THE ROLE OF MODERN NEURO-ONCOLOGY IN THE TREATMENT OF PRIMARY CNS TUMORS, AND BRAIN AND SPINAL METASTASES

EDITED BY: Marcos Vinicius Calfat Maldaun, Sujit Prabhu, Claudio Tatsui and Luis Souhami

PUBLISHED IN: Frontiers in Oncology and Frontiers in Neurology

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88963-852-9
DOI 10.3389/978-2-88963-852-9

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

THE ROLE OF MODERN NEURO-ONCOLOGY IN THE TREATMENT OF PRIMARY CNS TUMORS, AND BRAIN AND SPINAL METASTASES

Topic Editors:
Marcos Vinicius Calfat Maldaun, Hospital Sírio-Libanês, Brazil
Sujit Prabhu, University of Texas MD Anderson Cancer Center, United States
Claudio Tatsui, University of Texas MD Anderson Cancer Center, United States
Luis Souhami, McGill University, Canada

Citation: Maldaun, M. V. C., Prabhu, S., Tatsui, C., Souhami, L., eds. (2020). The Role of Modern Neuro-oncology in the Treatment of Primary CNS Tumors, and Brain and Spinal Metastases. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88963-852-9

Table of Contents

frontiers in Oncology

EDITORIAL
published: 03 June 2020
doi: 10.3389/fonc.2020.00759

Editorial: The Role of Modern Neuro-oncology in the Treatment of Primary CNS Tumors, and Brain and Spinal Metastases

Marcos Maldaun[1]*, *Sujit Prabhu*[2], *Claudio Tatsui*[2] and *Luis Souhami*[3]

[1] IEP Hospital Sírio-Libanês, São Paulo, Brazil, [2] University of Texas MD Anderson Cancer Center, Houston, TX, United States, [3] McGill University Health Centre, Montreal, QC, Canada

Keywords: neuro-oncology, CNS tumors, brain metastases, spinal metsatases, gliomas, meningeomas

Editorial on the Research Topic

The Role of Modern Neuro-oncology in the Treatment of Primary CNS Tumors, and Brain and Spinal Metastases

This special multi-disciplinary article collection presents an exciting summary of what is new, promising, and controversial in the neuro-oncology field. Despite major advances in brain and spine tumor research as well as important developments and progress made in treatment delivery, unlike some other malignancies, we are unfortunately still far away from achieving a cure or even significantly improving survival rates in most pathologies in the neuro-oncology domain. On the other hand, many new developments in several areas in neuro-oncology have lately been reported, including new imaging technology, a better molecular and genetic pathology understanding, newer and safer surgical techniques, and promising target-oriented immunotherapy and chemotherapy strategies. In this special edition of Frontiers Neuro-Oncology, several of these Research Topics are presented, bringing new hope for improving outcomes in many areas.

Over the last 20 years, advances in surgery, radiation oncology, and systemic therapy associated with a better understanding of molecular and genetics profile in glioblastoma has lead to an improvement in median survival from 9 to 24 months. Although this is a significant change, it is clear that further improvement is necessary. Chaddad et al., in a comprehensive review, discuss how radiomics may aid in building predictive models for diagnosis, prognosis, and therapeutic response. Daniel et al. also review potential reasons for treatment resistance post-temozolomide treatment and describe the *hypermutant* genomic outcome (temozolomide-induced) and its possible impact on disease recurrence and newer therapeutic approaches. Del Bene et al. describe how useful advanced intra-operative ultrasound can be by guiding the surgeon to achieve a maximal safe resection in real time. On the same line, Chowdhury et al. report on a systematic review of the role of intra-operative MRI in awake neurosurgical procedures, pointing out that it is an imaging technique feasible and safe to perform.

In the pituitary field, Waddle et al., using validated instruments, for the first time characterized, in a prospective fashion, usual symptoms, complications, and quality of life before and after the sub-acute period of post-surgical intervention. A disturbed sleep pattern was identified as the culprit for worsened quality of life in such patients. Of interest, Guo et al. describe novel mutant genes in a patient with pituitary carcinoma. The authors were able to identify an uncommon P53 mutation in addition to novel mutations in ATRX and PTEN genes. This discovery can lead to important therapeutic changes by targeting very specific mutations. It may also help our understanding of the innate biology of these tumors.

OPEN ACCESS

Edited and reviewed by:
David D. Eisenstat, University of Alberta, Canada

***Correspondence:**
Marcos Maldaun
marcosmaldaun@gmail.com

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *31 October 2019*
Accepted: *21 April 2020*
Published: *03 June 2020*

Citation:
Maldaun M, Prabhu S, Tatsui C and Souhami L (2020) Editorial: The Role of Modern Neuro-oncology in the Treatment of Primary CNS Tumors, and Brain and Spinal Metastases. Front. Oncol. 10:759. doi: 10.3389/fonc.2020.00759

Health-related quality of life (HRQOL) metrics are unequivocally a very important aspect of treatment outcomes for all neuro-oncological disorders and a growing concern among investigators. There is now an increasing interest toward incorporating measurements of quality of life as endpoints in most studies. Two reports in this collection deal with this aspect of patients' management. Gabel et al. report the first use of PROMIS and NEURO-QOL, two validated questionnaires, to assess functional domain that could alter HRQOL in adult patients with low- and high-grade gliomas. The authors show that low-grade gliomas patients experience more pain intensity and greater distress compared to high-grade patients, while the latter do develop more significant neuro cognitive dysfunction. They also demonstrate that these two HRQOL tools are valuable questionnaires. From another front, Cacho-Díaz et al. from Mexico used a Mexican-Spanish version of the QLQ-BN20 instrument in patients with primary or metastatic brain tumors and showed its validity and reliability. Of importance is that the authors studied a bivariate association of HRQOL and overall survival, and they report that several domains affecting HRQOL were associated with a poorer overall survival. These findings challenge us to utilize patient reported outcomes metrics as measures to facilitate specific interventions.

Lastly, Suki et al., from the M.D. Anderson Hospital, describe a structured database from their institution that provides extremely useful guidelines for other investigators who are initiating such process in their centers. This large repository of clinical information has allowed them to obtain significant resources over time leading to hundreds of publications including landmark papers and practical and helpful information for the scientific community all over the world. Big data may further elucidate unknown mechanisms of chemo-resistance, for example, and will hopefully help in developing opportunities for novel treatments.

We hope the papers reported in this special collection (Ballester et al.;Cacho-Díaz et al.; Chaddad et al.; Chowdhury et al.; Daniel et al.; Del Bene et al.; de Oca Delgado et al.; Gabel et al.; Guo et al.; Ian Robins et al.; Suki et al.; Waddle et al.; Wang et al.) will aid investigators in their daily battle to improve outcomes in patients harboring nervous system tumors. We all appreciate how heterogeneous disease of the nervous system can be, and we agree that individualizing treatment based on clinical and pathological parameters remains a valid strategy in many situations. The modern neuro-oncology must integrate findings from the bench, including development of new systemic agents, to newer technological surgical and radiotherapy advances. We firmly believe this collection describes novel treatment paradigms and highlights the need for a multi-disciplinary neuro-oncological approach that emphasizes good perspectives for better and solid results in the management of nervous system tumors.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CASE REPORT
published: 27 August 2018
doi: 10.3389/fneur.2018.00700

Primary Leptomeningeal Oligodendroglioma, IDH-Mutant, 1p/19q-Codeleted

Leomar Y. Ballester[1,2], Erin Dunbar[3], Nandita Guha-Thakurta[4], John W. Henson[3], Howard Chandler[3], Jeremiah Watkins[3] and Gregory N. Fuller[5]*

[1] Department of Pathology and Laboratory Medicine, Houston, TX, United States, [2] Neurosurgery, University of Texas Health Science Center at Houston, Houston, TX, United States, [3] Piedmont Brain Tumor Center, Piedmont Cancer, Atlanta, GA, United States, [4] Department of Diagnostic Radiology, University of Texas MD Anderson Cancer Center, Houston, TX, United States, [5] Department of Pathology, University of Texas MD Anderson Cancer Center, Houston, TX, United States

We present a case of a 43-year-old woman with a history of headaches and blurry vision. Ophthalmologic examination identified papilledema. MR imaging demonstrated a right parietal region mass with patchy areas of contrast enhancement and focal calcifications. Intraoperative examination and exploration revealed an extra-axial mass with no apparent parenchymal involvement. Microscopic examination revealed solid sheets of tumor cells with clear cell cytologic features and no discernable intra-parenchymal tumor component. Molecular studies demonstrated the presence of *IDH1 IDH1* c.395G>A p.R132H and *CIC* c.601C>T p.R281W mutations and 1p/19q codeletion. The radiographic features, gross appearance, and microscopic and molecular characteristics of the mass support the diagnosis of primary leptomeningeal oligodendroglioma, IDH-mutant, 1p/19-codeleted. This case represents one of a very few reported instances of molecularly-defined solitary, primary, intracranial oligodendroglioma, without definitive involvement of the brain parenchyma.

Keywords: leptomeningeal oligodendroglioma, IDH1, 1p/19q-codeletion, diffuse glioma, CIC, ATRX, FUBP1

OPEN ACCESS

Edited by:
Luis Souhami, McGill University, Canada

Reviewed by:
Sunit Das, St. Michael's Hospital, Canada
David D. Eisenstat, University of Alberta, Canada

****Correspondence:***
Leomar Y. Ballester
Leomar.y.ballester@uth.tmc.edu

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *13 June 2018*
Accepted: *02 August 2018*
Published: *27 August 2018*

Citation:
Ballester LY, Dunbar E, Guha-Thakurta N, Henson JW, Chandler H, Watkins J and Fuller GN (2018) Primary Leptomeningeal Oligodendroglioma, IDH-Mutant, 1p/19q-Codeleted. Front. Neurol. 9:700. doi: 10.3389/fneur.2018.00700

CLINICAL PRESENTATION AND IMAGING RESULTS

A 43-year-old woman presented with several months of blurry vision and headaches. Ophthalmologic examination revealed papilledema. She had no personal or family history of malignancy, but had lived near the Chernobyl, Ukraine nuclear disaster site from birth until her late 20s. Brain magnetic resonance imaging (MRI) demonstrated a right paramedian parietal region mass, ~5 × 6cm in perpendicular dimensions, with patchy areas of contrast enhancement and coarse calcification (**Figure 1D**). The mass exerted substantial local mass-effect but with only minimal vasogenic edema. Pre-operatively, it was difficult to distinguish whether the mass was intra- or extra-axial. Gadolinium-enhanced MRI of the entire spine showed no evidence of additional lesions. No other masses were identified CT imaging of the body. A right parietal craniotomy for maximal safe surgical resection of the mass was performed urgently. Intra-operatively, all visible tumor was removed. The tumor appeared to be entirely extra-axial, without a defined site of origin in the brain parenchyma. There was no evidence of brain invasion and no distal dural deposits were observed. No residual tumor was identified on post-operative MR imaging studies. After extensive multidisciplinary discussion, treatment with concurrent radiation and temozolomide, as per the STUPP protocol, was initiated (1).

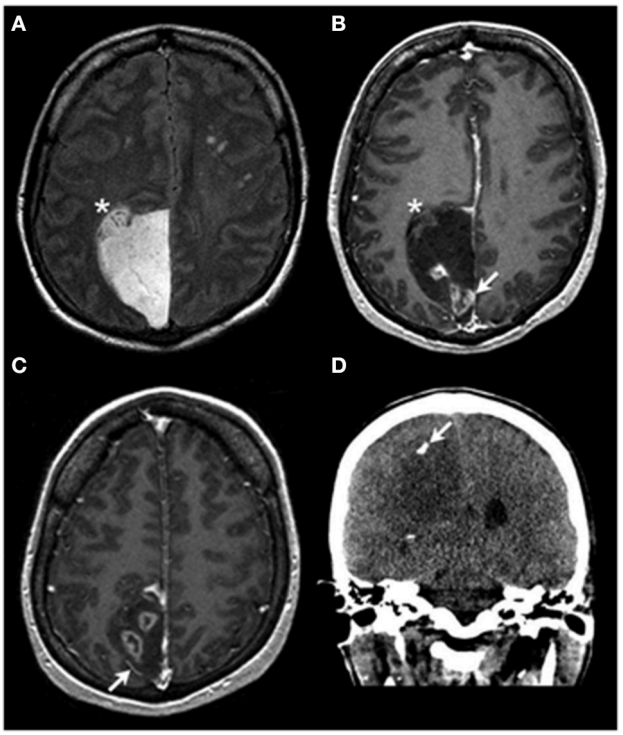


FIGURE 1 | Radiologic findings. Axial T2-weighted FLAIR imaging **(A)** demonstrates an extra-axial hyperintense mass centered within the right paramedian parietal region with a focus that appears to be inseparable from the adjacent cortex (asterisk in **A,B**). On the axial T1 post contrast images **(B,C)** the lesion is predominantly nonenhancing and hypointense, with areas of heterogeneous enhancement (arrow in **B**). Also noted is lateral displacement of a cortical vessel (arrow in **C**), suggestive of an extra-axial location of the mass. Coronal non-contrast CT imaging demonstrates a focus of coarse calcification (arrow in **D**) in the hypoattenuating mass.

