0.50, or after resection, $t(61) = 0.755$, p = 0.45. Among all 63 patients with a KPS assessment both at diagnosis and post-operatively, resection was not associated with a significant change in functional status, as per a two-tailed paired t-test (mean = -1.59, standard deviation = 8.65), $t(62) = -1.456$, p = 0.15. The decline was comparable between supra- and infratentorial patients, $t(61) = 0.077$, p = 0.94.

Infratentorial location, extracranial disease, and OS

No significant association was found between BM location and timing of presentation (synchronous or metachronous), as shown in a chi-square test, $\chi^2(1, N = 85) = 0.30$, p = 0.58. Further, there was no significant difference in the presence of extracranial disease activity between the two patient groups, $\chi^2(1, N = 84) = 0.27$, p = 0.61. Analysis of the survival distributions of patients with and without active extracranial disease (figure II) suggested there was no significant relationship between the two variables (log rank test = 1.221, p = 0.27). The log rank test was used despite the crossing of Kaplan-Meier survival curves for the reasons stated previously. Patients with and without extracranial disease varied with respect to size and censorship. 17/83 (20.5%) patients did not have any extracranial disease present, and of these, 11.8% were censored. In comparison, 17/66 (25.8%) patients with systemic disease were censored.

Multivariate analysis of survival

Multivariate analysis was conducted using a Cox proportional hazards model incorporating sex, age, extracranial disease activity (present or absent), adjuvant therapy use (none, SRT or WBRT), post-operative complications (none, neurological, non-neurological or both) and BM region (supratentorial or infratentorial). Pre- and post-operative Karnofsky Performance Scales were not included in the model due to a high level of missingness from our dataset (~25%). All included variables satisfied the proportional hazards assumption, as evaluated by the addition of time-dependent covariates to the model. Age was found to be independently prognostic of survival, HR 1.037 per year (95% CI 1.007-1.067, $p = 0.02$). Brain metastasis location was not found to be associated with survival, HR 1.51 (95% CI 0.780-2.92) for infratentorial lesions ($p = 0.22$). Similarly, extracranial disease activity did not have a significant prognostic effect on survival, HR 0.619 (95% CI 0.315-1.22) for those with extracranial disease activity present ($p = 0.17$).

Discussion

Our retrospective cohort study of 85 patients who underwent resection for either supra- or infratentorial BM found there to be no significant differences in their survival when compared using univariate and multivariate analyses. The median overall survival times found in the two groups (323 days for supratentorial, 277 days for infratentorial) are similar to those found in related studies [6, 9]. It is important to note that our cohort only included patients undergoing resection, meaning these findings of comparable survival depend on the selection of operative cases at our centre. This concept is well illustrated by a study of 708 patients, where cerebellar BM location was initially associated with poorer survival when all patients were included in analysis. However, amongst those having surgery, survival was comparable for patients with infra- and supratentorial metastases [6].

A Cox proportional hazards model incorporating six key demographic and clinical variables found no significant relationship between BM location and overall survival. While this multivariate analysis reduces the effects of certain potential confounders, others, such as KPS, contribute to a complex relationship between brain tumour location and overall survival. The statistical effects of some covariates can be partially mitigated by stratifying patients by recursive partitioning analysis (RPA) class, which combines assessment of age, KPS, extracranial metastasis and primary cancer control. This method was used in a previous study of 93 patients, which also found cerebellar metastases to have comparable survival after resection to supratentorial lesions [4]. These findings suggest that reports of poorer survival associated with infratentorial BM may at least in part be explained by worse pre-operative condition (KPS, primary tumour control, age and extracerebral metastases), rather than the intraoperative challenges faced in these cases. In contrast, a study matching patients in terms of adjuvant therapy use and KPS found posterior fossa location to be independently predictive of shorter survival [10].

Patients undergoing resection for infratentorial metastases were significantly more likely to experience either neurological or non-neurological post-operative complications than patients with supratentorial BM. Similar results have been replicated elsewhere [11]. These findings provide insight into the significant morbidity experienced by patients with posterior fossa metastases, which may not be apparent in survival

analyses. Many studies investigating the outcomes of patients with supra- and infratentorial BM focus entirely on survival, which may not provide an accurate representation of when surgery is safe and effective [12]. Given the finding of frequent post-operative complications following posterior fossa cases, prognostic scoring systems should arguably include BM location in order to provide accurate predictions of patients' quality-of-life after surgery.

