Management Evaluation of Metastasis in the Brain (MEMBRAIN) – A United Kingdom & Ireland prospective, multicenter observational study

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Abstract

Background: Over the recent years an increasing number of patients with cerebral metastasis (CM) are being referred to the neuro-oncology multi-disciplinary team (NMDT). Our aim was to obtain a national picture of CM referrals, to assess referral volume and quality and factors affecting NMDT decision-making.

Methods: Prospective multicenter cohort study including all adult patients referred to NMDT with ≥1CM. Data was collected in neurosurgical units from 11/2017 to 02/2018. Demographics, primary disease, Karnofsky Performance Status (KPS), imaging and treatment recommendation were entered into an online database.

Results: 1048 patients were analyzed from 24 neurosurgical units. Median age was 65[range 21-93] years with a median number of 3[range 1-17] referrals per NMDT. The most common primary malignancies were lung (36.5%, n=383), breast (18.4%, n=193) and melanoma (12.0%, n=126). 51.6% (n=541) of the referrals were for solitary metastasis, and resulted in specialist intervention being offered in 67.5% (n=365). 38.2% (n=186) of patients being referred with multiple CMs were offered specialist treatment. NMDT decision-making was associated with number of CMs, age, KPS, primary disease status and extent of extracranial disease (univariate logistic regression, $p<0.0001$) as well as sentinel location and tumor histology ($p<0.05$). A delay in reaching an NMDT decision was identified in 18.6% (n=195).

Conclusions: This study demonstrates a changing landscape of metastasis management in the UK and Ireland, including a trend away from adjuvant whole brain radiotherapy and specialist intervention being offered to a significant proportion of patients with multiple CMs. Poor quality or incomplete referrals cause delay in NMDT decision-making.

Keywords: brain tumor; BNTRC; metastasis; multi-disciplinary team

Introduction

The National Institute of Health and Care Excellence (NICE)[1] Improving Outcomes Guidance (IOG) for brain and central nervous system (CNS) tumours of 2006 recommended that management of all patients with brain tumours should be guided by a neuro-oncology multi-disciplinary team (NMDT) to ensure consensus opinion on patient care is reached.[2] Since cerebral metastasis (CM) referrals to the weekly NMDT originate from a variety of sources, including the local Emergency Department (ED), District General Hospital (DGH), Oncologists or General Practitioners (GPs) and NMDT members have not seen these patients a priori, the provided referral information can be incomplete,[3] potentially instigating a treatment delay while further clinical information is gathered and NMDT decision awaited.

The initial design and set-up of the NMDT was aimed at patients requiring specialist intervention, and therefore commonly limited to a small group of patients presenting with a single metastasis and good prognosis from their systemic cancer.[2] Over the recent years there has been a rise in the incidence of CMs encountered in clinical practice due to improved diagnostic imaging techniques, a global increase in the incidence of primary cancer and improved systemic treatments and overall survival.[4-6] As a result, there are increasing numbers of patients being referred to the NMDT with CM, some of whom may be suitable for treatment and others who will not benefit and thus are not appropriate for any intervention due to advanced disseminated disease.

The rationale for active intervention in CM was based upon studies from the late 1990s showing a survival advantage and/or decrease from neurologic death conferred by a combined approach of neurosurgery or stereotactic radiosurgery (SRS) with adjuvant whole-brain radiotherapy (WBRT) in patients with oligometastatic disease.[7-10] A widely adopted prognostic scoring system used age, performance status, systemic disease burden and presence of extracranial metastases to stratify patients into three recursive partitioning analysis (RPA) classes with significantly different survival which was subsequently validated in various populations.[7] More recent prognostic scoring systems have included the type of primary cancer and identified that the survival of patients with CMs varies significantly by diagnosis.[11] For each type of primary tumor, a disease-specific graded prognostic assessment (ds-GPA) score was derived to estimate survival.[11-14]

