Management evaluation of metastasis in the brain (MEMBRAIN)—a United Kingdom and Ireland prospective, multicenter observational study

Neuro-Oncology Practice

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

--Manuscript Draft--

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Corresponding Author:	Josephine Jung, PhD King's College Hospital NHS Foundation Trust London, London UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	King's College Hospital NHS Foundation Trust
Corresponding Author's Secondary Institution:	
First Author:	Josephine Jung, PhD
First Author Secondary Information:	
Order of Authors:	Josephine Jung, PhD
	Jignesh Tailor, PhD, FRCS
	Emma Dalton
	Laurence J Glancz
	Joy Roach
	Rasheed Zakaria, PhD
	Simon Lammy
	Aswin Chari
	Karol P Budohoski
	Laurent J Livermore
	Kenny Yu, PhD, FRCS
	Michael D Jenkinson, PhD, FRCS
	Paul M Brennan, PhD, FRCS
	Lucy Brazil
	Catey Bunce
	Elli Bourmpaki
	Keyoumars Ashkan, MD, FRCS
	Francesco Vergani, PhD, FRCS
Order of Authors Secondary Information:	
Manuscript Region of Origin:	UNITED KINGDOM
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.

Suggested Reviewers:	Lorenzo Bello Director of Neuro-oncological Surgery, Universita degli Studi di Milano Facolta di Medicina e Chirurgia lorenzo.bello@unimi.it Authority in the field
	Michael Brada Professor of Radiation Oncology & Hon. Consultant in Clinical Oncology, Clatterbridge Cancer Centre NHS Foundation Trust michael.brada@liverpool.ac.uk Leading expert in Neuro-Oncology (Awarded Lifetime Achievement Award of ESTRO)
	Andrew Gaya Guy's and Saint Thomas' NHS Foundation Trust andrew.gaya@gstt.nhs.uk Expert in the field
	Paul Sanghera Consultant Clinical Oncologist, University Hospitals Birmingham NHS Foundation Trust paul.sanghera@uhb.nhs.uk Specialist in Neuro-Oncology and stereotactic radiotherapy
	Nick Plowman Consultant Clinical Oncologist, Barts Health NHS Trust nick.plowman@bartshealth.nhs.uk Expert in Neuro-Oncology
	Gelareh Zadeh Associate Professor, Toronto Western Hospital gelareh.zadeh@uhn.ca She is a Neurosurgeon Scientist with research focussed on brain tumours.
Opposed Reviewers:	
Response to Reviewers:	

Josephine Jung, MD PhD
Department of Neurosurgery, King's College Hospital
Denmark Hill, London SE5 9RS, UK

Susan Chang MD
Editor-in-Chief Neuro-Oncology Practice
Oxford Academic Oxford Journal

London, 14th August 2019

Dear Editor,

Please find enclosed the revised manuscript entitled "Management Evaluation of Metastasis in the Brain (MEMBRAIN) – A United Kingdom & Ireland prospective, multicenter observational study" (Ref.: Ms. No. NOP-D-19-00065) by Josephine Jung, Jignesh Tailor, Emma Dalton, Laurence J Glancz, Joy Roach, Rasheed Zakaria, Simon Lammy, Aswin Chari, Karol P Budohoski, Laurent J Livermore, Kenny Yu, Michael D Jenkinson, Paul M Brennan, Lucy Brazil, Catey Bunce, Elli Bourmpaki, Keyoumars Ashkan and Francesco Vergani that we submit for possible publication in Neuro-Oncology Practice**.**
This study was conducted using the British Neurosurgical Trainee Research Collaborative which is a member organisation of the UK Neurosurgical Research Network supported by the Royal College of Surgeons of England and the Society of British Neurological Surgeons.

In this study we investigated the management of brain metastases referrals to the neuro-oncology multi-disciplinary team in 24 neurosurgical units in the United Kingdom and Ireland over the period of 4 months. We can show in our manuscript that there is a delay in decision-making in approximately ~20% of 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. We believe that our findings contribute greatly to the knowledge within the scientific community.

All authors have agreed with the manuscript submission and approved the final version of this manuscript. None of the authors have any conflicts of interest regarding the submitted article. We have closely followed the guidelines for authors. The content of this manuscript has not been published elsewhere in any form except as described here.

I, Josephine Jung, certify that this manuscript is a unique submission and is not being considered for publication, in part or in full, with any other source in any medium.

Each of the above stated authors has participated sufficiently in the work to take public responsibility for appropriate portions of the content. None of the authors have any financial disclosure or any conflict of interest. We have adhered to the local ethical guidelines of the hospital for publication of original articles.

Correspondence regarding this manuscript should be sent to Josephine Jung at the address shown in this letter or via E-mail to Josephine.Jung@nhs.net.

Thank you for the privilege of submitting our manuscript to your journal.

Sincerely yours,

Josephine Jung

September 4, 2019

Re: Resubmission of manuscript *Management Evaluation of Metastasis in the Brain (MEMBRAIN) – A United Kingdom & Ireland prospective, multicenter observational study*, Ms. Ref. No.: NOP-D-19-00065

The Editors

Neuro-Oncology Practice

Dear Editors:

Thank you for the opportunity to revise our manuscript, *Management Evaluation of Metastasis in the Brain (MEMBRAIN) – A United Kingdom & Ireland prospective, multicenter observational study*. We appreciate the careful review and constructive suggestions of the Reviewers. Considerable changes have been made to the paper, in accordance with the improvements suggested by the reviewers. It is our belief that the manuscript has substantially improved after making the suggested edits, so to meet the high standard required for publication in *Neuro-Oncology Practice.*

Please find below the reviewers' comments with our responses in italics, including how and where the text was modified in the clean version of the manuscript. Changes made in the manuscript are marked using the 'track changes' mode. The revision has been developed in consultation with all co-authors, and each author has given approval to the final form of this revision.

Thank you for your consideration.

Yours sincerely,

Josephine Jung, MD PhD

REVIEWER #1:

This is an interesting study describing management decisions for over 1000 patients with cerebral metastases in the UK.

The results would be of great interest for comparison to other populations of patients with cerebral metastases. However, it is not at all clear that the results are referable to international patient populations, particularly in the US and possibly Europe and Asia.

1. The study emphasizes the number of patients recommended for "specialist" treatment, which includes surgery or radiosurgery, but apparently does not include whole brain radiation. Such a distinction would have to be considered a feature of the UK health system approach to management of these patients. At the very least, definition of the criteria for "specialist" versus "non-specialist" management needs to be provided.