HISTOLOGY AND MOLECULAR RESULTS

H&E-stained sections showed diffuse sheets of a tumor composed of relatively small cells with round-to-oval nuclei and scant-to-cleared cytoplasm (**Figure 2**). There were several small areas of stromal sclerosis with cell dropout, and collections of hemosiderin-laden macrophages were identified; in one of these foci, endothelial cell hypertrophy bordering on early hyperplasia was noted. No brain parenchyma was identified in the sections. Molecular signature and immunophenotype determination studies were performed. The tumor cells were immunopositive for GFAP, S100 protein, and mutant IDH1 p.R132H. ATRX immunostaining showed retained wildtype expression, with weak expression of p53 protein in a minor subset of tumor cells. Additional immunostains for synaptophysin, SMA, desmin, EMA, and keratins were negative. Mitotic figures were rare on H&E-stained sections, and were quantified at a maximum of 2 mitoses per 10 high-power fields using the phosphohistone H3 (PHH3) antibody. Computer-assisted quantitation yielded a correspondingly low Ki67 antigen (MIB1) labeling index of 4.8% (6,857 nuclei counted). Fluorescence *in situ* hybridization (FISH) studies showed a 1p/1q ratio of 0.58 and a 19q/19p ratio of 0.58, indicating the presence of 1p/19q codeletion in the tumor cells. Additional molecular testing (CARIS Molecular Intelligence, please visit https://www.carismolecularintelligence.com for a complete list of the genes evaluated) confirmed the presence of the *IDH1* c.395G>A p.R132H mutation and revealed a *CIC* c.601C>T p.R201W mutation (**Table 1**). The *MGMT* promoter (analyzed by pyrosequencing) was methylated. *ATRX* or *FUBP1* mutations and *BRAF-KIAA1549* fusion/tandem duplication at 7q34 were not detected. No mutations in the *BRAF* gene were identified. A final diagnosis of "Oligodendroglioma, IDH-mutant, 1p/19q-codeleted (leptomeningeal)" was rendered.

DISCUSSION

In this case, the preoperative imaging studies showed an extra-axial mass with a small focus that appears inseparable from cortex (**Figures 1A,B**), raising the possibilities of either tumor pushing against the brain or a potential connection of the tumor to the brain parenchyma. The intraoperative observations of the neurosurgeon (solid tumor without an identifiable connection to brain parenchyma) and the results of the assessment of the resected tissue (as detailed above) indicate that this is an example of primary leptomeningeal oligodendroglioma (2–4). The other entity in the differential diagnosis is diffuse leptomeningeal glioneuronal tumor (DLGT), which very rarely can show combined 1p/19q codeletion (isolated 1p deletion is more common). IDH mutations have not been described in DLGT (2, 5–7). In contrast, DLGT or disseminated oligodendroglioma-like leptomeningeal neoplasms (DOLN) have been shown to frequently carry the *BRAF-KIAA1549* fusion/tandem duplication at 7q34 (6).

Review of the preoperative imaging studies demonstrated the presence of multiple prominent and unequivocal foci of ring-like contrast enhancement (**Figure 1**). A ring enhancement pattern is traditionally indicative of anaplastic changes (8). In this case, the tissue available for examination did not show frank vascular proliferation or necrosis; thus, the presence of unsampled WHO grade III tumor (anaplastic oligodendroglioma) is possible. However, recent studies indicate only a very modest, if any, prognostic impact of traditional histologic criteria-based grading for WHO grade II-III *IDH*-mutant diffuse gliomas, including oligodendrogliomas, with the most important prognostic factors being *IDH1/IDH2* mutation status and 1p/19q codeletion status (9, 10). CT imaging showed focal calcification (**Figure 1D**), supporting the clinical suspicion of the tumor's protracted natural history.

Several cases of primary leptomeningeal oligodendroglioma have been reported in the literature (4). An origin from meningeal glial heteroptopia has been postulated (3). However, many of the reported cases were not evaluated for 1p/19q codeletion or *IDH1/IDH2* mutation status, raising the question of whether the tumors represent true oligodendrogliomas, as defined in the 2016 WHO classification system. In contrast to primary leptomeningeal oligodendroglial tumors, involvement of the leptomeninges by parenchymal oligodendroglial tumors

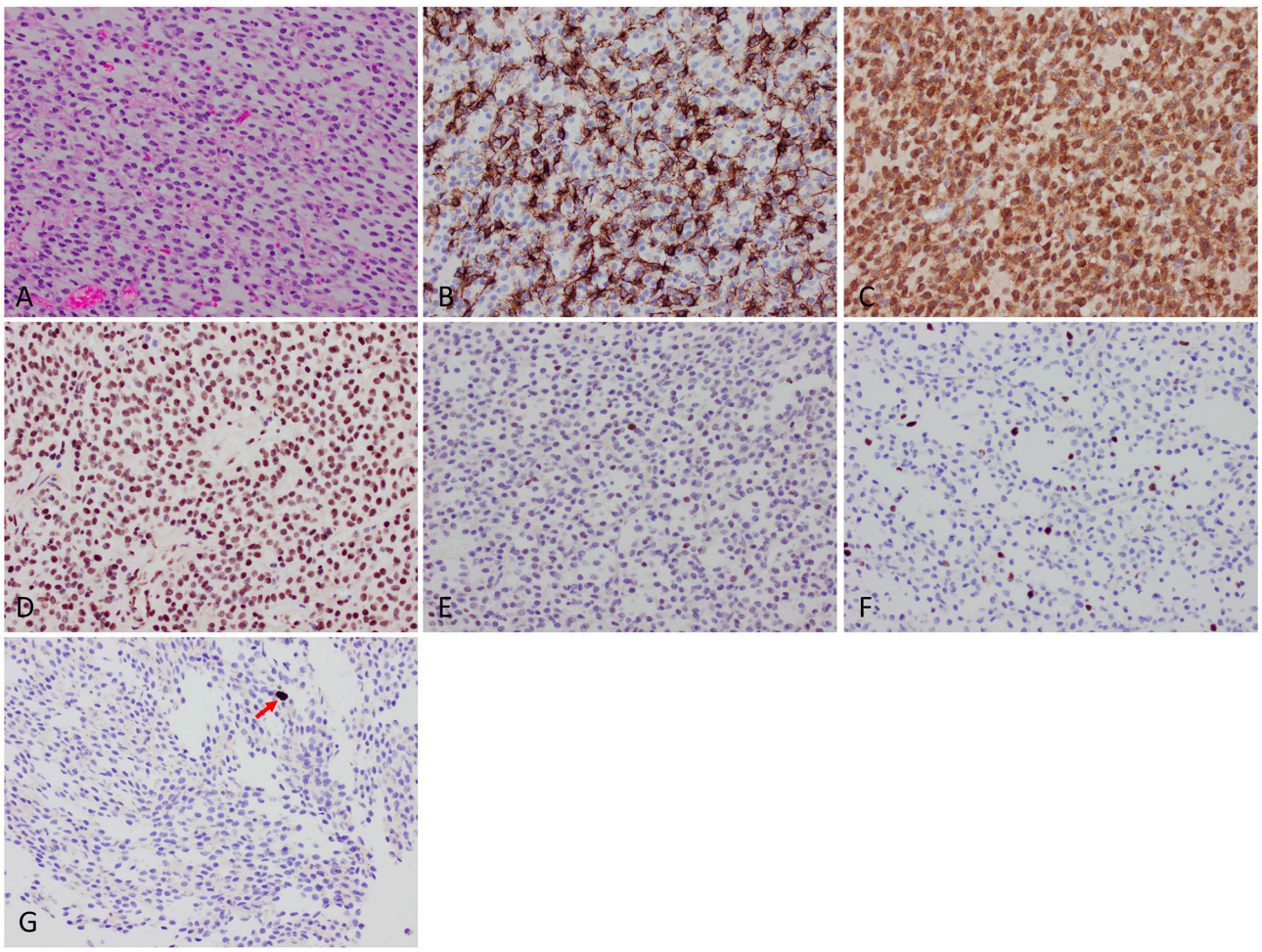


FIGURE 2 | Histologic findings. **(A)** Microscopic examination showed diffuse sheets of a tumor composed of relatively small cells with round-to-oval nuclei and scant-to-cleared cytoplasm. **(B)** GFAP was positive in a subset of tumor cells. **(C)** IDH1 p.R132H mutant protein immunohistochemistry was strongly positive. **(D)** ATRX protein wildtype expression was retained. **(E)** Weak expression of p53 protein. **(F)** Low Ki67 labeling index of 4.8%. **(G)** Mitotic activity (arrow) was quantified at a maximum of 2 per 10 high-power fields using phosphohistone H3 (pHH3) immunostaining.

TABLE 1 | Summary of genetic alterations.

Gene/chromosome	Alteration
IDH1	p.R132H
ATRX	Wildtype
CIC	p.R201W
FUBP1	Wildtype
MGMT	Methylated
1p	Deleted
19q	Deleted

occurs only in a minority of patients (11). In this case, no parenchymal component was identified by imaging, intra-operative observation, or histologic studies, thus making this possibility unlikely.

In addition to *MGMT* promoter methylation, *IDH1* c.395G>A p.R132H mutation and 1p/19q codeletion, the tumor showed a *CIC* c.601C>T p.R201W mutation. Mutations in *CIC* are a frequent finding in oligodendroglioma (10). This case thus represents one of only a very few reports of molecularly-characterized, primary leptomeningeal oligodendroglioma in an adult patient. Primary leptomeningeal oligodendrogliomas are molecularly distinct from DLGT/DOLN, which are tumors that present in pediatric patients and frequently exhibit *BRAF-KIAA1549* fusion and 1p deletions. Although rare, primary leptomeningeal oligodendroglioma should be considered in the differential diagnosis of an extra-axial tumor with clear cell cytology. Testing for the critical molecular alterations (i.e., *IDH1/IDH2* mutations and 1p/19q codeletion) is essential for accurate diagnosis of this rare presentation of oligodendroglioma.

There is no standard evaluation and management for primary leptomeningeal oligodendroglioma. The authors suggest baseline staging of the CNS axis by imaging, and,

if possible, by cerebrospinal fluid examination. There are no studies regarding long-term outcomes of adjuvant management in primary leptomeningeal oligodendroglioma comparing observation vs. adjuvant radiation with or without chemotherapy. This patient's age, health, preferences, and the possibility of microscopic disease involving the meninges and CSF, factored into the recommendation for adjuvant treatment. Given the presence of *MGMT* promoter methylation, as well as the accumulation of long-term results of several international prospective randomized clinical trials demonstrating improved outcomes with the addition of chemotherapy to radiation, the patient was commenced on radiation and temozolomide chemotherapy, as per the STUPP protocol (1). An alternative treatment strategy would have been the use of radiation followed by PCV (12). Long-term clinical-radiographic surveillance of the CNS is warranted.

ETHICS STATEMENT

This study was performed with approval of the institutional ethics committee (IRB) and with the patient's written informed consent for publication.

This study was carried out in accordance with the recommendations of the UT-MDACC IRB with written informed consent from all subjects.

AUTHOR CONTRIBUTIONS

LB: Manuscript writing and figure preparation; ED: Clinical information and manuscript editing; NG-T: Figure preparation and manuscript editing; JH: Clinical information and manuscript editing; HC: Clinical information, specimen; JW: Specimen processing, slide review, manuscript editing; GF: Pathology and manuscript editing.

REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. (2005) 352:987–96. doi: 10.1056/NEJMoa043330
2. Bourne TD, Mandell JW, Matsumoto JA, Jane JA, Lopes MBS. Primary disseminated leptomeningeal oligodendroglioma with 1p deletion. *Case Rep J Neurosurg*. (2006) 105:465–9. doi: 10.3171/ped.2006.105.6.465
3. Chen R, Macdonald DR, Ramsay DA. Primary diffuse leptomeningeal oligodendroglioma. *Case Rep J Neurosurg*. (1995) 83:724–8. doi: 10.3171/jns.1995.83.4.0724
4. Michotte A, Chaskis C, Sadones J, Veld PI, Neyns B. Primary leptomeningeal anaplastic oligodendroglioma with a 1p36-19q13 deletion: report of a unique case successfully treated with temozolomide. *J Neurol Sci*. (2009) 287:267–70. doi: 10.1016/j.jns.2009.08.047
5. Preuss M, Christiansen H, Merkenschlager A, Hirsch FW, Kiess W, Muller W, et al. Disseminated oligodendroglial-like leptomeningeal tumors: preliminary diagnostic and therapeutic results for a novel tumor entity [corrected]. *J Neurooncol*. (2015) 124:65–74. doi: 10.1007/s11060-015-1735-z
6. Rodriguez FJ, Schniederjan MJ, Nicolaides T, Tihan T, Burger PC, Perry A. High rate of concurrent BRAF-KIAA1549 gene fusion and 1p deletion in disseminated oligodendroglioma-like leptomeningeal neoplasms (DOLN). *Acta Neuropathol*. (2015) 129:609–10. doi: 10.1007/s00401-015-1400-9
7. Schniederjan MJ, Alghamdi S, Castellano-Sanchez A, Mazewski C, Brahma B, Brat DJ, et al. Diffuse leptomeningeal neuroepithelial tumor: 9 pediatric cases with chromosome 1p/19q deletion status and IDH1 (R132H) immunohistochemistry. *Am J Surg Pathol*. (2013) 37:763–71. doi: 10.1097/PAS.0b013e31827bf4cc
8. Zlatescu MC, TehraniYazdi A, Sasaki H, Megyesi JF, Betensky RA, Louis DN, et al. Tumor location and growth pattern correlate with genetic signature in oligodendroglial neoplasms. *Cancer Res*. (2001) 61:6713–5.
9. Olar A, Wani KM, Alfaro-Munoz KD, Heathcock LE, van Thuijl HF, Gilbert MR, et al. IDH mutation status and role of WHO grade and mitotic index in overall survival in grade II–III diffuse gliomas. *Acta Neuropathol*. (2015) 129:585–96. doi: 10.1007/s00401-015-1398-z
10. Suzuki H, Aoki K, Chiba K, Sato Y, Shiozawa Y, Shiraishi Y, et al. Mutational landscape and clonal architecture in grade II and III gliomas. *Nat Publ Group* (2015) 47:458–68. doi: 10.1038/ng.3273
11. Roldan G, Chan J, Eliasziw M, Cairncross JG, Forsyth PA. Leptomeningeal disease in oligodendroglial tumors: a population-based study. *J Neurooncol*. (2011) 104:811–5. doi: 10.1007/s11060-011-0551-3
12. Buckner JC, Shaw EG, Pugh SL, Chakravarti A, Gilbert MR, Barger GR, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med*. (2016) 374:1344–55. doi: 10.1056/NEJMoa1500925

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

SYSTEMATIC REVIEW
published: 10 October 2018
doi: 10.3389/fonc.2018.00434

The Role of Intraoperative MRI in Awake Neurosurgical Procedures: A Systematic Review

Tumul Chowdhury[1], Frederick A. Zeiler[2,3,4], Gyaninder P. Singh[5], Abseret Hailu[6], Hal Loewen[7], Bernhard Schaller[8], Ronald B. Cappellani[1] and Michael West[2]*

[1] Department of Anesthesiology, Perioperative and Pain Medicine, University of Manitoba, Winnipeg, MB, Canada, [2] Section of Neurosurgery, Department of Surgery, University of Manitoba, Winnipeg, MB, Canada, [3] Clincian Investigator Program, University of Manitoba, Winnipeg, MB, Canada, [4] Division of Anaesthesia, Department of Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, United Kingdom, [5] Department of Neuroanaesthesiology & Critical Care, Neurosciences Centre, All India Institute of Medical Sciences, New Delhi, India, [6] Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada, [7] College of Rehabilitation Sciences Librarian, Neil John Maclean Health Science Library, University of Manitoba, Winnipeg, MB, Canada, [8] Department of Primary Care, University of Zurich, Zurich, Switzerland

OPEN ACCESS

Edited by:
Marcos Vinicius Calfat Maldaun, Hospital Sírio-Libanês, Brazil

Reviewed by:
Sunit Das, St. Michael's Hospital, Canada
Seunggu Jude Han, Oregon Health & Science University, United States

***Correspondence:**
Tumul Chowdhury
tumulthunder@gmail.com

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *06 July 2018*
Accepted: *17 September 2018*
Published: *10 October 2018*

Citation:
Chowdhury T, Zeiler FA, Singh GP, Hailu A, Loewen H, Schaller B, Cappellani RB and West M (2018) The Role of Intraoperative MRI in Awake Neurosurgical Procedures: A Systematic Review. Front. Oncol. 8:434. doi: 10.3389/fonc.2018.00434

Background: Awake craniotomy for brain tumors remains an important tool in the arsenal of the treating neurosurgeon working in eloquent areas of the brain. Furthermore, with the implementation of intraoperative magnetic resonance imaging (I-MRI), one can afford the luxury of imaging to assess surgical resection of the underlying gross imaging defined neuropathology and the surrounding eloquent areas. Ideally, the combination of I-MRI and awake craniotomy could provide the maximal lesion resection with the least morbidity and mortality. However, more resection with the aid of real time imaging and awake craniotomy techniques might give opposite outcome results. The goal of this systematic review.is to identify the available literature on combined I-MRI and awake craniotomy techniques, to better understand the potential morbidity and mortality associated.

Methods: MEDLINE, EMBASE, and CENTRAL were searched from inception up to December 2016. A total of 10 articles met inclusion in to the review, with a total of 324 adult patients.

Results: All studies showed transient neurological deficits between 2.9 to 76.4%. In regards to persistent morbidity, the mean was ∼10% (ranges from zero to 35.3%) with a follow up period between 5 days and 6 months.

Conclusion: The preliminary results of this review also suggest this combined technique may impose acceptable post-operative complication profiles and morbidity. However, this is based on low quality evidence, and is therefore questionable. Further, well-designed future trials with the long-term follow-up are needed to provide various aspects of feasibility and outcome data for this approach.

Keywords: intraoperative magnetic resonance imaging (iMRI), awake craniotomies, outcome, complications, brain tumors

INTRODUCTION

The role of maximal surgical resection in the case of brain tumors especially, intrinsic gliomas has been widely debated in neurosurgery, neuro-oncology, and radiation oncology with the underlying principle of this technique focused of extensive surgical cytoreduction prior to aggressive chemotherapeutic and radiation therapies. Current literature suggests the increasingly strong link between maximal safe surgical resection of high-grade glial neoplasms and both progression free and overall survival (1–8). The role of aggressive surgical approaches for low grade gliomas remains unclear especially in the case of asymptomatic incidental presentations, though some circles argue for similar aggressive resection in younger patient cohorts prior to neuropathologic transformation to high grade lesions (7, 9, 10). In addition, across the spectrum of intrinsic glial tumors, as we begin to better understand the molecular signatures associated with these lesions, it is becoming clearer that certain subtypes of gliomas may benefit from aggressive resection (11–15). However, one must acknowledge the decision to pursue aggressive operative intervention is one that is made weighing the risk and benefit profile, allowing the individual patient to decide what are the "acceptable" risks and potential morbidities.

In order to improve the safety profile associated with extensive surgical resections, awake craniotomy techniques have been implemented, particularly in those lesions located in or near eloquent structures (16). Awake craniotomy is a commonly performed neurosurgical procedure for the resection of brain lesions near to an eloquent area (17–21). This technique increases the safety profile and potentially improves the overall neurological outcome of the patient (17, 18, 20). Importantly, it has become a standard of care in many centers in the world. Such techniques require specialized neurosurgical, neuroanesthesia, and intra-operative neurophysiologic monitoring and nursing personal. The premise relies on the fact that the patient is under "light" sedation throughout the procedure, comfortable enough to tolerate a craniotomy, and tumor resection, but able to awaken and participate in intra-operative clinical examination during resection and direct electrical stimulation of neural structures. This allows the treating team to identify eloquent territories, avoiding aggressive resection in these areas and reducing the risk of permanent post-operative morbidity (22).

In line with the premise of awake craniotomy, intraoperative magnetic resonance imaging (I-MRI) provides real-time imaging and can potentially increase the degree of resection of brain tumors, either identifying missed areas or residual disease not grossly apparent to the neurosurgeon by direct inspection of the surgical field (1, 23). I-MRI has been used in many neurosurgical procedures including primary brain tumor resection, pituitary tumors surgeries and deep brain stimulation for various movement disorders (1, 23–25). In glioma surgery, I-MRI has been employed in patients under general anesthesia in order to optimize surgical results (26–28). To date, literature supports improved resection of gross imaging based T1 and T2 weighted MRI abnormalities. However, under such anesthetic conditions, some argue that with use of I-MRI may increase post-operative transient and permanent morbidity, particularly language and motor deficits (26, 29, 30).

Combining awake craniotomy techniques and I-MRI may provide optimal safe conditions for aggressive surgical resection of intrinsic glial neoplasms. It is plausible that the combination of I-MRI and awake craniotomy can provide maximum tumor resection with less post-operative morbidity and mortality. Therefore, the addition of these two techniques should produce favorable neurological outcomes (31). However, I-MRI assisted maximum resection can also lead to more language deterioration and new neurological deficits (26, 29, 30). In addition, there can be many complications including surgical, anesthetic or radiological during I-MRI use (32–36). Theoretically, combing two techniques may sometimes act as a double-edge sword, and it remains currently unknown the risk profile associated with using both techniques, and it may improve extent of resection at the cost of functional outcomes. Therefore, the goal of this systematic review is to identify the available literature on combined I-MRI and awake craniotomy techniques, to better understand the potential morbidity and mortality associated.

METHODS

Protocol

This systematic review was registered with PROSPERO, International prospective register of systematic reviews (CRD42016052733). This review involves various steps including preliminary searches, piloting of the study selection process, formal screening of search results against eligibility criteria, data extraction, risk of bias (quality) assessment and data analysis. Though, statistical analysis was not carried out due to heterogeneity.

The protocol is developed on the basis of PICOS [Patient Population or Problem, Intervention (treatment/test), Comparison (group or treatment), Outcomes, and Setting question]. Whether or not, the inclusion of I-MRI with awake craniotomy imposes additional benefit or harm is the basis of this research. This review is reported in keeping with the systematic review guidelines in the preferred reporting in systematic reviews and meta-analysis (PRISMA) statement.

Search Criteria

The search strategy was developed by the primary investigator (TC) in consultation with a professional librarian at Neil John Maclean Health Science Library, Winnipeg, Canada (HL). A search was conducted in the databases: MEDLINE, from 1946 to December 1, 2016 EMBASE, from 1996 to December 2, 2016, and the Cochrane Central Register of Controlled Trials (CENTRAL), issue 11 of 12 (December 1, 2016). The search strategy included appropriate subject headings and keywords for the concepts terms of awake neurosurgical procedure, awake craniotomy, and intraoperative magnetic resonance imaging. There were no language restrictions on the search. The detailed search terms are given in Appendix A in **Supplementary Material**. The study population of interest included adult patients undergoing awake neurosurgical procedures under I-MRI for brain tumors. Pediatric patients (aged $<$ 18 years), and pregnant patients

undergoing the above mentioned procedures were excluded. Retrospective as well as prospective observational studies, randomized clinical trials, and case series involving more than four cases were included for this systematic review.

Data Collection and Quality Assessment

On the basis of above defined terms, Initial titles and abstracts were provided by HL (librarian). All data (titles, abstract, exclusion criteria) were recorded in Microsoft Excel 15.0 version (password protected). Three separate sheets were created. The first sheet was for the titles and abstracts, second for the screened titles and abstracts (on the basis of inclusion/exclusion criteria) and third one for the final articles (on the basis of full texts). This part of data collection was done by two independent investigators (AH and GP) and any discrepancy was sorted out by the third (TC). In case, if primary or secondary outcomes defined for the project were not mentioned in the articles, corresponding authors were contacted to provide the data or clarification by the principal investigator (TC). The quality assessment was done by two reviewers (AH and GP). We used the Cochrane Collaboration' tool to assess the risk of selection, performance, detection, attrition, and reporting biases. For reducing selection bias, the fourth reviewer (FZ) reviewed all the data provided on sheet 2 and sheet 3 as well as cross-references. All studies were also categorized as direct, if mentioned awake craniotomies as the primary study subjects, and indirect, if mentioned awake craniotomies as one of the parts of total study subjects.

Outcome(S)

Primary Outcome(s)

The primary objective of this study is to note the effect of I-MRI on overall morbidity in patients undergoing awake neurosurgical procedures. Morbidity is defined as any new neurological deficit or worsening of pre-existing neurological deficits. This is further divided into two: transient (short term) and persistent (long term). Transient deficits were defined as any morbidity that improved during the study period whereas persistent is defined as any morbidity that persisted through out the study period.

Secondary Outcome(s)

We noted the effect of I-MRI on various other parameters including extent of resection of brain tumor, intraoperative surgical complications, intraoperative anesthetic complications, intraoperative radiological complications, total duration of procedure and overall mortality.

Data Synthesis

A descriptive data summary is presented as events numbers/proportions/percentages. To explain the data further, various tabulated aspects are presented in **Tables 1**–**5**. No formal statistical analysis was done. Meta-analysis was not carried out, as we did not have sufficient homogenous data, and there were lack of randomized controlled trials.

RESULTS

Study Selection and Characteristics

Our search strategy retrieved 438 titles and abstracts, and the subsequent filtering process is presented as a PRISMA flow chart [**Figure 1**]. After the deletion of duplicate results, 320 titles and abstracts were selected. Out of these, 280 articles were excluded on the basis of the pre-defined inclusion and exclusion criteria, 40 were screened further. After going through full texts for all 40 articles, only 10 articles met the criteria, and selected for final inclusion (37–46). All studies were conducted in a single center except one that involved 6 German centers (45). Seven were retrospective and 3 were prospective studies

TABLE 1 | Study characteristics and level of evidence.