However, there have been several recent changes in practice amongst specialists entailing a much more individualized approach in treatment decisions: Firstly, there is a move away from using WBRT, and SRS is now being favored for multiple metastases as well as being used as treatment to the surgical cavity after resection.[15,16] Secondly, immunotherapy and targeted chemotherapy, such as checkpoint inhibitors, proto-oncogene BRAF V600E antibodies, or Anaplastic Lymphoma Kinase (ALK) inhibitors, have revolutionized the management of CMs from certain cancers such as melanoma and lung cancer.[17,18]

While NICE guidelines in 2006 recommended referral to the NMDT only for cases in which either patients presented with solitary metastasis in good performance status with a prognosis warranting neurosurgical intervention or in cases where a referral was mandated in order to establish a diagnosis,[2] the newly published NICE guidelines from 2018 recommend referral for all CMs.[19] Equally, treatment recommendations have been updated: whilst formerly complete surgical removal of the solitary metastasis followed by postoperative WBRT was considered the mainstay of treatment, the new guidelines suggest a more complex approach, recommending: 1.) Surgery or SRS for solitary metastases with adjuvant SRS to surgical cavity in patients with one to three metastases, without adjuvant WBRT; 2.) SRS/radiotherapy for patients with multiple metastases; 3.) WBRT only for patients who have not received surgery or SRS and who do not have non-small cell lung cancer.[19]

The aim of this study was to draw up a national picture of CM referrals and to assess whether decision-making matches the changing landscape of metastasis management both worldwide, and in light of the newly reformed NICE guidelines.[20]

Furthermore, observational studies of CMs have been primarily of a retrospective nature and prospective studies have been restricted to a single centre.[3,5,7,11] These limitations lead to inherent biases in practice and patient selection and may not reflect the current national practice in order to generate health economic models and allow future resource planning.[21] Using prospectively collected data from multiple neuro-surgical units (NSUs), we aimed to assess the volume of CM referrals to the NMDT, the quality of referral information provided and its impact on NMDT decision-making. Thereby, the data presented in this study can be used as a baseline against which any future multicenter randomized controlled trials (RCTs) can be designed and adequately powered.

Materials and Methods

Study design

A prospective multicenter observational study of CM management was conducted across 24 NSUs in the United Kingdom and Ireland. Primary data collection took place over 4 months between November 2017 and February 2018 after an initial trial period at one center from September 2017 to October 2017 (see supplementary Figures 1-3 for information on monthly recruitment and center participation, respectively). All adult patients (≥18 years of age) referred to the NMDT with CM were included in the study. The NMDT was composed of a variety of team members including but not limited to: Consultant Neurosurgeon, Neurologist, Neuro-Radiologist, Neuro-Oncologist, Neuropathologist; Neuro-Oncology Clinical Nurse Specialists; Occupational and Speech and Language Therapists, Physiotherapists, coordinators and a Neuro-Psychologist, where available. The study protocol was designed by the British Neurosurgical Trainee Research Collaborative (BNTRC)[22] and approved by the Society of British Neurological Surgeons (SBNS) Academic Committee. The manuscript was written following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[23]

Data collection and outcome measures

Anonymized data were entered into Castor Electronic Data Capture (EDC), which is a secure online database, complying with the Department of Health Information Governance policy and meeting the data security standards of the Information Governance Toolkit of the Health and Social Care Information Centre. The audit and clinical governance committee of each participating hospital approved the study protocol.

The following demographic and operative parameters were captured in the electronic Case Report Form (eCRF): age, gender, date of NMDT, presenting symptoms, Karnofsky (KPS) and Eastern Cooperative Oncology Group (ECOG)[24] performance status, status/location/diagnosis of primary disease, treatment of primary disease, presence of extracranial metastasis, positive/negative molecular markers of primary tumor, status of extracranial disease (local vs metastatic, controlled vs uncontrolled), cranial imaging undertaken, number/size/location of cranial metastases, delay of NMDT decision, treatment recommendation ("specialist" interventions as recommended by a dedicated Neuro-Oncology center (Neuro-Oncologist, Neurosurgeon) located in a large tertiary referral unit: surgical resection, cerebrospinal fluid (CSF) diversion, SRS, cavity SRS; "non-specialist" treatment as provided by a General Oncologist: chemotherapy, immunotherapy, WBRT, local fractionated radiotherapy, best supportive care, other) and previous treatment of CM. RPA[7] and ds-GPA[11] was calculated for all referred cases, providing the required information was completed.