Thank you for this valuable comment. The difference between "Specialist" vs. "Non-Specialist" treatment is that surgery or SRS are provided by dedicated neuro-oncology centers, which are usually located in large tertiary referral hospitals whereas whole brain radiotherapy is administered by Clinical Oncologists working in general oncology departments and therefore it is more widely and readily available than SRS. This is a feature of the United Kingdom National Health Service but also similar in most European countries. We acknowledge that this may not be obvious to the general reader. This section has been expanded further in the methods section of our manuscript.

Lines 87-91

"[…] 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) […]."

2. A remarkable feature in the results reported is the high number of patients treated with "Surgical Resection alone". The very fact that such a high number of patients are managed with surgical resection ALONE indicates that the study population is not easily compared to patients in the US, where the majority of patients are offered SRS or RT following surgery, even for solitary metastases.

Thank you for allowing us to clarify this point further. Current NICE (The National Institute for Health and Care Excellence) guidelines support SRS to the resection cavity after initial surgery if there was any residual tumor and if that is documented by post-operative MRI. If complete resection has taken place, NICE recommends close follow up MRI observation only. That is why usually the initial MDT recommendation is for surgery alone - but a number of patients will receive SRS after surgery but this may not have been captured in this study. A small section has been added in the discussion section to reflect this fact.

The authors agree that the results reflect the UK population, where probably less patients overall get the combination of surgery + cavity SRS as compared to the US. However, we think that it is relevant to report different practice and treatment modalities in an international journal such as Neuro-Oncology Practice. While the authors recognize that there is some clinical evidence of better local control and less neuro-cognitive toxicity with cavity SRS (Choi CY et al., Int J Radiat Oncol Biol Phys. (2012), doi: 10.1016/j.ijrobp.2011.12.009; Roberge D et al., Int J Radiat Oncol Biol Phys. (2012, doi: 10.1016/j.ijrobp.2011.09.032; Soltys SG et al., Int J Radiat Oncol Biol Phys. (2008), doi: 10.1016/j.ijrobp.2007.06.068), however there is still a lack of long-term data available (Soffietti R et al., Neuro-Oncology (2016), doi: 10.1093/neuonc/nov286).

Lines 328-331

"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."

3. The authors indicate that the study shows major changes in management patterns for patients with cerebral metastases, but doesn't actually provide the basis for such assertions. Are they comparing their results to some historical data?

Thank you for this comment. When comparing the data collected in this study to our previously collected and published data (Loh et al., BJNS, 2018) analyzing 1640 patients from 2013-15, we found that in our current study WBRT/Oncology treatment is recommended less often (39% in Loh et al. vs. 20% in this current study). Furthermore, in Loh et al. approximately half of patients with solitary metastasis were recommended either SRS or surgery compared to only about 10% of patients with multiple metastases ($p<0.001$). In our current study the percentage of patients with multiple *metastases having surgery or SRS recommended is higher (38%). A paragraph has been added to the discussion to emphasize this point.*

Lines 227-229

"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." (Loh et al., BJNS, 2018)

4. It seems that the study results would be better submitted to a journal based in the UK, since the data would be of much greater value to UK-based neuro-oncologists and investigators.

As mentioned above, we do believe that reporting different management and recommended treatment modalities in different countries should be of interest to an international journal like Neuro-Oncology Practice. Additionally, we would welcome a debate concerning how other international practices differ (including an invitation to letters in response) which can then in turn potentially inform and change UK practice.

REVIEWER #2:

I have minor concerns:

1. Please detail who is required to form a « neuro-oncology multidisciplinary team ». It may vary between countries.

Thank you for this comment. The neuro-oncology multidisciplinary team in the UK is comprised of: Consultant Neurosurgeon, Neurologist, Neuro-Radiologist, Neuro-Oncologist, Neuro-Histopathologist; Neuro-Oncology Clinical Nurse Specialists; Occupational and Speech & Language Therapists; Physiotherapists; MDT coordinator and Neuro-Psychologist (where available). A paragraph detailing this has been added to the manuscript.

Lines 69-73
"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."

2. Several parameters are entered into a electronic Case Report Form. Are they the same for the study and for the clinical practice ? In other words, what are the parameters required to submit a case to the neuro-oncology multidisciplinary team ?

Thank you for this interesting question and valuable point. The parameters described in this study for the electronic Case Report Form were used exclusively for the purpose of this study The criteria for submission to the neuro-oncology multidisciplinary team vary amongst individual centers which is why we proposed the use of a "uniform national proforma" for all neuro-oncology multidisciplinary teams in the UK in our discussion (lines 279-383).

3. In the Results part, it is noted that « a combination of (cavity) SRS and surgical resection was offered to 5.7% ». It is a very low rate while it is the current standard of care. The authors should discussion this point and analyse this specific information in the most recent data set.

Thank you for this valuable comment. As mentioned to Reviewer #1, SRS to the surgical cavity is not the "standard of care" in the UK. Our National Health Service supports cavity SRS if there is residual disease after the operation and only after MDT discussion with post-operative imaging. Therefore, the proportion of patients having cavity SRS will be lower than compared to the US. This has been outlined in the discussion. However, the authors believe that it is important to report differences in practice in different countries, to generate debate and potentially inform/change practice and therefore hope that this article will be a valuable contribution to an international journal like Neuro-Oncology Practice.

Lines 328-331

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

- The discussion regarding delaying submission to neuro-oncology multidisciplinary team is of particular interest. Is there a recommended maximal time interval to submit a case?

Thank you for this interesting question. We are not aware of a maximal time interval recommended in the UK. All patients with a suspected new diagnosis of malignancy should be referred via a "2 week wait" pathway as per national guidelines. However, there is no timeframe for patients with existing diagnosis of cancer and these are usually referred to the neuro-oncology multidisciplinary team after diagnosis of brain metastasis.

Reviewer #3:

This study described the real world of the treatment on the cerebral metastases. At the same time, they also analyzed the factors influencing the decision-making from the neuro-oncology multi-disciplinary team. Although a large number of information was missing, the data presented in this study is very interesting, and could be used as a baseline against which future multicenter, randomized controlled trials in CMs can be designed and adequately powered.

One concern point.

In the present study, surgical resection alone was given for 196 patents. A combination of (cavity) SRS and surgical resection was offered to 5.7% (n=60). A combination of surgery or SRS with radiotherapy was offered to 1.7% (n=18) and 0.5% (n=5), respectively. Therefore, a total of 279 patients underwent surgical resection, which indicated that surgery was suggested more and more popular in NMDT. Could you analysis which factors are associated with the recommendation of surgical resection, KPS, the number of lesions, etc. ?