References	Study Type	Level	SubjectsI-(n)	MRI	Volumetric Analysis	Objective	Follow up criteria
Nabavi et al. (37)	R, D	IV	34*	1.5T	N	Feasibility, Adverse events	NA
Weingarten et al. (38)	P, D	IV	10	1.5T	N	Feasibility of integration of neuronavigation and electrostimulation with I-MRI	NA
Goebel et al. (39)	P, D	IV	25	1.5T	N	Patients' perception	5 days
Leuthardt et al. (40)	R, D	1V	12	1.5T	N	EOR, Functional outcome	1 month
Lu et al. (41)	P,D	IV	30	3T	Y	EOR, Functional outcome	6 months
Tuominen et al. (42)	R (CC), D	III	20	0.23T	N	Functional outcome	2 months
Maldaun et al. (43)	R, D	IV	41**	1.5T	Y	Feasibility, EOR, Functional outcome	1 month
Zhuang et al. (44)	R, In	IV	20	3T	Y	Feasibility, EOR, Functional outcome	6 months
Coburger et al. (45)	MR, In	IV	9, 17	0.2T, 1.5T	N	Functional outcome, PFS	3 months
Ghinda et al. (46)	R, D	IV	106	3T	Y	Functional outcome, PFS, EOR	1[a] month

*T, tesla, I-MRI, intraoperative magnetic resonance imaging; n, number; R, retrospective; P, prospective, CC, case control, MR, multicenter retrospective, D, direct, In, indirect, EOR, extent of resection, NA, not available, PFS, progression free survival, N, No, Y, Yes, *Number of patients were 34 (number of procedures-38), **Number of patients 41 (number of procedures-42), [a]Average follow up period was 24. 8 months but criteria to divide transient to persistent was one month.*

TABLE 2 | Primary outcome (s) in patients undergoing awake craniotomies under I-MRI.

References	Age Median (range)	Demographics n (M, F)	I-MRI strength (Tesla)	Anesthetics	Morbidity (Primary outcome) (neurological deficits %)
Nabavi et al. (37)	42 (23–69)	34 (20 M, 14 F)	1.5 T	P+R	Transient-2.9a, Persistent-no
Weingarten et al. (38)	41 (25–57)	10 (6 M, 4 F)	1.5 T	Sedation (NA)	Transient-25b, Persistent-no
Goebel et al. (39)	46.2 (23–71)	25 (14 M, 11 F)	1.5 T	P+R	Transient-28c, Persistent-32d
Leuthardt et al. (40)	41 (32–60)	12 (9 M, 3 F)	1.5 T	P+D+A (AWA)	Transient-41.6e, Persistent−25f
Lu et al. (41)	45.5 (19–75)	30 (21 M, 9 F)	3 T	M+D+R+P	Transient-40b, Persistent-3.3b
Tuominen et al. (42)	44 (16–67)	20 (9 M, 11 F)	0.23 T	P+F	Transient-10b, Persistent-10g
Maldaun et al. (43)	41 (22–70)	41 (25 M, 16 F)	1.5 T	P+R+D (AWA)	Transient-26.2*, Persistent-2.4*
Zhuang et al. (44)	42 (26–62)	20 (13 M, 7 F)	3 T	M+D+R+P	Transient-55.5b, Persistent-5.6b
Coburger et al. (45)	NA	9 (NA)	0.2 T	NA	Transient-33.3*, Persistent−11.1*
		17 (NA)	1.5 T	NA	Transient-76.4*, Persistent-35.3*
Ghinda et al. (46)	41.7 (18–76)	106 (74 M, 32 F)	3T	P+D+R	Transient-46*, Persistent-8.7*

*T, tesla; I-MRI, intraoperative magnetic resonance imaging; n, number; (M; F), (Male; Female); P, propofol; R, remifentanil; NA, not available; D, dexmedetomidine; A, alfentanil; AWA, asleep wake asleep; M, midazolam; F, fentanyl; [a]right arm weakness; [b]speech problems; [c]All patients had preoperative deficits; [d]one of the deficits (motor; speech or sensory); [e]4 patients had word-finding difficulties; one had left sided inattention; [f]one left-sided weakness and two had word-finding difficulties; [9]one patient developed both aphasia and hemiparesis and other had hemiparesis; *Either speech problems or motor deficits or both.*

TABLE 3 | Secondary outcome(s) including resection of tumor, intraoperative complications and mortality in patients undergoing awake craniotomies under I-MRI.

References	I-MRI	Patients (%) with GTR		Intraoperative complications (n)				Mortality
	Strength	First Scan	Final Scan	Anesthetic	Surgical	Radiological	Excluded	
Nabavi et al. (37)	1.5T	NA	NA	None	3*	None	1 (postictal paresis)	NA
Weingarten et al. (38)	1.5T	10	70	None	none	None	None	NA
Goebel et al. (39)	1.5T	NA	56	1	5+	1	3 (no I-MRI)	0
Leuthardt et al. (40)	1.5T	8.3	42	None	None	None	None	NA
Lu et al. (41)	3T	36.7	60	None	4*	None	None	0
Tuominen et al. (42)	0.23T	NA	50	None	2!	None	None	0
Maldaun et al. (43)	1.5T	24	40.5	none	3*	None	None	NA
Zhuang et al. (44)	3T	5	15	NA	4*	NA	2 (PH)	1
Coburger et al. (45)	0.2T	NA	NA	NA	1#	NA	None	NA
	1.5T	NA	NA	NA	5∧	NA	None	NA
Ghinda et al. (46)	3T	NA	60.4	None	4*	None	2 (no follow up)	NA

*T, tesla; I-MRI, intraoperative magnetic resonance imaging; n, number; GTR, gross total resection; NA, not available; S, seizure; PH, postoperative hematoma; *three patients had seizures during cortical stimulation (out of these; one developed post-ictal right arm weakness); [+]two patients had seizures during cortical stimulation; one had intracranial hemorrhage; one had infarct and one had brain swelling; [!]one patient had seizure during stimulation; other had seizure but not during stimulation; [#]one patient had intracranial hemorrhage; ∧one patient had ischemia; three patients developed neurological deficits; and one had intracerebral hemorrhage.*

(**Table 1**). Only one study included a control group [craniotomy under general anesthesia]. Three articles discussed 3 Tesla (T) I-MRI, five articles 1.5 T, two articles 0.2 T and one article mentioned both 0.23 T and 1.5 T. All articles showed level IV evidence except one that had a level III evidence. All studies were published between 2008 and 2016. These included 324 patients. Most of the studies primarily aimed at exploring the feasibility, functional outcome, and extent of resection. Few highlighted the progress free survival, adverse events and patient perception. Only four articles conducted the volumetric assessment for tumors.

Outcome Results

We included all those studies that mentioned morbidity data (**Table 2**). All studies had mentioned transient and persistent morbidity. All studies showed transient neurological deficits (speech disturbances, and/or motor weakness, and/or sensory deficits) between 2.9 and 76.4% with a mean of 35.6%. In regards to persistent morbidity, the mean was ∼10% (ranges from zero to 35.3%) with a follow up period between 5 days and 6 months. Two studies failed to disclose the exact follow-up duration.

For the secondary outcomes, 9 studies reported percentage of patients with gross total resection (15–70%) on final scans, however, only four included the GTR information (5–36.7%) after the first scan (**Table 3**). Among intraoperative complications, eight studies noted surgical complications whereas anesthetic as well as radiological problems were mentioned in a single study (**Table 3**). Majority of the surgical complications included seizures during cortical

TABLE 4 | Imaging and operative characteristics in patients undergoing awake craniotomies under I-MRI.

References	I-MRI	Pre-op scans (n)	Imaging	Scans	Scan time (min)	Patients [n (%)] with further resection	Operation time (h)
Nabavi et al. (37)	1.5 T	Y (−1, 0)	T1, T2 (i), C	NA	20–60	NA	NA
Weingarten et al. (38)	1.5 T	Y (−1, 0)	T1, T2, C	1–3	30–40	7	6.8 (3.8–8.7)
Goebel et al. (39)	1.5 T	Y (−1, 0)	T1, T2 (i), C	0–2	NA	20	4.8 (3.5–6.75)
Leuthardt et al. (40)	1.5 T	NA	T1, T2, C	1	48–75	6	4.76 (2.7–6.0)
Lu et al. (41)	3 T	Y (−1)	Various, C	NA	NA	11	NA
Tuominen et al. (42)	0.23 T	Y	NA	NA	NA	NA	4.5 (3.2–7.5)
Maldaun et al. (43)	1.5 T	Y	Various, C	NA	5.3–58	7	7.3 (4–13.9)
Zhuang et al. (44)	1.5 T	Y	Various, C	1–3	40	7	NA
Coburger et al. (45)	0.2 T, 1.5 T	NA	NA	NA	NA	NA	NA
Ghinda et al. (46)	3T	Y (−1)	Various, C	1–2	NA	30	NA

T, tesla, I-MRI, intraoperative magnetic resonance imaging; n, number, NA, not available; min, minutes; h, hours; Y, yes, (−1, 0), 1 day prior and same day; C; contrast, T2 (i), T2 sequence for the initial scan.

stimulations. Only, one study reported the mortality in one patient (44). Imaging, operative, and tumor information are also presented; however, these data are quite variable (depend upon institutional and I-MRI characteristics) and preclude any relevant interpretation (**Tables 4**, **5**). Along with I-MRI, all studies have utilized multi-modal monitoring techniques to further localize tumors (**Table 5**).

DISCUSSION

Our review of the literature on awake craniotomy plus I-MRI in the resection of intrinsic brain tumors has yielded important results, which deserve highlighting.

First, regarding the primary outcome of patient morbidity, the cumulative results are in keeping with literature on those patients undergoing resection of eloquently located glial neoplasms in the absence of awake craniotomy or I-MRI (17, 18, 47–49). Thus, from the 10 studies included within this review, the combined use of awake craniotomy techniques with I-MRI may not increase the post-operative transient and persistent neurological morbidity, with the range identified from 2.9 to 76.4% and 0 to 35.3%, for transient and persistent morbidity respectively. Though, it should be acknowledged that the overall patient numbers for all included studies are low, given the complexities of such techniques and the need for costly equipment. In addition, the studies suffered from a global lack of controls for comparison, in the setting of heterogeneous pathology, location, surgical teams/techniques, and I-MRI types/field strength. Thus, one must be reserved in implying that the combination of awake craniotomy and I-MRI is equivalent in safety to resection in the absence of such techniques, or in the presence of either only awake craniotomy or I-MRI. Therefore, the results of this systematic review provide preliminary evidence only to support safety, with much further investigation required to demonstrate equivalence or superiority. Furthermore, it must be emphasized that the use of these techniques, awake craniotomy and I-MRI, are typically reserved for those patients with eloquently located intrinsic tumors, as was the case for all studies included in this review. As such, the expected post-operative morbidity for resections carried out in such territories is high, and not necessarily a reflection of the combined technique, but the risk of operating in such cortical areas. Furthermore, as we've demonstrated, despite relatively high transient post-operative morbidity, these deficits typically resolve quickly during follow-up.

Second, with the application of this combined technique, the extent of GTR appears to be in keeping with standard I-MRI studies, where patients were under general anesthesia (17, 20, 21) This result provides preliminary evidence to support the notion that awake craniotomy techniques during I-MRI cases do not limit the ability to obtain acceptable operative resections for intrinsic tumors. With appropriate anesthetic techniques, one can perform similar resections to patients under general anesthetics. Though based on the small patient numbers in the included studies, these comments should be considered preliminary, with further investigation required.

Third, the surgical complication profile for these studies is in keeping with that described in other glioma surgical series and I-MRI series (17, 36, 50). This patient population classically carries a high pre-operative rate of epilepsy, and intra-operative rate of seizures. Our review demonstrated almost all intra-operative surgical complications were seizures, a well-described complication of cranial surgery, especially in cortically located intrinsic tumors. Thus, the combined technique of awake craniotomy and I-MRI does not appear to increase the intra-operative surgical complication profile. Though one must acknowledge, the use of I-MRI requires extensive surgical team training prior to implementation. Furthermore, the use of awake craniotomy techniques is also a specialized skill set, requiring collaborative efforts between the neurosurgical and neuroanesthesia teams. The appropriate awake craniotomy techniques are acquired through specialized training and require both knowledgeable and attentive teams to carry out successfully for extended duration cases, such as the resection of eloquently located intrinsic tumors while using I-MRI. Thus, the low surgical complication profiles seen in the studies included in this review are likely a reflection of the highly trained teams involved in these operative cases. This is also emphasized by the lack of operative mortality within the described studies.

TABLE 5 | Tumor characteristics, number of patients with pre-operative deficits or symptoms, number of patients with redo-operations and intraoperative localization techniques during awake craniotomies under I-MRI.