Statistical analysis

Descriptive statistics were used to characterize the patient population. Statistical analysis was performed using GraphPad Prism V7 and Stata/IC v.15.1 statistical package. Chi-squared test was used to assess the statistical significance of observed differences between cohorts undergoing specialist or non-specialist treatment. Univariate logistic regression was used to explore the relationship between primary outcome (Specialist vs. Non-specialist treatment) and a set of predictors. Differences in the primary outcome (Specialist vs. Non-specialist treatment) between RPA classes I-III were represented with bar plots and analyzed with a Chi-squared test for trend.

Results

Patient demographics, performance status, presenting symptoms

In total 1048 patients were analyzed (Table1) and 55.5% (n=582) were female. Median age at referral was 65 years [range 21-93 years] and the median number of referrals per weekly NMDT was 3 [range 1-17]. The most common presenting symptoms were motor deficit (30.1%, n=315), headache (24.1%, n=253) and confusion (17.9%, n=188). 6.8% of patients (n=71) in our cohort presented with symptoms of raised intracranial pressure (ICP) and in 3.0% of cases (n=31) CMs were found incidentally. KPS was ≥70 in 54.8% (n=564), <70 in 18.3% (n=193) and not provided in 24.3% (n=255).

Pre-treatment characteristics: Primary Cancer

681 patients (65.0%) had a known primary diagnosis of cancer. The most common primary tumor locations were lung (36.5%, n=383), breast (18.4%, n=193) and melanoma (12.0%, n=126) (Table 2). In 5.2% (n=54) there was no extracranial disease. The primary tumor was controlled in 33.5% (n=351), not controlled in 22.0% (n=231) and this information was not

provided in 39.3% (n=412). 44.6% (n=467) of patients had extracranial metastases. The time interval between diagnosis of primary tumor and CM was ≤2 years in 33.7% (n=353) and unknown/not recorded in 43.5% (n=456). The status of markers of sensitivity to targeted chemotherapy in the primary cancer was unknown/not recorded in 71.3% of patients (n=747).

Pre-treatment characteristics: Cerebral Metastasis

51.6% (n=541) of patients were referred with a solitary CM. 31.0% (n=325) had two to four metastases (two metastases: 18.2% (n=191); three metastases: 8.9% (n=93); four metastases: 3.9% (n=41)) and 15.4% (n=162) had five or more metastases (Table 3). Out of all patients referred, 14.7% (n=154) had undergone previous surgery for removal of CM and were referred back to the NMDT for discussion of recurrent disease.

The most common sentinel locations of CM were the frontal lobe (38.7%, n=406), the cerebellum (19.4%, n=203) and the parietal lobe (14.6%, n=153). 83.3% (n=873) of patients underwent Magnetic Resonance Imaging (MRI) and 60.6% (n=635) of patients had a Computer Tomography (CT) scan of the head prior to NMDT referral. Gadolinium contrast was administered in n=836 (95.8% of MRI scans). In cases where MRI was not undertaken the most common reason given was that the scan was indicated but not performed before the NMDT (52.0%, n=91), followed by the second most common reason being that the referring team did not have a clinical indication to perform a MRI scan (27.4%, n=48).