Thank you for this interesting question. We looked at all the factors influencing multi-disciplinary team decision-making (as described in Table 5) and found that patients with age <65 years, Karnofsky-Performance Status ≥70, controlled primary disease status and brain metastases only were more likely to have surgery or SRS recommended (p<0.001). Also the location and histology of the primary tumor influenced the decision-making but to a lesser extent (p<0.05). Other factors like brain metastasis size, previous brain surgery, pre-operative neurological deficit did not influence the decision to recommend surgery for these patients (p>0.05). Furthermore, surgery compared to SRS was much more likely when patients had a single metastasis whereas patients with multiple metastases had SRS recommended more often (please see Table 4 for more details).

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

Josephine Jung PhD[1,2], Jignesh Tailor PhD FRCS (SN)[3,4], Emma Dalton[5], Laurence J Glancz[6], Joy Roach[7], Rasheed Zakaria PhD[8,9], Simon Lammy[10], Aswin Chari[5], Karol P Budohoski[11], Laurent J Livermore[12], Kenny Yu PhD FRCS(SN)[13,14], Michael D Jenkinson PhD FRCS (SN)[8,15], Paul M Brennan PhD FRCS (SN)[16], Lucy Brazil[17], Catey Bunce[18], Elli Bourmpaki,[18] Keyoumars Ashkan MD FRCS(SN)[1,2*], Francesco Vergani PhD FRCS (SN)[1*], on behalf of the British National Trainee Research Collaborative (BNTRC)

[1] Department of Neurosurgery, King's College Hospital, London, UK

[2] Neurosciences Clinical Trials Unit, King's College Hospital, London, UK

[3] Department of Neurosurgery, St. George's Hospital, London, UK

[4] The Hospital for Sick Children, Toronto, Canada

[5] Department of Neurosurgery, The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

[6] Department of Neurosurgery, Queen's Medical Centre, Nottingham University Hospital, Nottingham, UK

[7] Wessex Neurological Centre, University Hospitals Southampton, Southampton, UK

[8] Department of Neurosurgery, The Walton Centre, Liverpool, UK

[9] Institute of Integrative Biology, University of Liverpool, Liverpool, UK

[10] Department of Neurosurgery, Queen Elizabeth University Hospital, Glasgow, UK

[11] Department of Neurosurgery, Addenbrooke's Hospital, Cambridge, UK

[12] Department of Neurosurgery, Oxford University Hospital, Oxford, UK

[13] Department of Neurosurgery, Salford Royal Hospital, Manchester, UK

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[14] Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

[15] Institute of Translational Medicine, University of Liverpool, Liverpool, UK

[16] Translational Neurosurgery, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

[17] Guy's and St. Thomas' Hospital NHS Foundation Trust, London, UK

[18] Department of Primary Care & Public Health Sciences, Kings College London, UK

[*] The two authors contributed equally to this work

Running title: Management Evaluation of Metastasis in the Brain (MEMBRAIN)

Corresponding author:

Josephine Jung

Department of Neurosurgery

King's College Hospital

Denmark Hill

London SE5 9RS, United Kingdom

Tel.: +44 (0)20 3299 1906

Fax: +44 (0)20 3299 3587

E-mail: Josephine.Jung@nhs.net

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Authorship:

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All authors have made substantial contributions to conception and design, acquisition of data or analysis and interpretation of data; drafting of the article or revising it critically for important intellectual content and provided final approval of the version to be published. Roles were as follows: JJ: research infrastructure organization, online database development/management, data collection, data analysis, manuscript writing/drafting. ED, LJG, JR, RZ, SL: research infrastructure organization, data collection, manuscript writing/drafting. KA, FV: study idea conception, protocol development, research infrastructure organization, data collection, manuscript writing/drafting. EB, CB: data analysis (principle), manuscript writing/drafting. JT, AC: study idea conception, protocol development, research infrastructure organization, online database development/management, manuscript writing/drafting. KY, MDJ, PMB: study idea conception, protocol development, research infrastructure organization, manuscript writing/drafting. KPB, LJL: study idea conception, protocol development, research infrastructure organization, data collection, manuscript writing/drafting. LB: study idea conception, protocol development, manuscript writing/drafting.

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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 ~~and to assess~~ referral volume and ~~,~~ quality ~~of information provided~~ 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.

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Keywords: brain tumor; British Neurosurgery Trainee Research Collaborative (BNTRC); cerebral metastasis; Management Evaluation of Metastasis in the BRAIN (MEMBRAIN); neuro-oncology multi-disciplinary team (NMDT)

Importance of the Study:

The study aim was to draw up a national picture of cerebral metastasis (CM) referrals and to assess whether decision making matches the changing landscape of CM management both worldwide, and in light of the most recent National Institute of Health and Care Excellence (NICE) guidelines. This is the largest UK and Ireland study focusing on the management of CMs, stemming from the collaborative effort of 24 neuro-oncology multi-disciplinary teams (NMDT) throughout the country. This project allowed to prospectively collect a large database of CM patients (more than 1000 cases recorded). The results capture a changing culture in the treatment of CMs, with a shift away from adjuvant radiotherapy (offered to less than 3% of patients after either surgery or SRS) and with a significant proportion (38.6%) of patients with multiple CMs being offered specialist intervention (either surgery or SRS). Finally, the data presented in this study can be used as a baseline against which future multicenter, randomized controlled trials in CMs can be designed and adequately powered.

Key points:

- Confirmation of a national change in culture of referral and treatment pattern
- 38.2% of patients with multiple metastases are offered either surgery or SRS
- Less than 3% of patients are offered adjuvant whole brain radiotherapy

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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

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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]

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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

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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.

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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

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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

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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 4b).

Validation of ds-GPA

We applied ds-GPA classification for lung, melanoma, breast, renal and gastrointestinal (GI) tract cancers (Figure 1be). 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

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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]

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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,[287] 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.[3029] 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.[310] Furthermore, a recent study suggests that re-do surgery may also be a viable option in patients with recurrent CMs.[321]

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.