References	Patients (*n*)	I-MRI	Tumor type	Laterality	Preop-deficits	Localization Techniques	Redo operations plus biopsies (n)
Nabavi et al. (37)	34*	1.5 T	Unknown Glial	32-L, 6-R	NA	Cortical stimulation	4
Weingarten et al. (38)	10	1.5 T	Unknown primary	6-L, 4-R		Cortical stimulation, MRI Neuronavigation	0
Goebel et al. (39)	25	1.5 T	Glial (WHO I-IV)	22-L, 3-R	19	Electrical stimulation, MRI Neuronavigation	10
Leuthardt et al. (40)	12	1.5 T	Glial (WHO II-IV)	9-L, 3-R	1	Cortical stimulation, MRI Neuronavigation	4
Lu et al. (41)	30	3 T	Glial (WHO II-IV)	30-L	8	Electrical stimulation, MRI Neuronavigation	5
Tuominen et al. (42)	20	0.23 T	Glial (WHO I-IV)	13-L. 7-R	12	Electrical stimulation, MRI Neuronavigation, F-MRI, USG	8
Maldaun et al. (43)	41**	1.5 T	Glial (WHO II-IV)	31-L, 11-R	9	Electric stimulation, MRI Neuronavigation, DTI Tractography	6
Zhuang et al. (44)	20	1.5 T	Glial (WHO II-IV)	20-L	3	Electrical stimulation, Functional MRI, MEPs, MRI Neuronavigation, DTI Tractography	2
Coburger et al. (45)	9	0.2 T	Glial (WHO II)	NA	6	Unknown	NA
	17	1.5 T	Glial (WHO II)	NA	12	Electric stimulation, USG	NA
Ghinda et al. (46)	106	3T	Glial (WHO II-IV)	94-L, 12-R	56	cortical stimulation, MEPs, MRI Neuronavigation, DTI Tractography	NA

*T, tesla; I-MRI, intraoperative magnetic resonance imaging; n, number; GTR, gross total resection; NA, not available; L, left; R, right; MEPs, motor evoked potentials; USG, ultrasound; DTI, diffuse tensor imaging; WHO, World Health Organization; F-MRI, functional magnetic resonance imaging; *number of patients were 34 (number of procedures-38), **number of patients 41 (number of procedures-42).*

Fourth, the overall operative durations, when reported, ranged from 2.7 to 13.9 h. This time is including the additional time required for I-MRI scan acquisition. As every tumor is a different entity, it can be difficult to provide hard guidelines on the expected duration for the resection of such lesions. In general, for the resection of eloquently located intrinsic tumors, this operative range is in keeping with other series where the combined awake craniotomy/I-MRI technique is not utilized (36). Thus, based on the small cohorts described in the parent studies included in this review, it appears that the overall operative times are not dramatically increased secondary to the application of this combined approach.

Fifth, one potential concern regarding I-MRI remains various radiologic complications including dye induced adverse reactions and anaphylaxis, image distortions, burn injury, interference with anesthetic monitors, and failure to complete the scan. Our review demonstrated only one complication. This complication was a technical one, precluding scanning, resulting in no direct patient related consequences (38). As such, with the appropriate training and safety precautions, I-MRI in the presence of awake craniotomy techniques, can be safely conducted.

Finally, meticulous anesthetic techniques and medications have provided a safe environment for carrying out these prolonged and complex neurosurgical cases under IMRI. Majority of centers have utilized a combined approach of nerve blocks, local anesthetic infiltration and sedation (37–39, 41, 42, 44–46). Two centers have used general anesthesia (deep sedation) with supra-glottic airway device, laryngeal mask airway to protect the airway during initial and later phases of the procedure, and patients were subsequently awaken during the stimulation and tumor excision phase (40, 43). Only one study had reported an anesthetic complication intraoperatively (39). Notably, very few patients showed agitation, fatigue and non-compliant with the procedure in this study; however, there was no robust study designed exclusively for these parameters (39). Therefore, it is apparent that the present anesthetic techniques with standard monitoring make this challenging procedure safe and comfortable to the patients.

Limitations

Despite the interesting results generated from this systematic review, there are some important limitations that deserve highlighting.

First, the overall number of studies where awake craniotomy techniques in combination with I-MRI were used is quite small, at 10 studies identified. Furthermore, most studies focused on small patient populations with heterogeneous patient characteristics, tumor locations and histopathology. As a result, the overall conclusions regarding this combined operative technique for the resection of eloquently located intrinsic brain tumors are limited. Subsequently, the results of this review should be considered preliminary; supporting the need for properly designed prospective studies into the use of such techniques in glioma surgery.

Second, patient morbidity post operatively is influenced by various factors. Such factors include tumor location, pre-operative deficits, extent of resection, tumor biology, duration of follow-up and also, surgical experiences. The studies

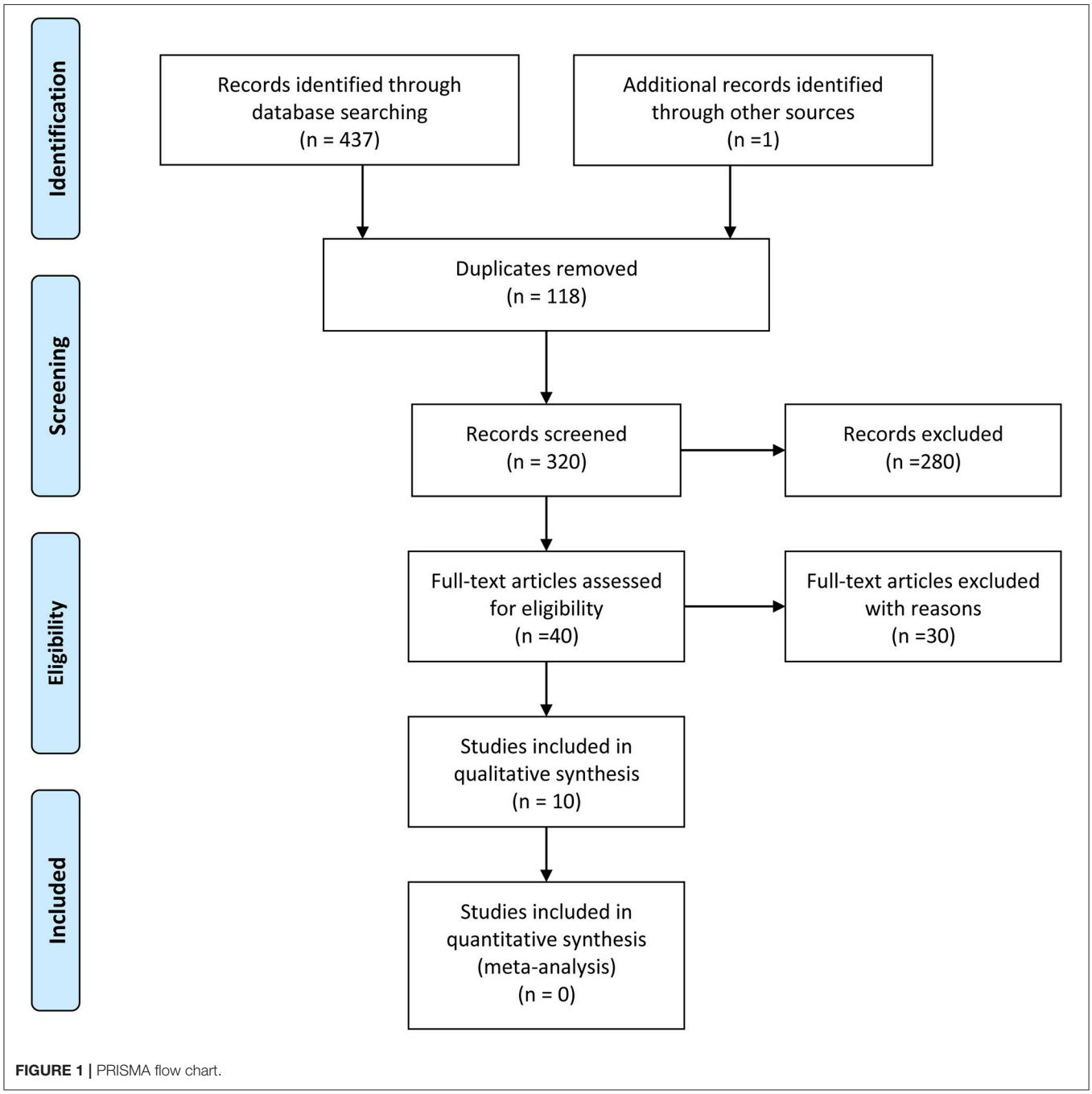


FIGURE 1 | PRISMA flow chart.

included were all focused on eloquently located lesions, however, the location and extent of such lesions varied significantly. In addition, the extent of pre-operative deficits was also heterogeneous. Extent of resection is influence by numerous factors, which will be discussed below. With that said, post operative morbidity is intimately linked with the extent of resection for eloquently located intrinsic tumors. Furthermore, tumor biology is important to acknowledge. The tumor histopathologic grade carries important implications for post-operative clinical course and the use of adjunctive chemotherapeutic and radiation techniques. Higher grade lesions tend to have a more complicated post operative and follow-up course, impeding the ability to determine if persistent deficits are related to surgical resection, inherent tumor biology or secondary effects of chemotherapeutic and radiation therapies. Finally, the duration of follow-up is important. The overall follow-up duration in the included studies ranged from 5 days to 6 months. Thus, any deficits seen during these periods may be permanent or in the process of ongoing evolution. It is difficult to comment on operative morbidity

accurately with such heterogeneous and short follow-up periods.

Third, the GTR rates described within the included studies is subject to numerous factors. These factors include pre-operative expectations for resectability, patient/surgeon threshold for "satisfactory" and "acceptable" outcome, type of I-MRI used, and the use of various other intra-operative surgical adjuncts. Based on tumor location, size and extension, there is usually a pre-operative notion of how resectable an intrinsic lesion will be. These views based on pre-operative imaging likely continue to influence an individual surgeon's willingness to continue aggressive resection, and the pre-determined goal of a given operation (i.e., "GTR" or subtotal resection). Further, based on pre-operative clinical phenotype of the patient and both the surgeon/patient's view on what is an "acceptable" outcome, the extent of surgical resection of intrinsic brain tumors is dictated by such notions. What is deemed "acceptable" for outcome and morbidity varies significantly from patient to patient, and from surgeon to surgeon. As such, the GTR rates in this review are also likely a reflection of this. In addition, the type of I-MRI utilized can influence the ability to obtain GTR. Low field strength I-MRI was demonstrated to be inferior to high field (i.e., 1.5 or 2T) in the ability to obtain GTR in one study (45). Thus, comparing the resection rates for low and high field I-MRI is controversial, given the information provided by such low field units is inferior. Finally, many of the studies describe the application of various other intra-operative surgical adjuncts to aid with resection, including: MRI neuronavigation, DTI tractography, pre-operative fMRI, electrophysiology including cortical mapping, and intra-operative ultrasound. All of these adjuncts aid with localization of tumor and eloquent cortex. Thus, the GTR rates, patient morbidity and operative complication profiles described within this review are likely influenced by all of these factors, making the exact impact of awake craniotomy/I-MRI on these outcomes difficult to discern.

Finally, and arguably the most important, is to re-emphasize that the comments and conclusions of this review should be considered preliminary. Based on the individual limitations highlighted above and the small patient numbers, one should be cautioned into considering the combination of awake craniotomy and I-MRI to be equivalent to standard glioma resection techniques, in the presence or absence of awake craniotomy or I-MRI alone. The significant heterogeneity in patients, pathology, lesion location, surgical teams, resection techniques, equipment, field strength, and follow-up information makes the results presented here preliminary for the combined efforts of awake craniotomy and I-MRI for glioma surgery. This is despite the data suggesting safety and comparable extent of resection and peri-operative complication profiles, in comparison to the existing literature. Much further work is required to investigate this combined technique, employing multi-center studies with control subjects and standardized surgical techniques, I-MRI technology and clinical follow-up principles.

CONCLUSION

This systematic review suggests that the awake craniotomy combined with intraoperative MRI is feasible and safe to conduct. The preliminary results of this review also suggest this combined technique may impose acceptable post-operative complication profiles and morbidity. However, this is based on low quality evidence, and is therefore questionable. Further, well-designed future trials with the long-term follow-up are needed to provide various aspects of feasibility and outcome data for this approach.

AUTHOR CONTRIBUTIONS

TC developed the hypothesis, assisted substantially in data collection, screening, reviewing, analyzing, contacting the authors, compiling, and writing the manuscript. FZ reviewed and screened the data, and helped substantially in writing the manuscript. GS collected and screened the data and helped writing the manuscript. AH assisted in collecting the data. HL provided the initial data, abstracts, full-texts and formulated the search tables and prisma flow chart. BS assisted in writing, reviewing and editing the manuscript. RC assisted in developing the hypothesis, reviewing and editing the manuscript. MW assisted in writing and editing the manuscript.