Treatment recommendation

Specialist intervention (either SRS or surgical resection) was recommended in 52.6% (n=551) of patients (Table 4). Specialist intervention was recommended in 67.5% (n=365) of patients with a solitary metastasis, and in 38.2% (n=186) of patients with multiple CMs. In particular, 48.6% (n=158) of patients with two to four metastases and 17.3% (n=28) of patients with five or more metastases were offered specialist intervention. The most commonly offered intervention was SRS alone (20.8%, n=218), followed by surgical resection alone (18.7%, n=196). A combination of (cavity) SRS and surgical resection was offered to 5.7% (n=60). A combination of surgery or SRS with radiotherapy (WBRT or local fractionated radiotherapy) was offered to 1.7% (n=18) and 0.5% (n=5), respectively. Other surgical treatments offered to patients included a biopsy in 1.0% (n=11), out of which two were for cancer of unknown primary (CUP) and five for newly diagnosed patients, and a form of CSF diversion in 0.9% (n=9).

In 42.7% (n=447) of patients, NMDT decision was to recommend non-specialist treatment either in the form of active oncology treatment (chemotherapy 1.7% (n=18), immunotherapy 0.8% (n=8) or local fractionated radiotherapy 1.5% (n=16)) or palliative treatment (WBRT 11.0% (n=115), best supportive care 17.2% (n=180)).

In 18.6% (n=195) of patients there was a delay in the NMDT treatment recommendation given (median time to decision-making after initial discussion in MDT was 11 ± 112 days) due to lack of imaging (52.3%, n=102), missing referral information (27.2%, n=53) or waiting for further investigations/results (13.8%, n=27).

Factors influencing NMDT decision-making

Using univariate logistic regression we explored the relationship between the primary outcome (Specialist vs Non-specialist treatment recommendation) and independent predictors. We identified number of CM, age, KPS, primary disease status and extracranial disease as factors associated with the NMDT decision-making (Table 5, $p<0.0001$). Location of sentinel metastasis and histology of the primary tumor also showed a statistically significant association with NMDT decision-making ($p=0.047$ and $p=0.009$, respectively). Factors that were not found to be associated with decision-making were time interval to diagnosis, size of sentinel metastasis, prior brain surgery, pre-operative neurological deficit, headache and delay in NMDT decision ($p>0.05$).

Recursive tree

With regards to RPA classes,[7] only a small proportion of patients within our cohort were allocated to Class I (n = 84, Figure 1a). The majority of patients were either class II (n = 281) or class III (n = 190). RPA class I patients were managed surgically in the majority of cases (80.0%, n=68), class II was managed either surgically (63.7%, n=179) or non-surgically (36.3%, n=102; out of which WBRT was recommended in n=43 and best supportive care in n=30) and class III was managed non-surgically in the majority of cases (66.8%, n=127; out of which WBRT was recommended in n=25 and best supportive care in n=83).There was a statistically significant difference in surgical vs. non-surgical treatment between those three classes (Chi^2_{trend} $p<0.0001$; Figure 1a and supplementary Figure 4).

Validation of ds-GPA

We applied ds-GPA classification for lung, melanoma, breast, renal and gastrointestinal (GI) tract cancers (Figure 1b). Overall, the proportion of recommendation for specialist treatment tended to be higher in patients with a high ds-GPA score and therefore longer expected median survival as compared to patients with a low ds-GPA score but these differences were not statistically significant with our data. It is noteworthy that due to incomplete referrals, lacking KPS, molecular profile and patient age there was a loss in numbers of patients, which was particularly evident in the breast and melanoma cancer group but also in GI cancers where KPS was the only prognostic factor for median survival within this particular classification.