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Sills et al.[332] commented in 2005 on the evolution of treatment modalities in patients with CMs, due to improvements in surgical technique, using neuronavigation, pre-surgical mapping[343] and intra-operative monitoring techniques, alongside diagnostic/therapeutic advances in the management of systemic cancers.[310,354] 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.[332,365-410] 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

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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.[343]

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.[421] More recently, molecular subtypes of tumours have also been taken into account, first in breast[432] and then in lung cancer.[443] 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[11,454], 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.[4527]

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

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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 ~~, and after~~by post-operative ~~imaging~~MRI, this may not be recommended at the initial NMDT. Therefore, a ~~large~~ 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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Contributors: Shailendra Achawa, Rafid Al-Mahfoudh, Erminia Albanese, Michael Amoo, Reiko Ashida, Kirsty Benton, Harsh Bhatt, Ian Coulter, Pietro D'Urso, Andrew Dapaah, Kelly Dawson, Gareth Dobson, John Duddy, Edward W Dyson, Ellie Edlmann, Laurence Glancz, Pablo Goetz, Athanasios Grivas, Paul Grundy, Cathal Hannan, Lianne Harrison, Syed Hassan, Damian Holliman, Aimun Jamjoom, Mohse~~o~~n Javadpour, James Laban, Chris Lim, Donald MacArthur, Helen McCoubrey, Ed McIntosh, Mark Neilly, John Norris, Adam Nunn, Gerry O'Reilly, Konstantinos Petridis, Puneet Plaha, Jonathan Pollock, Chittoor Rajaraman, Fahid Tariq Rasul, William Sage, Rohit Sinha, Naomi Slator, Lewis Thorne, Sebastian Trifoi, Micaela Uberti, Moham~~m~~ed Ali Ugas, Ravi Vemaraju, James Walkden, Mueez Waqar, Stefan Yordanov

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Figures:

Figure 1: Recursive Partitioning Analysis (RPA) of our study patients and treatment recommendation per disease specific-Graded Prognostic Assessment (ds-GPA)

(A) The recursive tree (adapted from Gaspar et al) is a tool to classify patients into Class I-III. Patients with KPS<70 are categorized as Class III. Patients with KPS≥70, controlled primary disease, age<65 years and no extracranial metastases are classified as Class I. All other patients are classified as Class II. In our cohort the KPS was not available (NA) in ~25% of patients; (B) Treatment recommendation (specialist/surgery vs non-specialist/no surgery) per RPA class depicted in bar plots. Chi^2_{trend} showed p<0.0001. (C) Patients were grouped into ds-GPA as previously described by Sperduto et al. The bar plots demonstrate the treatment recommendation (specialist/surgery vs non-specialist/no surgery) per ds-GPA. There tended to be a higher proportion of recommended specialist treatment in patients with a higher ds-GPA score, however these differences were not statistically significant with our data.

Supplementary material:

Supplementary Figure 1: Participation of neurosurgical centers.

The graph demonstrates the monthly participation of neurosurgical centers across the country with the non-cumulative number of centers depicted at the bottom. Overall 24/32 neurosurgical units participated during this study.

Supplementary Figure 2: Recruitment of patients.

A total number of 1048 patients were included in this study. The non-cumulative number of patients entered onto Castor EDC per month is depicted at the bottom.

Supplementary Figure 3: Recruitment per region in the country.

London and England contributed the most patients during this study. A total number of 6 centers in Scotland, Wales and Ireland participated in this study. Northern Ireland did not take part.

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

Josephine Jung PhD[1,2], Jignesh Tailor PhD FRCS (SN)[3,4], Emma Dalton[5], Laurence J Glancz[6], Joy Roach[7], Rasheed Zakaria PhD[8,9], Simon Lammy[10], Aswin Chari[5], Karol P Budohoski[11], Laurent J Livermore[12], Kenny Yu PhD FRCS(SN)[13,14], Michael D Jenkinson PhD FRCS (SN)[8,15], Paul M Brennan PhD FRCS (SN)[16], Lucy Brazil[17], Catey Bunce[18], Elli Bourmpaki,[18] Keyoumars Ashkan MD FRCS(SN)[1,2*], Francesco Vergani PhD FRCS (SN)[1*], on behalf of the British National Trainee Research Collaborative (BNTRC)

[1] Department of Neurosurgery, King's College Hospital, London, UK

[2] Neurosciences Clinical Trials Unit, King's College Hospital, London, UK

[3] Department of Neurosurgery, St. George's Hospital, London, UK

[4] The Hospital for Sick Children, Toronto, Canada

[5] Department of Neurosurgery, The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

[6] Department of Neurosurgery, Queen's Medical Centre, Nottingham University Hospital, Nottingham, UK

[7] Wessex Neurological Centre, University Hospitals Southampton, Southampton, UK

[8] Department of Neurosurgery, The Walton Centre, Liverpool, UK

[9] Institute of Integrative Biology, University of Liverpool, Liverpool, UK

[10] Department of Neurosurgery, Queen Elizabeth University Hospital, Glasgow, UK

[11] Department of Neurosurgery, Addenbrooke's Hospital, Cambridge, UK

[12] Department of Neurosurgery, Oxford University Hospital, Oxford, UK

[13] Department of Neurosurgery, Salford Royal Hospital, Manchester, UK

[14] Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

[15] Institute of Translational Medicine, University of Liverpool, Liverpool, UK

[16] Translational Neurosurgery, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

[17] Guy's and St. Thomas' Hospital NHS Foundation Trust, London, UK

[18] Department of Primary Care & Public Health Sciences, Kings College London, UK

[*] The two authors contributed equally to this work

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Corresponding author:

Josephine Jung

Department of Neurosurgery

King's College Hospital

Denmark Hill

London SE5 9RS, United Kingdom

Tel.: +44 (0)20 3299 1906

Fax: +44 (0)20 3299 3587

E-mail: Josephine.Jung@nhs.net

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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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Contributors: Shailendra Achawa, Rafid Al-Mahfoudh, Erminia Albanese, Michael Amoo, Reiko Ashida, Kirsty Benton, Harsh Bhatt, Ian Coulter, Pietro D'Urso, Andrew Dapaah, Kelly Dawson, Gareth Dobson, John Duddy, Edward W Dyson, Ellie Edlmann, Laurence Glancz, Pablo Goetz, Athanasios Grivas, Paul Grundy, Cathal Hannan, Lianne Harrison, Syed Hassan, Damian Holliman, Aimun Jamjoom, Mohsen Javadpour, James Laban, Chris Lim, Donald MacArthur, Helen McCoubrey, Ed McIntosh, Mark Neilly, John Norris, Adam Nunn, Gerry O'Reilly, Konstantinos Petridis, Puneet Plaha, Jonathan Pollock, Chittoor Rajaraman, Fahid Tariq Rasul, William Sage, Rohit Sinha, Naomi Slator, Lewis Thorne, Sebastian Trifoi, Micaela Uberti, Mohamed Ali Ugas, Ravi Vemaraju, James Walkden, Mueez Waqar, Stefan Yordanov