ACKNOWLEDGMENTS

We sincerely appreciate Dongxiao Zhuang and colleagues (Department of neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, Neurosurgical Center, Shanghai, China) and Jan Coburger and colleagues (Department of Neurosurgery, University of Ulm, Germany) for providing clarification and data pertaining to their studies.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2018.00434/full#supplementary-material

REFERENCES

1. Kuhnt D, Becker A, Ganslandt O, Bauer M, Buchfelder M, Nimsky C. Correlation of the extent of tumor volume resection and patient survival in surgery of glioblastoma multiforme with high-field intraoperative MRI guidance. *Neuro Oncol.* (2011) 13:1339–48. doi: 10.1093/neuonc/nor133
2. McGirt MJ, Chaichana KL, Gathinji M, Attenello FJ, Than K, Olivi A et al. Independent association of extent of resection with survival in patients with malignant brain astrocytoma. *J Neurosurg.* (2009) 110:156–62. doi: 10.3171/2008.4.17536
3. Hardesty DA, Sanai N. The value of glioma extent of resection in the modern neurosurgical era. *Front Neurol.* (2012) 3:140. doi: 10.3389/fneur.2012.00140
4. McCutcheon IE, Chernov MF. Rationale for aggressive resection and general surgical principles for intracranial gliomas. *Prog Neurol Surg.* (2018) 30:63–105. doi: 10.1159/000464369

5. Sanai N, Berger MS. Surgical oncology for gliomas: the state of the art. *Nat Rev Clin Oncol*. (2018) 15:112–25. doi: 10.1038/nrclinonc.2017.171
6. Duffau H. Is non-awake surgery for supratentorial adult low-grade glioma treatment still feasible? *Neurosurg Rev*. (2018) 41:133–9. doi: 10.1007/s10143-017-0918-9
7. Hervey-Jumper SL, Berger MS. Maximizing safe resection of low- and high-grade glioma. *J Neurooncol*. (2016) 130:269–82. doi: 10.1007/s11060-016-2110-4
8. Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. *Neurosurgery* (2008) 62:753–64; discussion: 264–6. doi: 10.1227/01.neu.0000318159.21731.cf
9. Jiang B, Chaichana K, Veeravagu A, Chang SD, Black KL, Patil CG. Biopsy versus resection for the management of low-grade gliomas. *Cochrane Database Syst Rev*. (2017) 4:CD009319. doi: 10.1002/14651858.CD009319.pub2
10. Xia L, Fang C, Chen G, Sun C. Relationship between the extent of resection and the survival of patients with low-grade gliomas: a systematic review and meta-analysis. *BMC Cancer* (2018) 18:48. doi: 10.1186/s12885-017-3909-x
11. Monticelli M, Zeppa P, Zenga F, Altieri R, Mammi M, Bertero L, et al. The post-surgical era of GBM: how molecular biology has impacted on our clinical management. a review. *Clin Neurol Neurosurg*. (2018) 170:120–6. doi: 10.1016/j.clineuro.2018.05.015
12. Barthel FP, Wesseling P, Verhaak RGW. Reconstructing the molecular life history of gliomas. *Acta Neuropathol*. (2018) 135:649–70. doi: 10.1007/s00401-018-1842-y
13. Nandakumar P, Mansouri A, Das S. The role of ATRX in glioma biology. *Front Oncol*. (2017) 7:236. doi: 10.3389/fonc.2017.00236
14. Diamandis P, Aldape KD. Insights from molecular profiling of adult glioma. *J Clin Oncol*. (2017) 35:2386–93. doi: 10.1200/JCO.2017.73.9516
15. Beiko J, Suki D, Hess KR, Fox BD, Cheung V, Cabral M, et al. IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection. *Neuro Oncol*. (2014) 16:81–91. doi: 10.1093/neuonc/not159
16. Saito T, Tamura M, Chernov MF, Ikuta S, Muragaki Y, Maruyama T. Neurophysiological monitoring and awake craniotomy for resection of intracranial gliomas. *Prog Neurol Surg*. (2018) 30:117–58. doi: 10.1159/000464387
17. Hervey-Jumper SL, Li J, Lau D, Molinaro AM, Perry DW, Meng L, et al. Awake craniotomy to maximize glioma resection: methods and technical nuances over a 27-year period. *J Neurosurg*. (2015) 123:325–39. doi: 10.3171/2014.10.JNS141520
18. Eseonu CI, Rincon-Torroella J, ReFaey K, Lee YM, Nangiana J, Vivas-Buitrago T, et al. Awake craniotomy vs craniotomy under general anesthesia for perirolandic gliomas: evaluating perioperative complications and extent of resection. *Neurosurgery* (2017) 81:481–9. doi: 10.1093/neuros/nyx023
19. Stevanovic A, Rossaint R, Veldeman M, Bilotta F, Coburn M. Anaesthesia management for awake craniotomy: systematic review and meta-analysis. *PLoS ONE* (2016) 11:e0156448. doi: 10.1371/journal.pone.0156448
20. Lu VM, Phan K, Rovin RA. Comparison of operative outcomes of eloquent glioma resection performed under awake versus general anesthesia: a systematic review and meta-analysis. *Clin Neurol Neurosurg*. (2018) 169:121–7. doi: 10.1016/j.clineuro.2018.04.011
21. Gravesteijn BY, Keizer ME, Vincent AJPE, Schouten JW, Stolker RJ, Klimek M. Awake craniotomy versus craniotomy under general anesthesia for the surgical treatment of insular glioma: choices and outcomes. *Neurol Res*. (2018) 40:87–96. doi: 10.1080/01616412.2017.1402147
22. Dziedzic T, Bernstein M. Awake craniotomy for brain tumor: indications, technique and benefits. *Expert Rev Neurother*. (2014) 14:1405–15. doi: 10.1586/14737175.2014.979793
23. Mislow JMK, Golby AJ, Black PM. Origins of intraoperative MRI. *Neurosurg Clin North Am*. (2009) 20:137–46. doi: 10.1016/j.nec.2009.04.002
24. Sidiropoulos C, Rammo R, Merker B, Mahajan A, LeWitt P, Kaminski P, et al. Intraoperative MRI for deep brain stimulation lead placement in Parkinson's disease: 1 year motor and neuropsychological outcomes. *J Neurol*. (2016) 263:1226–31. doi: 10.1007/s00415-016-8125-0
25. Giordano M, Samii A, Lawson McLean AC, Bertalanffy H, Fahlbusch R, Samii M, et al. Intraoperative magnetic resonance imaging in pediatric neurosurgery: safety and utility. *J Neurosurg Pediatr*. (2017) 19:77–84. doi: 10.3171/2016.8.PEDS15708
26. Jenkinson MD, Barone DG, Bryant A, Vale L, Bulbeck H, Lawrie TA, et al. Intraoperative imaging technology to maximise extent of resection for glioma. *Cochrane Database Syst Rev*. (2018) 1:CD012788. doi: 10.1002/14651858.CD012788.pub2
27. Mahboob SO, Eljamel M. Intraoperative image-guided surgery in neuro-oncology with specific focus on high-grade gliomas. *Future Oncol*. (2017) 13:2349–61. doi: 10.2217/fon-2017-0195
28. Rao G. Intraoperative MRI and maximizing extent of resection. *Neurosurg Clin N Am*. (2017) 28:477–85. doi: 10.1016/j.nec.2017.05.003
29. Duffau H, Capelle L, Denvil D, Sichez N, Gatignol P, Lopes M et al. Functional recovery after surgical resection of low grade gliomas in eloquent brain: hypothesis of brain compensation. *J Neurol Neurosurg Psychiatry* (2003) 74:901–7. doi: 10.1136/jnnp.74.7.901
30. Barone DG, Lawrie TA, Hart MG. Image guided surgery for the resection of brain tumours. *Cochrane Database Syst Rev*. (2014) 1:CD009685. doi: 10.1002/14651858.CD009685.pub2
31. Motomura K, Natsume A, Iijima K, Kuramitsu S, Fujii M, Yamamoto T, et al. Surgical benefits of combined awake craniotomy and intraoperative magnetic resonance imaging for gliomas associated with eloquent areas. *J Neurosurg*. (2017) 127:790–7. doi: 10.3171/2016.9.JNS16152
32. Sarnthein J, Lüchinger R, Piccirelli M, Regli L, Bozinov O. Prevalence of complications in intraoperative magnetic resonance imaging combined with neurophysiologic monitoring. *World Neurosurg*. (2016) 93:168–74. doi: 10.1016/j.wneu.2016.05.097
33. Bergese SD, Puente EG. Anesthesia in the intraoperative MRI environment. *Neurosurg Clin N Am*. (2009) 20:155–62. doi: 10.1016/j.nec.2009.04.001
34. Henrichs B, Walsh RP. Intraoperative magnetic resonance imaging for neurosurgical procedures: anesthetic implications. *AANA J*. (2011) 79:71–7.
35. Farling P, Flynn P, Darwent G, De Wilde J, Grainger D, King S, et al. Safety in magnetic resonance units: an update. *Anaesthesia* (2010) 65:766–70. doi: 10.1111/j.1365-2044.2010.06377.x
36. Ahmadi R, Campos B, Haux D, Rieke J, Beigel B, Unterberg A. Assessing perioperative complications associated with use of intraoperative magnetic resonance imaging during glioma surgery - a single centre experience with 516 cases. *Br J Neurosurg*. (2016) 30:397–400. doi: 10.3109/02688697.2016.1161726
37. Nabavi A, Goebel S, Doerner L, Warneke N, Ulmer S, Mehdorn M. Awake craniotomy and intraoperative magnetic resonance imaging: patient selection, preparation, and technique. *Top Magn Reson Imaging* (2009) 19:191–6. doi: 10.1097/RMR.0b013e3181963b46
38. Weingarten DM, Asthagiri AR, Butman JA, Sato S, Wiggs EA, Damaska B, Heiss JD. Cortical mapping and frameless stereotactic navigation in the high-field intraoperative magnetic resonance imaging suite. *J Neurosurg*. (2009) 111:1185–90. doi: 10.3171/2009.5.JNS09164
39. Goebel S, Nabavi A, Schubert S, Mehdorn HM. Patient perception of combined awake brain tumor surgery and intraoperative 1.5-T magnetic resonance imaging: the Kiel experience. *Neurosurgery* (2010) 67:594–600. doi: 10.1227/01.NEU.0000374870.46963.BB
40. Leuthardt EC, Lim CC, Shah MN, Evans JA, Rich KM, Dacey RG, et al. Use of movable high-field-strength intraoperative magnetic resonance imaging with awake craniotomies for resection of gliomas: preliminary experience. *Neurosurgery* (2011) 69:194–205. doi: 10.1227/NEU.0b013e31821d0e4c
41. Lu J, Wu J, Yao C, Zhuang D, Qiu T, Hu X, et al. Awake language mapping and 3-Tesla intraoperative MRI-guided volumetric resection for gliomas in language areas. *J Clin Neurosci*. (2013) 20:1280–7. doi: 10.1016/j.jocn.2012.10.042
42. Tuominen J, Yrjänä S, Ukkonen A, Koivukangas J. Awake craniotomy may further improve neurological outcome of intraoperative MRI-guided brain tumor surgery. *Acta Neurochir*. (2013) 155:1805–12. doi: 10.1007/s00701-013-1837-3
43. Maldaun MV, Khawja SN, Levine NB, Rao G, Lang FF, Weinberg JS, et al. Awake craniotomy for gliomas in a high-field intraoperative magnetic resonance imaging suite: analysis of 42 cases. *J Neurosurg*. (2014) 121:810–7. doi: 10.3171/2014.6.JNS132285

44. Zhuang DX, Wu JS, Yao CJ, Qiu TM, Lu JF, Zhu FP, et al. Intraoperative multi-information-guided resection of dominant-sided insular gliomas in a 3-T intraoperative magnetic resonance imaging integrated neurosurgical suite. *World Neurosurg.* (2016) 89:84–92. doi: 10.1016/j.wneu.2016.01.067
45. Coburger J, Merkel A, Scherer M, Schwartz F, Gessler F, Roder C, et al. Low-grade glioma surgery in intraoperative magnetic resonance imaging: results of a multicenter retrospective assessment of the German Study Group for intraoperative magnetic resonance imaging. *Neurosurgery* (2016) 78:775–86. doi: 10.1227/NEU.0000000000001081
46. Ghinda D, Zhang N, Lu J, Yao CJ, Yuan S, Wu JS. Contribution of combined intraoperative electrophysiological investigation with 3-T intraoperative MRI for awake cerebral glioma surgery: comprehensive review of the clinical implications and radiological outcomes. *Neurosurg Focus* (2016) 40:E14. doi: 10.3171/2015.12.FOCUS15572
47. Breitkopf M, Bisdas S, Liebsch M, Behling F, Bender B, Tatagiba M, et al. Safety, utility, and clinical results of continuous intraoperative electrophysiologic monitoring in 1.5T iMRI-guided surgery. *World Neurosurg.* (2017) 106:198–205. doi: 10.1016/j.wneu.2017.06.054
48. Olubiyi OI, Ozdemir A, Incekara F, Tie Y, Dolati P, Hsu L, et al. Intraoperative magnetic resonance imaging in intracranial glioma resection: a single-center, retrospective blinded volumetric study. *World Neurosurg.* (2015) 84:528–36. doi: 10.1016/j.wneu.2015.04.044
49. Senft C, Forster MT, Bink A, Mittelbronn M, Franz K, Seifert V, et al. Optimizing the extent of resection in eloquently located gliomas by combining intraoperative MRI guidance with intraoperative neurophysiological monitoring. *J Neurooncol.* (2012) 109:81–90. doi: 10.1007/s11060-012-0864-x
50. Eseonu CI, Rincon-Torroella J, Lee YM, ReFaey K, Tripathi P, Quinones-Hinojosa A. Intraoperative seizures in awake craniotomy for perirolandic glioma resections that undergo cortical mapping. *J Neurol Surg A Cent Eur Neurosurg.* (2018) 79:239–46. doi: 10.1055/s-0037-1617759