No significant differences were found between the KPS assessments of supra- and infratentorial patients at BM diagnosis or after resection. These findings are supported by a similar study that reports comparable performance status between cerebellar and non-cerebellar cases [6]. Further, the effect of resection on KPS was found to be non-significant, as well as comparable between the two patients cohorts. At first glance, these results may seem surprising, but the findings are likely explained by the cohort's high mean KPS at diagnosis. A high degree of missingness in KPS data (~25%) makes the effects of selection bias unclear. While the differences in presentation of supra- and infratentorial lesions have been widely reported, comparable functional status between the groups suggests that the two diagnoses may impact quality-of-life to similar degrees [13, 14]. While the reliability of KPS to predict post-operative outcomes has been debated, a pre-operative KPS ≥ 70 has been associated with prolonged survival, and therefore the scale remains clinically relevant [4, 15-17].

There was no significant difference in the survival of patients with and without extracranial disease activity, both in univariate and multivariate analyses. These results were unexpected given the extensive literature associating poor prognosis with systemic disease activity [18, 19]. However, the two groups (extracranial disease absent v present) were significantly imbalanced with respect to size and censorship, making these conclusions challenging to interpret. The incorporation of systemic disease activity into patient classification systems, such as RPA, supports the consideration of this variable during surgical case selection.

Several possible explanations for the suspected negative prognostic effect of infratentorial BM location have been proposed. First, the presence of the medulla, pons, respiratory centres and fourth ventricle in the posterior fossa may make the region more vulnerable to mass effect. Second, the cranial anatomy of the region may amplify the effects of space-occupying lesions. Finally, differences between infra- and supratentorial regions in terms of cell type, cell composition, and blood supply may contribute to possible variation in post-operative outcomes. Cerebellar location has also been associated with poorer survival in other pathologies, such as gliomas, trauma, and intracranial haemorrhage, which may reflect the clinical implications of these three factors [6].

It is well-supported that some primary cancers, such as lung, breast, and melanoma, are more likely to metastasise to the brain, and there is clinical suspicion that certain primaries may preferentially spread to the posterior fossa [20]. The present cohort is not large enough for robust analysis relating to this question, but a disproportionately high incidence of posterior fossa metastases has been reported in the presence of pelvic and gastrointestinal primaries [21]. These results present the possibility of predicting metastasis to different brain regions based on a patient's primary cancer. The use of prophylactic cranial

irradiation in patients diagnosed with small-cell lung cancer reflects the clinical value of early identification of patients at greatest risk of brain metastasis [22]. The precision of these interventions would be improved if the region of metastasis within the brain could be predicted with confidence.

Amongst patients with BM, surgery is generally indicated in the presence of a single large, symptomatic tumour exerting significant mass effect and/or obstructive hydrocephalus. Patients are often required to have good performance status (e.g. KPS >70) and well-controlled or absent systemic disease. The National Institute for Health and Care Excellence (NICE) guidelines recommend surgical intervention for the rapid control of symptoms and to obtain an up-to-date pathological diagnosis to guide future treatment [23]. Surgery is often combined with focal radiation in these patients. In contrast, stereotactic radiosurgery alone is recommended for patients with multiple small metastatic lesions. Whole brain radiotherapy is usually reserved for patients with good performance status, but who are ineligible for SRS and surgery due to a high number of metastases or multiple bulky lesions. Finally, care for patients with poor performance status should be individualised with respect to patient preferences, potentially involving WBRT, SRS and supportive measures [24].

Multi-centre, prospective cohort studies are needed to better understand the factors that may be associated with survival and post-operative complications following brain metastasis resection. A collaborative approach towards outcomes monitoring in surgical practice helps curb the limitations of small sample sizes accessible to individual institutions, while also reducing the requirement for long study periods. This would enable cohort studies to analyse patient outcomes from a shorter time window, reducing the effects of evolving surgical and medical practice. Findings from such research may inform future surgical case selection and accelerate the adoption of evidence-based protocols. More generally, an improved understanding of the post-operative outcomes of patients with infratentorial metastases will provide insight into the true improvements in quality-of-life to be gained from surgical intervention.

Conclusion

This retrospective cohort study of 85 patients undergoing resection for brain metastases reports no significant difference in the overall survival of patients with supratentorial and infratentorial lesions. However, posterior fossa location was associated with a significant rise in the incidence of neurological and non-neurological post-operative complications, likely as a result of the operative challenges faced in these cases. The uncertain association between posterior fossa location of metastasis and poor prognosis warrants further multi-centre, prospective study of possible prognostic factors for patients undergoing resection. This has the potential to provide valuable clinical insight into the precise indications for safe and effective surgical intervention amongst patients with infratentorial metastases.

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Table

Due to technical limitations, Table 1 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Kaplan-Meier survival curve for patients undergoing resection for supratentorial versus infratentorial metastases (log rank test = 0.276, $p = 0.60$)

Figure 2

Kaplan-Meier survival curve for patients with active extracranial disease versus those without active extracranial disease (log rank test = 1.221, $p = 0.27$)

Supplementary Files

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- [Table1.docx](#)