Discussion

Pattern of CM referrals

There have been three large RCTs investigating the role of surgical resection in the treatment of solitary CM,[9,10,25,26] comparing surgical resection followed by radiotherapy versus radiotherapy alone. Two out of three RCTs found a statistically significant longer median survival and better quality of life in the surgical resection group. Two other large RCTs looked at the effect of SRS in combination with WBRT[15,27] in the management of single or multiple CMs and found that a combination of the two treatment modalities may show improved neurological function and intracranial tumor control, however does not show improved median survival. These findings were confirmed by a meta-analysis of 27 RCTs.[28] Current NMDT management is based on a combination of these studies with the evolving literature. While WBRT has been the mainstay of treatment for decades, it has recently fallen out of favor due to its association with neurocognitive decline.[16] Newer studies propose the use of SRS for multiple metastases and cavity SRS after surgical metastasis removal.[15,16] Additionally, advances in immunotherapy and targeted chemotherapy treatments offer alternatives to patients with a favorable mutation profile in melanoma and lung cancer.[17,18]

In our cohort, 51.6% of patients were referred for treatment of a solitary metastasis. Within the subgroup of patients with multiple metastases, patients with two metastases were most commonly referred (18.2% of total) followed by patients with five or more CMs (15.5% of total). The change in practice reflects the fact that 38.2% (n=186) of the patients referred with multiple metastases were recommended specialist intervention, as compared to ~10% of patients in a single-center series of 1640 patients from 2013-2015.[27] While treatment recommendation was limited to single CM in the former NICE guidelines of 2006, the newer NICE guidelines of 2018 give some recommendations regarding multiple metastases management, however lacking any recommendation about surgical resection. Therefore offering an intervention (surgery or SRS) in patients with multiple metastases remains entirely at the discretion of the NMDT and the treating surgeon or oncologist. In our cohort specialist treatment was recommended in 38.2% of patients with multiple metastases suggesting evolving management strategies,[28] even before the publication of the 2018 NICE guidelines.

There have been some recent studies confirming an increase in the use of SRS alone for many patients with multiple CMs as a strategy to gain local control while minimizing cognitive effects associated with WBRT.[30] While the benefit of surgical management of multiple CMs is currently lacking class I evidence, there are indications that surgery in these patients may be safe and beneficial to achieve intracranial tumor control, particularly to address large metastases, causing mass effect.[31] Furthermore, a recent study suggests that re-do surgery may also be a viable option in patients with recurrent CMs.[32]

Referrals requiring specialist intervention

In our cohort, 52.6% of patients required specialist intervention in the form of SRS or surgery. It is clear that the proportion of patients undergoing specialist treatment is negatively correlated with the number of metastases present at the time of referral.

Sills et al.[33] commented in 2005 on the evolution of treatment modalities in patients with CMs, due to improvements in surgical technique, using neuronavigation, pre-surgical mapping[34] and intra-operative monitoring techniques, alongside diagnostic/therapeutic advances in the management of systemic cancers.[31,35] This may lead to a change in the role and timing of surgical resection as more and more (neo-)adjuvant systemic therapies become available making more patients eligible candidates for surgical resection. However, our cohort study confirmed that previously established factors[7,11] (such as age, KPS, number of CMs, presence of extracranial disease and systemic disease status) still play a key role in specialist treatment recommendation in the form of either surgery or SRS, while stressing the importance of accurate disease staging at referral.[33,36-41] One factor that could not be analyzed due to lack of data is the influence of molecular marker status on NMDT decision-making which may be crucial in some cancer subtypes to make the best decisions.

In fact, after categorizing our cohort into groups based on the recursive tree two main things can be observed: firstly, a significant proportion of patients (18.3%) are referred with a KPS<70 and therefore per se, fall into the category of patients with poor median survival[7] and are therefore poor surgical candidates (albeit ~30% of those had specialist treatment recommended suggesting that there is a necessity to discuss these patients in the NMDT). Secondly, there was a large proportion of patients (24.3%) in whom the KPS was not provided by the referring team. Increasing compliance with KPS reporting at referral would therefore help streamline decision-making at NMDT.