Conflict of Interest Statement: TC served as a guest associate editor for Frontiers in Neurosciences and is presently serving as an associate editor for Intensive Care Medicine and Anesthesiology section in Frontiers in Medicine. FZ has received salary support for dedicated research time, during which this manuscript was completed. Such salary support came from: the Cambridge Commonwealth Trust Scholarship, the Royal College of Surgeons of Canada—Harry S. Morton Travelling Fellowship in Surgery and the University of Manitoba Clinician Investigator Program. FZ's research is also supported through the Thorlakson Chair in Surgical Research Establishment Grant. BS served as a guest associate editor for Frontiers in Neurosciences.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

CASE REPORT
published: 15 October 2018
doi: 10.3389/fonc.2018.00451

Molecular Evolution of a Glioblastoma Controlled With Tumor Treating Fields and Concomitant Temozolomide

H. Ian Robins[1,2,3], HuyTram N. Nguyen[4], Aaron Field[5], Steven Howard[3], Shahriar Salamat[6] and Dustin A. Deming[1,7]*

[1] Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States, [2] Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States, [3] Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States, [4] University of Wisconsin School of Medicine and Public Health, Madison, WI, United States, [5] Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States, [6] Department of Pathology, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States, [7] Department of Oncology, McArdle Laboratory for Cancer Research, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States

OPEN ACCESS

Edited by:
Marcos Vinicius Calfat Maldaun, Hospital Sírio-Libanês, Brazil

Reviewed by:
Christoph Straube, Technische Universität München, Germany
Kamalakannan Palanichamy, The Ohio State University, United States

***Correspondence:**
H. Ian Robins
hirobins@wisc.edu

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *27 July 2018*
Accepted: *26 September 2018*
Published: *15 October 2018*

Citation:
Robins HI, Nguyen HN, Field A, Howard S, Salamat S and Deming DA (2018) Molecular Evolution of a Glioblastoma Controlled With Tumor Treating Fields and Concomitant Temozolomide. Front. Oncol. 8:451. doi: 10.3389/fonc.2018.00451

Tumor Treating Field (TTFields) therapy has demonstrated efficacy in a Phase 3 study of newly diagnosed glioblastoma (GB) following radiation (RT) and temozolomide (TMZ). We report the appearance of an isolated satellite anterior temporal lobe lesion, 2 months post primary RT/TMZ directed at the primary GB (MGMT methylated) parietal lobe lesion and one adjuvant cycle of TMZ and TTFields. The mean RT dose delivered to the temporal lobe lesion was negligible, i.e., 4.53 ± 0.95 Gy. Mapping of the generated TTFields demonstrated that both lesions were encompassed by a field intensity in a therapeutic range. The temporal lobe lesion remained under the control of TTFields up to 12 months, at which point progression on a T1 contrast MRI resulted in surgery and a definitive diagnosis of GB without MGMT methylation. The primary parietal lobe at this time was in remission. Molecular sequencing on the GB tissue from multiple time points demonstrates clonal evolution of the cancer over time and in response to treatment.

Keywords: glioblastoma, tumor treating fields, optune®, genomics, temozolomide

INTRODUCTION

Tumor Treating Field (TTFields) therapy has demonstrated efficacy in a Phase 3 study of newly diagnosed glioblastoma (GB) following radiation (RT) and temozolomide (TMZ) (1), as well as in the recurrent setting (2). Interestingly, there have been no reports of TTFields therapy in GB patients who have not received prior RT. In addition, the potential mechanisms by which resistance to TTFields therapy develops has been understudied.

In the report to follow, an analysis of a satellite lesion that developed after standard RT and TMZ therapy in a newly diagnosed GB patient is presented. Therapy with TTFields had been initiated 1 month prior to the appearance of the satellite lesion. The patient was followed longitudinally with MRIs every 2 months; additional analysis of the radiation dose exposure, as well as the TTFields intensity, was performed. The differential diagnosis at the time included an MRI artifact or lesion induced by TTFields, vs. progressive disease. After 12 months, the aforementioned lesion

was resected. Molecular alterations from baseline, post-progression on TTFields and following a further recurrence were assayed. The results below summarize these collective findings.

CLINICAL DETAILS AND DATA ANALYSIS

In March 2016, a 51-year old male presented with left-sided numbness and weakness. A MRI demonstrated a 35 × 25 × 29 mm partially cystic or necrotic, enhancing mass with internal hemorrhage in the right parietal lobe. Subtotal resection was accomplished in March 2016 confirming a grade 4 astrocytoma with IDH1/2 wild type, MGMT methylated, and negative 1p19q co-deletion.

Standard radio-chemotherapy was completed in June 2016 (3), including daily TMZ with a total of 60 Gy radiation give in 30 fractions; adjuvant TMZ began in July 2016. TTFields therapy (1) was initiated in July 2016 and continued until August 2017. A post-radiation MRI was done in August 2016, showing increased thickness of the residual enhancing region in the right parietal lobe in addition to a new lesion in the right middle temporal gyrus (**Figure 1**).

Changes of residual tumor in the right parietal lobe was presumed to be progression vs. pseudo-progression, and the patient continued with six cycles of adjuvant TMZ, which was completed in December 2016. The changes in the parietal lobe lesion resolved over time, confirming pseudo-progression. In spite of the appearance of the temporal lobe lesion, it was decided to continue therapy with both TMZ and TTFields (with frequent monitoring), as the possibility of an artifact of TTFields therapy and/or an unusual form pseudo-progression was raised.

On a series of follow-up MRIs from August 2016 to August 2017, the initial parietal lobe lesion regressed with adjuvant TMZ and appeared stable on both T1+contrast and T2/FLAIR MRIs. The new enhancing lesion in the temporal lobe (during adjuvant TTFields/TMZ therapy) decreased from 9 to 7.7 mm in diameter with decreasing enhancement from August 2016 to November 2016 (**Figure 1**), and stayed stable on bi-monthly follow up MRIs until August 2017. At this time the temporal lobe lesion was at 17.9 mm in diameter (on T1+contrast); the parietal lobe lesion was essentially resolved, confirming pseudo-progression of this tumor (**Figure 1**). T2/FLAIR images showed abnormality with an area of restricted diffusion and peripheral rim enhancement in the region of the right temporal lobe lesion. A gross total resection of the temporal lesion was achieved in August 2017, confirming a grade 4 astrocytoma, with wild type IDH1/2, unmethylated MGMT, and negative 1p19q co-deletion (**Figure 2**). The mean prior radiation dose for this temporal lesion was determined to be 4.53 Gy ± 0.95 Gy (5.7 Gy max; 3.5 Gy min; volume 0.1 mL). An isodose cloud is depicted (**Figure 3**). The lesion was 2.5 cm away from the edge of the planning target volume treated to full dose (46 Gy; center lesion dose 60 Gy).

The patient was then treated (September 2017–November 2017) with radiation (60 Gy in 30 fractions), targeting the temporal lobe resection cavity. An MRI in January 2018 demonstrated a possible new nodule (0.7 × 0.7 cm) on the edge of the resection cavity. A subsequent MRI in February 2018 confirmed progression with an increase in the aforementioned nodule to 1.4 × 1.8 cm. In March 2018, the patient underwent reoperation with a gross total resection as part of the TOCA 5 Tocagen Inc. clinical trial and was randomized to the control arm post-operatively. He started bevacizumab therapy in April 2018 which maintained his surgically obtained complete remission until relapse in August 2018.

Molecular analyses demonstrate that at resection of the primary parietal lobe lesion this cancer possessed mutations in *BRAF* (V600E), *PTEN* (319fs), and the *TERT* promoter (C228T). Following progression on TTFields, the separate anterior temporal lesion was resected. This lesion possessed these identical *BRAF*, *PTEN,* and *TERT* alterations, and was also found to possess a deep deletion of *CDK2NA* and an activating mutation in *mTOR* (V2006I). The lesion in the anterior temporal lobe that recurred following radiation was also sequenced following resection. This lesion was hypocellular, and similar to the prior resection exhibited mitosis, nuclear atypia and no necrosis; the same *BRAF*, *mTOR,* and *TERT* abnormalities were still able to be observed. No new alterations were detectable in this sample.

Additionally, a retrospective analysis demonstrated the TTFields intensity was in a therapeutic range for both the parietal lobe and temporal lobe lesion, i.e., 1 V/cm (**Figure 4**).

METHODS

Bio-Marker Testing

MGMT testing performed by LabCorp, NC; IDH testing done by PCR, UW Health Clinical labs, WI, 1p19q testing by FISH, Wisconsin State Laboratory of Hygiene.

Determination of Radiation Dose

Using image registration software (Mim Vistag Cleveland, OH) that imports the radiation dose, the axial contrast-enhanced 3D T1-weighted images (T1 3D-SPGR Bravo, GE Healthcare, Waukesha, WI) were fused into a coordinate system of the treatment planning CT. A region of interest was drawn around the anterior temporal lobe lesion, and dosimetric analysis revealed the prior RT dose to the lesion.

Mapping of TTFields Intensity

In order to estimate field intensity distributions within the lesions, numerical simulations were performed using finite differences Time Domain (FDTD) calculations and a realistic head model as described in Wenger et al. (4). Briefly, a realistic head computational model of a healthy male was created and scaled to match the dimensions the patient's head. Transducer arrays for the delivery of TTFields were positioned on the head model to mimic the personalized transducer array layout that was placed on the patient. In order to establish whether or not TTFields were delivered at therapeutic levels to the tumors, ellipsoidal regions approximately encompassing the lesions were manually marked on the field intensity maps. The field was considered to deliver TTFields at therapeutic levels to the lesion if the median field intensity within the respective ellipsoid exceeded 1 V/cm (5).

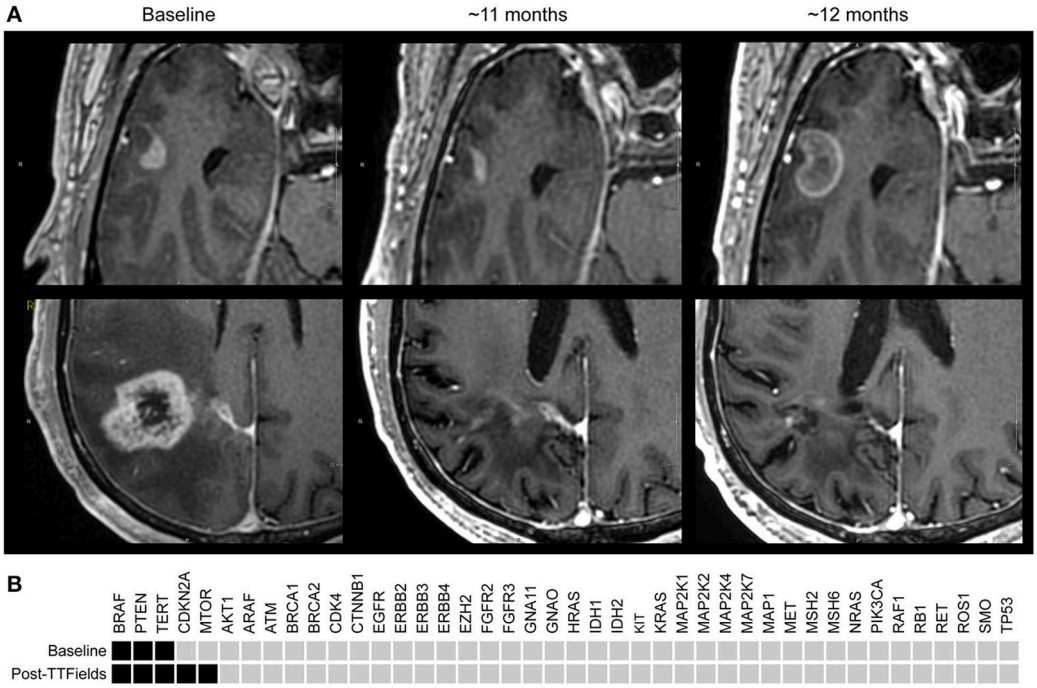


FIGURE 1 | (A) T1+contrast MRI images: Upper panels are right temporal lobe; lower panels are corresponding right parietal images. *Baseline* (Aug. 2016) demonstrates the first appearance a temporal lobe lesion ∼2 months post radiation/temozolomide; the lower panel demonstrates the primary GB. Middle section ∼*11 months* later (June 2017) demonstrates slightly less enhancement of the temporal lobe lesion, and a dramatic reduction in enhancement and size of the parietal lobe lesion with decreased edema and treatment related cerebral atrophy. At ∼*12 months* (Aug. 2017) the temporal lobe lesion has increased to 18 × 13 mm; the parietal lobe remains stable and in remission. **(B)** StrataNGS cancer hotspot sequencing was performed on the resection of the primary parietal lobe lesion, which possessed mutations in *BRAF* (V600E), *PTEN* (319fs), and the *TERT* promoter (C228T). Following progression on TTFields, the separate anterior temporal lesion was resected and demonstrated *BRAF*, *PTEN,* and *TERT* alterations, and the acquisition of a deep deletion of *CDK2NA* and an activating mutation in *mTOR* (V2006I). No other pathologic alterations were identified in the remaining 47 genes of the 88 genes assessed.