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Table 1

Table 1: Patient demographics, performance status, presenting symptoms

Variable	***N***	***%***
Total	**1048**	**100.0**
Gender		
- Female	582	55.5
- Male	466	44.5
Age		
- <40	43	4.1
- 40-44	38	3.6
- 45-49	57	5.4
- 50-54	84	8.0
- 55-59	120	11.5
- 60-64	143	13.6
- 65-69	176	16.8
- ≥70	379	36.2
- NA[a]	8	0.8
KPS[b]		
- 90-100	336	32.1
- 70-80	238	22.7
- 50-60	145	13.8
- 30-40	35	3.3
- 10-20	13	1.2
- NA[a]	255	24.3
WHO[c] Performance Status		
- 0	187	17.8
- 1	369	35.2
- 2	184	17.6
- 3	81	7.7
- 4	22	2.1
- NA[a]	205	19.6
Presenting Symptoms		
- Headache	253	24.1
- Motor deficit	315	30.1
- Speech deficit	128	12.2
- Visual deficit	67	6.4
- Seizure	115	11.0
- Confusion	188	17.9
- Screening	141	13.5
- Ataxia/LOC[d]/Falls	133	12.7
- Nausea/vomiting/raised ICP[e]	71	6.8
- Weight loss/fatigue/lethargy	26	2.5
- Incidental finding	31	3.0
- Other/unknown	61	5.8

[a] Not available = unknown or not recorded
[b] Karnofsky-Performance Status
[c] World Health Organization Performance Status
[d] Loss of consciousness
[e] Intracranial Pressure

Table 2: Pre-treatment characteristics: Primary Cancer

Variable		*N*	*%*
Total		**1048**	**100.0**
New diagnosis of cancer			
- yes		302	28.8
- no		681	65.0
- CUP[a]		58	5.5
- NA[b]		7	0.7
Location of Primary			
- Lung		383	36.5
- Breast		193	18.4
- Melanoma		126	12.0
- Upper GI[c] Tract		34	3.2
- Lower GI[c] Tract		58	5.5
- Kidney		49	4.7
- Prostate		13	1.2
- Genito-urinary		46	4.4
- Multiple		23	2.2
- Other		43	4.1
- CUP[a]/NA[b]		80	7.6
Extracranial disease			
- none		54	5.2
- controlled	➢ Primary site disease only	194	18.5
	➢ Metastatic disease	157	15.0
- uncontrolled	➢ Primary site disease only	63	6.0
	➢ Metastatic disease	168	16.0
- NA[b]		412	39.3
Molecular Markers			
- positive		216	20.6
- negative		108	10.3
- NA[b]		747	71.3
Time interval[d]			
- ≤ 2 years		353	33.7
- > 2years		239	22.8
- NA[b]		456	43.5
Extracranial metastasis			
- yes		467	44.6
- no		536	51.1
- NA[b]		45	4.3

[a] Cancer of unknown primary
[b] Not available = unknown or not recorded
[c] Gastro-Intestinal
[d] Time between diagnosis of primary tumor and CM where applicable

Table 3: Pre-treatment characteristics: Cerebral Metastasis

Variable	*N*	*%*
Total	**1048**	**100.0**
Number of brain metastases		
- 1	541	51.6
- 2	191	18.2
- 3	93	8.9
- 4	41	3.9
- ≥ 5	162	15.5
- LMD[a]	3	< 0.3
- NA[b]	17	1.6
Sentinel location of lesions		
- Frontal lobe	406	38.7
- Temporal lobe	79	7.5
- Parietal lobe	153	14.6
- Occipital lobe	96	9.2
- Cerebellum	203	19.4
- Brainstem	22	2.1
- Durally based	15	1.4
- Other	49	4.7
Size of sentinel metastasis		
- ≤ 30mm	637	60.7
- > 30 mm	292	27.9
- NA[b]	119	11.4
Cranial imaging		
- CTH[c]	635	60.6
- MRI[d] Head	873	83.3
- NA[b]	13	1.2
Reason MRI[d] not undertaken		
- Contraindicated	17	9.7
- Patient unwilling	3	1.7
- Indicated but not performed before MDT[e]	91	52.0
- No clinical indication	48	27.4
- NA[b]	16	9.1
MRI[d] sequences		
- Gadolinium contrast	836	95.8
- Navigation sequence	378	43.3
- DTI[f]	668	76.5
- DWI[g]	66	7.6
- Spectroscopy	3	0.3
Prior brain surgery		
- yes	154	14.7
- no	891	85.0
- NA[b]	3	< 0.3

[a] Leptomeningeal disease
[b] Not available = unknown or not recorded
[c] Computertomography of the head
[d] Magnetic Resonance Imaging
[e] Multi-disciplinary team meeting

[f] Diffusion tensor imaging
[g] Diffusion-weighted imaging

Table 4: Treatment recommendation

Variable	*1CM*	*2-4CM*	*≥5CM**	*NA*	*N*	*%*
Total	**541**	**325**	**165**	**17**	**1048**	**100.0**
Specialist intervention	**365**	**158**	**28**	**0**	**551**	**52.6**
- Surgical Resection alone	163	31	2		196	18.7
- Surgical Resection + SRS[a]	8	27	2		37	3.5
- Surgical Resection + SRS + cavity SRS	0	2	0		2	<0.2
- Surgical Resection + cavity SRS	21	0	0		21	2.0
- Surgical Resection + chemo-/immunotherapy	4	2	0		6	0.6
- Surgical Resection + WBRT[b]/local fx Rx[c]	12	5	1		18	1.7
- Surgical Resection + CSF[d] diversion	1	2	1		4	0.4
- SRS alone	126	74	18		218	20.8
- SRS + WBRT/local fx Rx	3	1	1		5	0.5
- SRS + chemo-/immunotherapy	14	5	1		20	1.9
- Biopsy alone	8	3	0		11	1.0
- Biopsy + SRS	0	1	0		1	<0.1
- CSF diversion	5	2	2		9	0.9
- Clinic assessment to discuss Surgery/SRS	0	3	0		3	<0.3
Non-Specialist treatment only	**165**	**147**	**133**	**1**	**447**	**42.7**
- Chemotherapy	8	4	6		18	1.7
- Immunotherapy	3	2	3		8	0.8
- WBRT	20	40	54[◊]	1	115	11.0
- Local fx Rx	11	4	1		16	1.5
- Oncology treatment NOS[e]	13	22	14		49	4.7
- Best supportive care	68	62	50[†]		180	17.2
- Re-imaging/surveillance	29	7	3		39	3.7
- Referral to other speciality	13	6	2		22	2.1
No MDT[f] decision	**11**	**20**	**4**	**16**	**51**	**4.9**
- NA					45	4.3
- Indeterminate					6	0.6