We found no evidence of an association between the following prognostic factors[7] and NMDT decision-making in our cohort: prior brain surgery, time interval between primary and secondary tumor diagnosis (before/after 2 years), neurological dysfunction and/or headache at presentation. The fact that having undergone prior brain surgery for removal of metastasis excluding further specialist intervention within our data supports the idea of re-do surgery as an option that can have good outcomes in selected patients.[34]

Delay in MDT decision-making

In approximately one fifth of patients referred (18.6%), there was a delay in NMDT decision-making. The most common reasons given were incomplete referral information provided, lack of imaging availability for review and/or awaiting further investigations/results from the referring team. This may lead to increase in NMDT workload, as those factors are considered essential for the decision-making process. Nonetheless, the fact that NMDT decision was delayed did not influence the outcome of the treatment recommendation given (Table 5, p=0.278). Whether the delay in offered treatment has a negative impact on patient survival will have to be assessed in future studies.

Potential solutions would include to: re-iterate to referring teams the importance of all the information required; identifying and supporting those teams, which repeatedly send incomplete referrals. New streamlining pathways could also be established including an emphasis on a uniform national proforma in which data (including molecular profiles) is collected continuously, perhaps even capturing national outcome data. A further advantage of this would be that all required data would be readily available and could be shared between all specialties (GPs, ED, Oncologists, Neurosurgeons, etc.).

Validation of RPA and ds-GPA

The use of RPA and ds-GPA has been previously validated.[42] More recently, molecular subtypes of tumours have also been taken into account, first in breast[43] and then in lung cancer.[44] Overall, our data showed that the better the RPA class[7] (i.e. RPA class I) the more likely the patient was to have specialist treatment recommended. Whilst there tended to be a greater chance of specialist treatment with a higher ds-GPA score[11,45], we did not find a statistically significant association with our data.

One of the reasons for the compliance rate falling short of 100% could be the recent developments in surgical techniques leading to a wider variety of patients being considered for such treatments. A recent study of 71 patients at a single institution showed that the actual survival outcome exceeded expected outcome significantly in a well selected cohort of patients.[5] This remains to be confirmed in a larger patient population. Another reason could be that more surgery is offered to the elderly as an increasing number of otherwise fit patients are referred in an ageing population.[27]

There have been efforts to develop new stratification tools such as the Barnholtz-Sloan index[46], Score Index for Radiosurgery (SIR) and Basic Score for Brain Metastases (BSBM) amongst others[6,47,48] to guide NMDT decision-making for this heterogeneous cohort of patients. These have not been widely adopted into clinical practice for a number of reasons, presumably due to the fact that most of these scores are based on survival data alone without considering other important factors such as quality of life and tumor recurrence. Other reasons may be related to the constant evolution of molecular profiling and new therapeutic targets.[18,49] Overall, population-based studies are not always as good in predicting individual outcome and it is evident that CM management has become very complex and a much more individualized approach is being applied. In the near future, one of these may be complemented by the use of imaging as a potential biomarker.[50]

Data Generalizability and limitations of this study

The primary advantage of this study is the multicenter nature allowing for a large sample size. Three quarters of neurosurgical centers in the United Kingdom & Ireland participated in this cohort study, which gives a reflection on national management of CM referrals. Regional homogeneity of the referred patient population and NMDT treatment recommendation provided is of vital importance to plan future RCTs, inform health policy makers (including NICE), generate health economic models and assist in national resource allocation. In future, we would welcome a prospective national database for CM referrals that captures national outcome data.

One of the limitations of this study has been that some of the referral information has been largely incomplete or missing as a whole. This limitation lies within the nature of this study and can be largely attributed to lack of information at the time of referral and does not reflect on the quality of data entry.

Furthermore, while SRS to the resection cavity is supported by NICE if there is residual disease documented by post-operative MRI, this may not be recommended at the initial NMDT. Therefore, a proportion of patients will have had cavity SRS without this being captured in this study.

Conclusions

The development of new NICE guidelines will lead to an increase in NMDT workload. Our prospective study identified a delay in NMDT decision-making in approximately one in five patients. Specialist intervention was offered to 67.5% of patients with single CM and 38.2% of patients with multiple CMs, hence confirming a national change in culture of referral and treatment patterns, including a general trend away from adjuvant WBRT and specialist treatment being more frequently offered in multiple CMs.

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