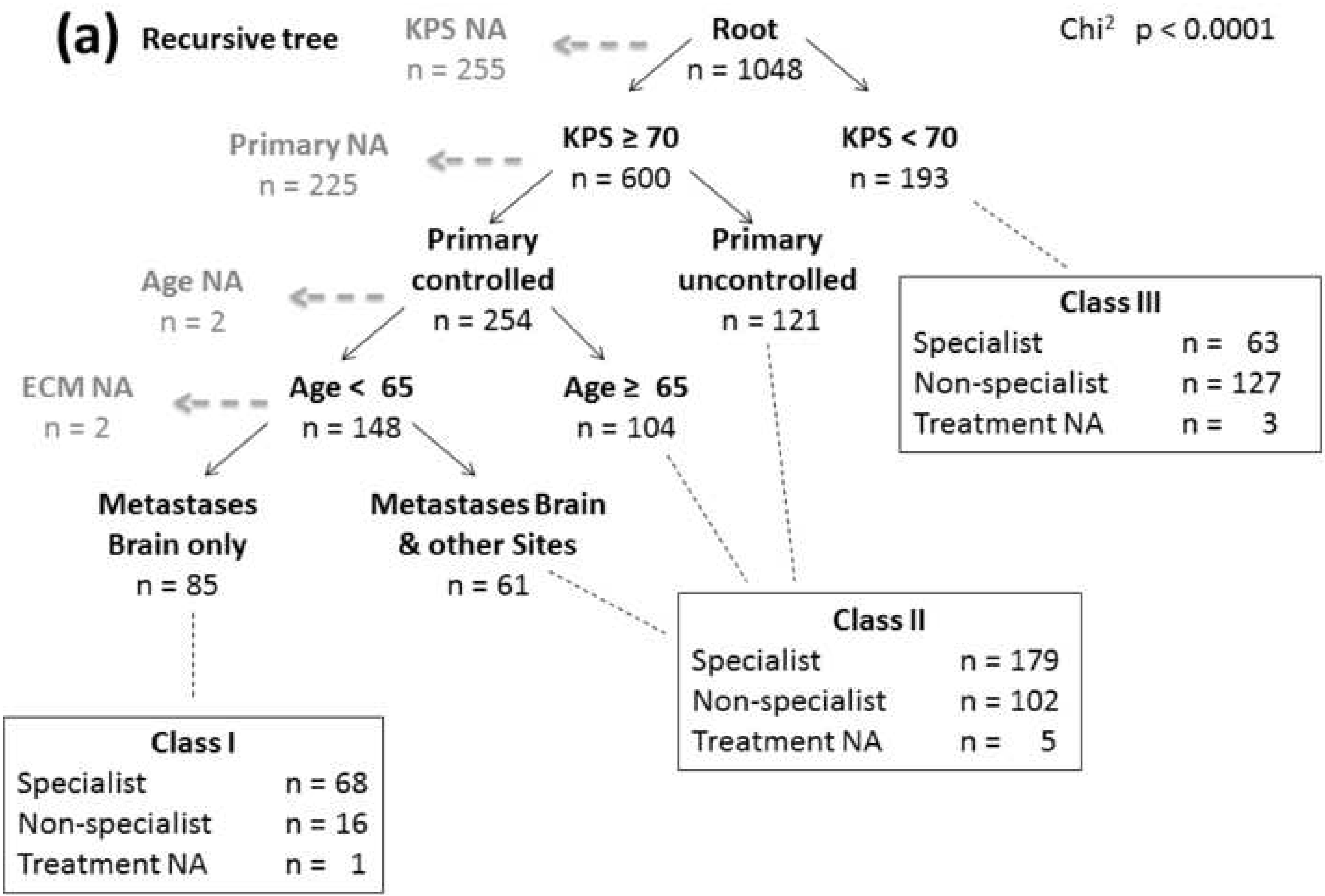
Delay in MDT decision		
- Yes	195	18.6
- No	767	73.2
- NA[g]	86	8.2
Reason for delay (multiple)		
- Imaging not available	102	52.3
- Insufficient information	53	27.2
- Awaiting further investigations/results	27	13.8
- Cancellation	2	<0.2
- Wrong MDT	15	7.7
- Intentional delay	9	4.6
- Assessment	8	4.1
- Other	7	3.6

[a] Stereotactic radiosurgery
[b] Whole brain radiation therapy
[c] Local fractionated radiotherapy
[d] Cerebrospinal fluid
[e] Not otherwise specified (either WBRT or chemo-/immunotherapy or best supportive care)
[f] Multi-disciplinary team meeting
[g] Not available = unknown or not recorded
[*] Includes patients with leptomeningeal disease (LMD) n=3
[◊] Includes n=1 with LMD
[†] Includes n=2 with LMD

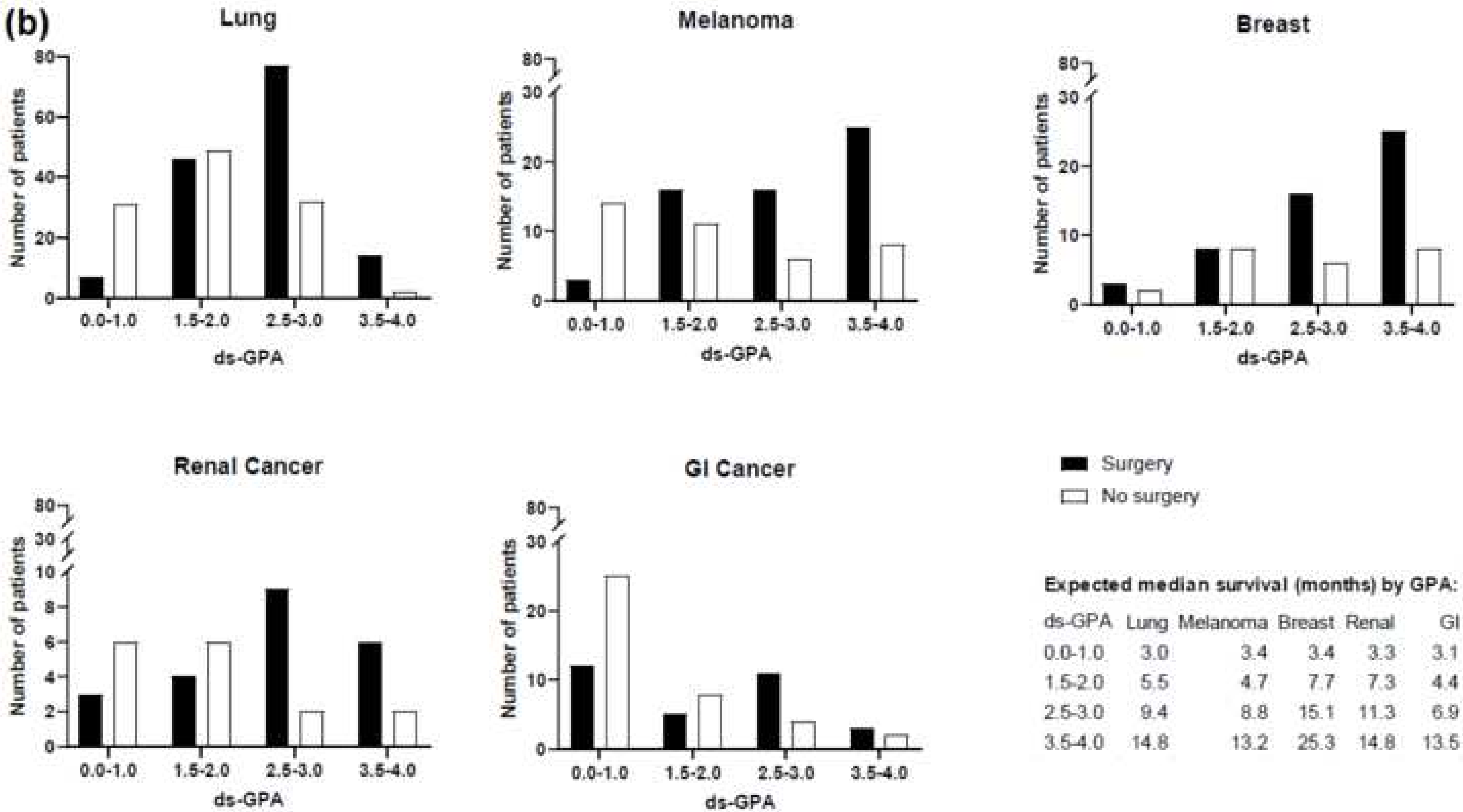
Table 5: Factors that are associated with MDT[a] decision-making using univariate logistic regression

Variable	***Comparison***	***p-value***
Number of cerebral metastases	single vs multiple	<0.0001
Age	< 65years vs ≥ 65 years	<0.0001
Karnfosky-Performance Status	< 70 vs ≥ 70	<0.0001
Primary disease status	controlled vs uncontrolled	<0.0001
Extracranial disease	Brain metastasis only vs Brain and other metastases	<0.0001
Sentinel location	Lobes/Cerebellum vs Brainstem/Basal ganglia/other	=0.047
Sentinel size	≤ 3cm vs > 3cm	= 0.114
Time interval	< 2 years vs > 2 years	= 0.925
Prior brain surgery	yes vs no	= 0.720
Histology of primary	SCLC[b] vs TNBC[c]	=0.009
Preoperative neurological deficit	yes (motor/speech/visual) vs no/missing	=0.090
Headache	yes vs no	= 0.100
Delay in MDT decision	yes vs no	= 0.278
MRI[d] available	yes vs no	<0.0001

[a] Multi-disciplinary team
[b] Small cell lung cancer
[c] Triple negative breast cancer
[d] Magnetic Resonance Imaging

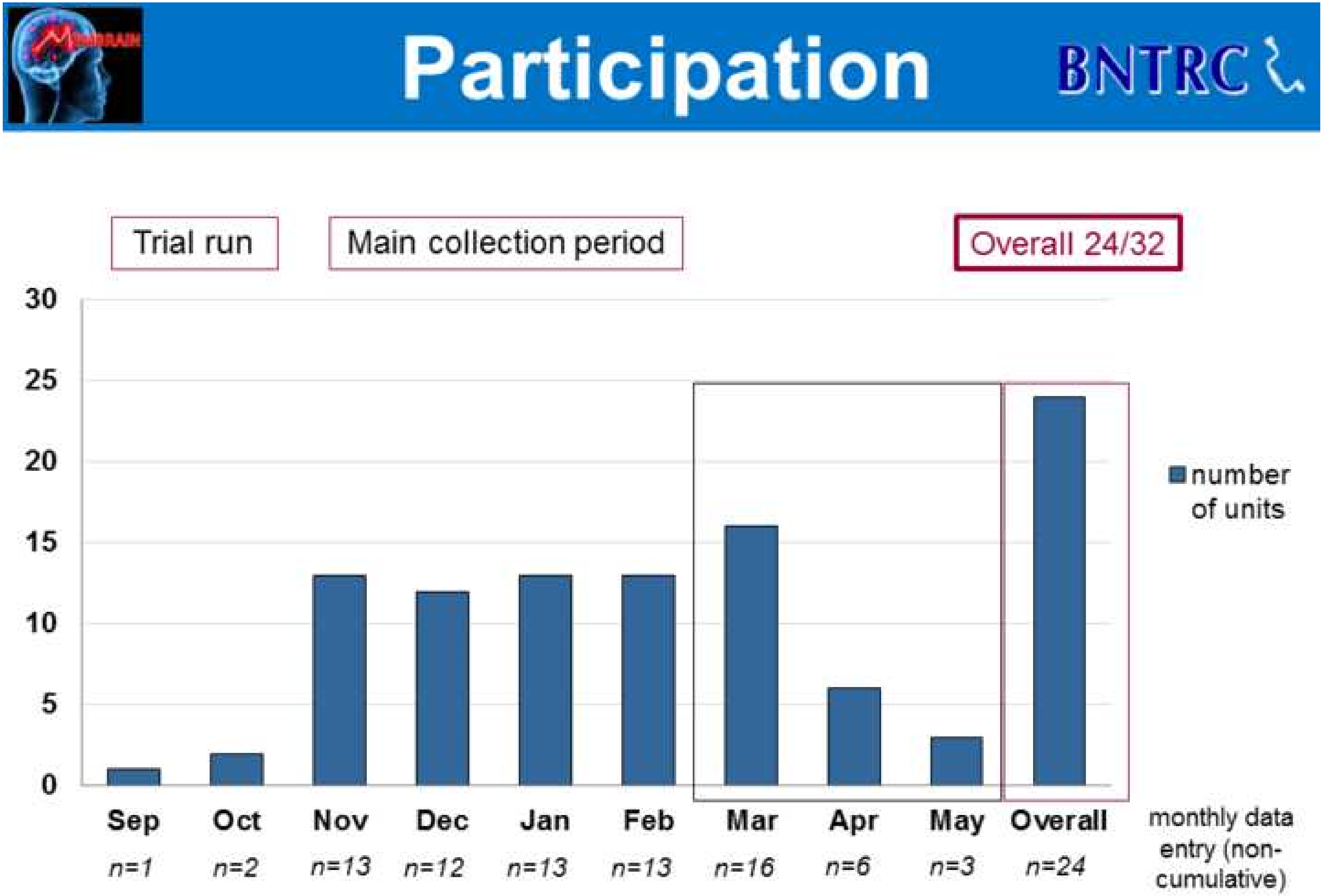


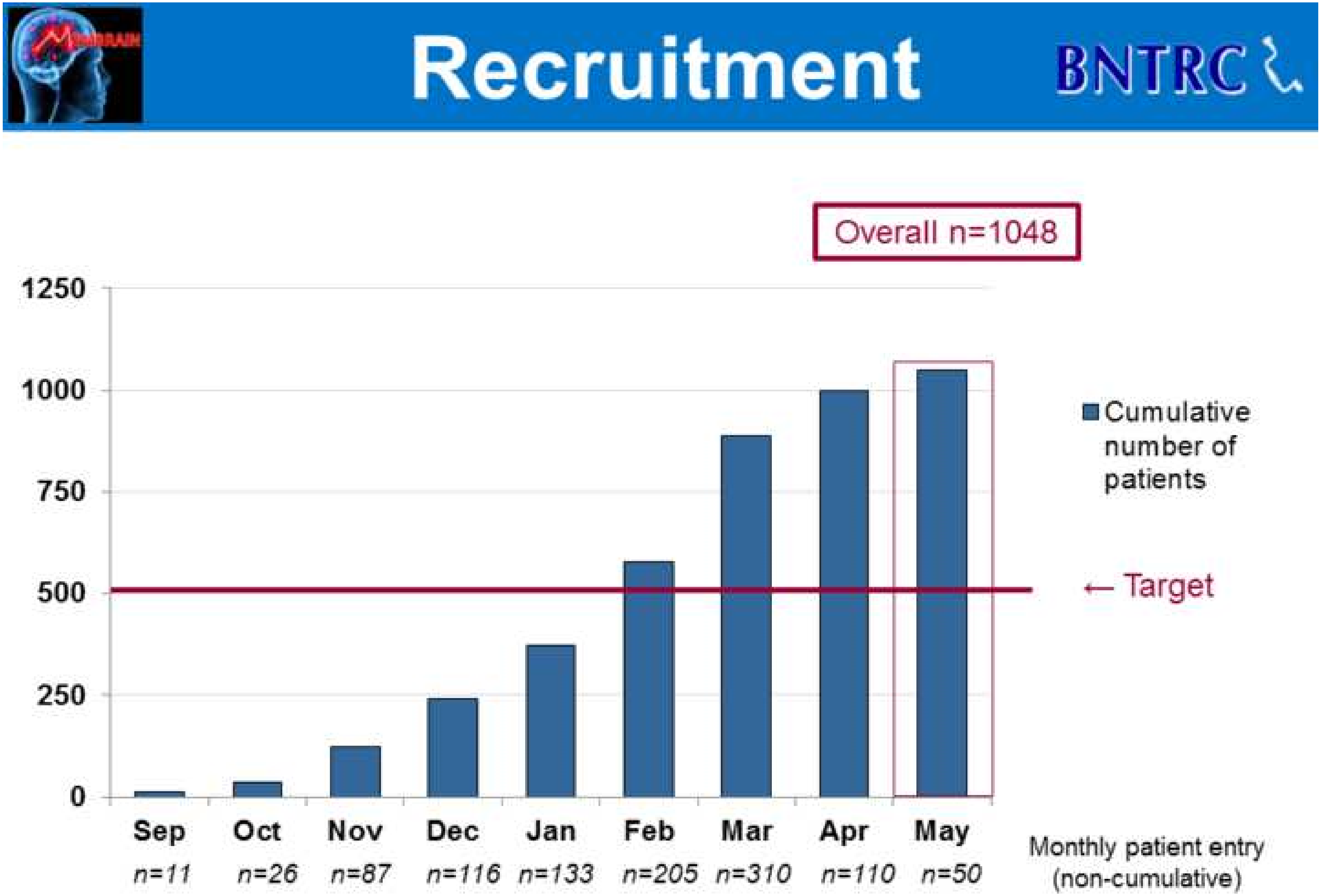
(a) Recursive tree
Chi² p < 0.0001
KPS NA
n = 255
Root
n = 1048
KPS ≥ 70
n = 600
KPS < 70
n = 193
Primary NA
n = 225
Primary controlled
n = 254
Primary uncontrolled
n = 121
Age NA
n = 2
Age < 65
n = 148
Age ≥ 65
n = 104
ECM NA
n = 2
Metastases Brain only
n = 85
Metastases Brain & other Sites
n = 61
Class III
Specialist n = 63
Non-specialist n = 127
Treatment NA n = 3
Class II
Specialist n = 179
Non-specialist n = 102
Treatment NA n = 5
Class I
Specialist n = 68
Non-specialist n = 16
Treatment NA n = 1



Expected median survival (months) by GPA:

ds-GPA	Lung	Melanoma	Breast	Renal	GI
0.0-1.0	3.0	3.4	3.4	3.3	3.1
1.5-2.0	5.5	4.7	7.7	7.3	4.4
2.5-3.0	9.4	8.8	15.1	11.3	6.9
3.5-4.0	14.8	13.2	25.3	14.8	13.5


Participation
BNTRC
Trial run
Main collection period
Overall 24/32
30
25
20
15
10
5
0
number of units
Sep n=1
Oct n=2
Nov n=13
Dec n=12
Jan n=13
Feb n=13
Mar n=16
Apr n=6
May n=3
Overall n=24
monthly data entry (non-cumulative)


Recruitment
BNTRC
Overall n=1048
1250
1000
750
500
250
0
Cumulative number of patients
← Target
Sep n=11
Oct n=26
Nov n=87
Dec n=116
Jan n=133
Feb n=205
Mar n=310
Apr n=110
May n=50
Monthly patient entry (non-cumulative)

Overview regions BNTRC

Region	Units (N)	Patients (N)
London	6	308
England	12	589
Scotland	3	96
Wales	1	30
Northern Ireland	0	0
Ireland	2	25
TOTAL	24	1048

Supplementary file 4