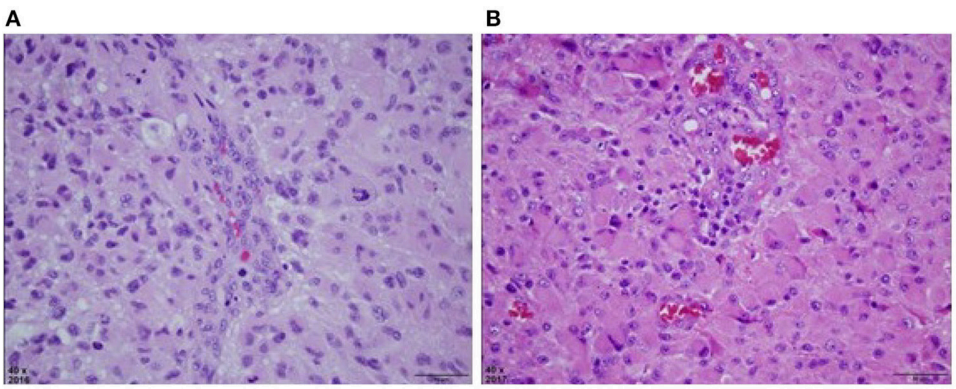


FIGURE 2 | (A) H&E stained section of right parietal tumor at original magnification of 40x, reveals a densely cellular astrocytic neoplasm with nuclear atypia, mitosis, and vascular endothelial proliferation. Palisaded necrosis was also present but not shown in this field. **(B)** H&E stained section of right temporal mass at original magnification of 40x, also reveals a densely cellular astrocytic neoplasm with slightly more gemistocytic features, nuclear atypia, mitosis, and vascular endothelial proliferation that was similar to the previously resected tumor. This material lacked necrosis.

Strata Oncology Hot Spot Sequencing

Patient samples were sequenced through STRATA Oncology CLIA-certified laboratory using the StrataNGS platform. This panel covers 88 genes and examines predefined variants including single and multinucleotide alterations, small insertions/deletions, fusions, exon skipping mutations, copy number variation, and microsatellite instability (www.strataoncology.com).

DISCUSSION

In this report, we present the first instance of a grade 4 astrocytoma controlled by systemic TMZ and TTFields, with negligible radiation exposure. The patient's initial parietal lobe lesion was MGMT methylated, not IDH mutated, and not 1p19q deleted; the resected temporal lobe lesion was similar histologically, but was not MGMT methylated. Based on the MRIs between June 28th to August 14th, 2016 (**Figure 1**), the volume doubling time was calculated (6) as 14 days for the temporal tumor.

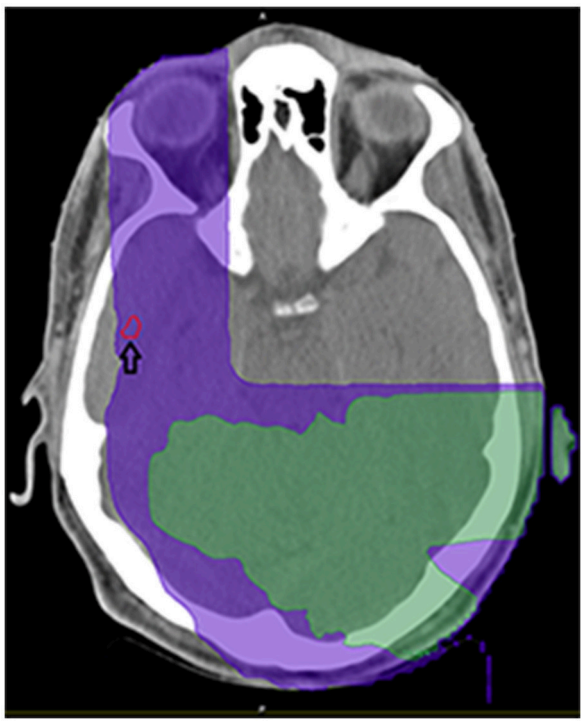


FIGURE 3 | Demonstration of isodose cloud for temporal lobe lesion (see arrow). Purple denotes 5Gy isodose; green denotes 8.57 Gy isodose.

As the temporal lobe tumor appeared after initial concurrent radiation and TMZ treatment, this tumor may have been TMZ resistant, which is consistent with the absence of methylation on MGMT promoter. Alternatively, a resistant TMZ clone may have evolved over time. The initial radiation field was reconstructed, showing that the temporal lobe was exposed to minimal radiation at the time, 4.53 ± 0.95 Gy. This region, however, was within the TTFields effective region, suggesting that the suppression of tumor growth from August 2016 to 2017 was under the control of adjuvant TMZ and/or TTFields.

The original plan for the placement of Optune^{TM} arrays using the NovoTAL^{TM} methodology (7) targeted the right parietal lesion. It was not intuitively obvious that the field distribution in the temporal lobe region would be sufficiently high to have a therapeutic effect. Hence, numerical simulations (**Figure 4**) were performed; the simulations demonstrate that the field intensity delivered to both lesions was at therapeutic levels (>1 V/cm). Taken collectively, these data support the efficacy of TTFields in a newly diagnosed GB regarding a lesion that received a negligible dose of ionizing radiation. The contribution of adjuvant TMZ in controlling this lesion is indeterminate as discussed above.

Based on the molecular sequencing we can see that the cells within the anterior temporal lobe lesion developed from cells in the original primary parietal lobe lesions as the exact alterations were identified in both instances. The additional alterations identified presumably arose through clonal selection. While many factors could have potentially played into this selection process, we propose that it is quite plausible that the activating mutation in mTOR and/or the deep loss of CDKN2A could be inducing the resistance to TTFields therapy.

Over the last few years, new mechanistic insights have been gained into the anti-cancer effects of TTFields. These potential mechanisms of action include disruption of key

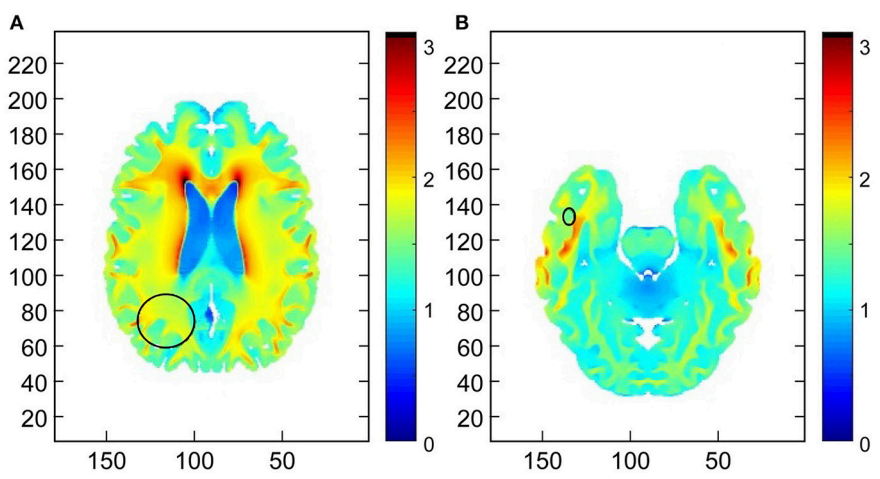


FIGURE 4 | Demonstration of the field intensity distribution in axial slices through the centers of the **(A)** primary right parietal lobe lesion and **(B)** the right temporal lobe secondary lesion. The median field intensity in the region of the primary lesion was 1.7 V/cm (mean of 1.66 V/cm). In the region of the secondary lesion the median intensity was 1.48 V/cm (mean of 1.56 V/cm). This suggests that TTFields intensities around both lesions exceeded the therapeutic threshold of 1 V/cm.

cellular functions, such as mitosis, DNA repair, mitochondrial function, and the folded protein response, leading to the induction of cellular stress, autophagy and apoptosis (5, 8–10). TTFields has also been implicated in enhancing the immune response through the induction of immunogenic cell death and modulation of antigen presentation (11). Loss of CDKN2A could lead to cell cycle dysregulation and mTOR activation could lead to inhibition of autophagy, apoptosis, and enhance cell proliferation overcoming some of the potential mediators of response to TTFields (12, 13). In addition, activation of the PI3K/AKT/mTOR signaling pathway has been associated with immune suppressive properties, including the up-regulation of the PD-L1 immune checkpoint.

In summary, this report provides evidence that TTFields may offer prolonged therapeutic benefit for some patients with recurrent GB. The molecular analysis of this patient's cancer over time provides potential insight to mechanisms by which resistance to TTFields might occur. This work also raises several interesting questions about how clonal evolution and spread through the central nervous system occurs, whether targeting therapies, such as mTOR or BRAF inhibitors, could be used in settings like this, and whether more routine molecular profiling should be obtained for patients with GB. Clearly, as we learn more about the biology of individual patients with GB this will lend itself to more precision-based treatment strategies for patients.

ETHICS STATEMENT

This is a case report regarding a patient treated with FDA approved standard of care treatment. Informed consent was obtained.

AUTHOR CONTRIBUTIONS

HN contributed to the clinical history review, literature review, and manuscript preparation. SH evaluated radiation dosing and reviewed the manuscript. SS reviewed pathology. AF reviewed the manuscript and MRI scans. HR identified the patient, reviewed the clinical history and the literature, and prepared the manuscript. DD performed the genomic analyses and edited the manuscript.

FUNDING

This research was supported in part by the: National Institutes of Health (NIH) (grant number P30 CA014520), UW Carbone Cancer pilot grant; the Decker Neuro-Oncology Research Fund.

ACKNOWLEDGMENTS

We would like to thank Ariel Naveh and Ze'ev Bomzon of Novocure Ltd., for performing the numerical simulations.

REFERENCES

1. Stupp R, Taillibert S, Kanner AA, Kesari S, Steinberg DM, Toms SA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. *JAMA* (2015) 314:2535–43. doi: 10.1001/jama.2015.16669
2. Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, Heidecke V, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *Eur J Cancer* (2012) 48:2192–202. doi: 10.1016/j.ejca.2012.04.011
3. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. (2005) 352:987–96. doi: 10.1056/NEJMoa043330
4. Wenger C, Bomzon Z, Salvador R, Basser PJ, Miranda PC. Simplified realistic human head model for simulating Tumor Treating Fields (TTFields). *Conf Proc IEEE Eng Med Biol Soc.* (2016) 2016:5664–7. doi: 10.1109/EMBC.2016.7592012
5. Kirson ED, Gurvich Z, Schneiderman R, Dekel E, Itzhaki A, Wasserman Y, et al. Disruption of cancer cell replication by alternating electric fields. *Cancer Res.* (2004) 64:3288–95. doi: 10.1158/0008-5472.CAN-04-0083
6. Schwartz M. A biomathematical approach to clinical tumor growth. *Cancer* (1961) 14:1272–94.
7. Wenger C, Salvador R, Basser PJ, Miranda PC. Improving tumor treating fields treatment efficacy in patients with glioblastoma using personalized array layouts. *Int J Radiat Oncol Biol Phys.* (2016) 94:1137–43. doi: 10.1016/j.ijrobp.2015.11.042
8. Shteingauz A, Porat Y, Giladi M, Schneiderman R, Voloshin T, Munster M, et al. Induction of autophagy following TTFields application serves as a survival mechanism mediated by AMPK activation. In: *Proceedings of the 109th Annual Meeting of the American Association of Cancer Research 2018 Apr 14-18*. Chicago, IL; Philadelphia, PA: AACR (2018).
9. Karanam N, Ding L, Sishc B, Saha D, Story MD. Newly identified role of tumor treating fields in DNA damage repair and replication stress pathways. In: *Proceedings of the 109th Annual Meeting of the American Association of Cancer Research (2018) Apr 14-18*. Chicago, IL; Philadelphia, PA: AACR (2018).
10. Michelhaugh SK, Kiousis S, Klinger NV, Mittal S. Tumor treating fields (TTFields) decrease proliferation of patient-derived lung cancer brain metastasis cell *in vitro*. In: *Proceedings of the 109th Annual Meeting of the American Association of Cancer Research 2018 Apr 14-18*. Chicago, IL; Philadelphia, PA: AACR (2018).
11. Wong ET, Timmons J, Swanson KD. Tumor treating fields exert cellular and immunologic effects. In: *Proceedings of the 109th Annual Meeting of the American Association of Cancer Research 2018 Apr 14-18*. Chicago, IL. Philadelphia (PA): AACR (2018) Abstract 1707.
12. Zhao R, Choi BY, Lee MH, Bode AM, Dong Z. Implications of genetic and epigenetic alterations of CDKN2A (p16 (INK4a)) in cancer. *Ebio Med.* (2016) 8:30–9. doi: 10.1016/j.ebiom.2016.04.017
13. Populo H, Lopes JM, Soares P. The mTOR signaling pathway in human cancer. *Int J Mol Sci.* (2012) 13:1886–918. doi: 10.3390/ijms13021886

Conflict of Interest Statement: HR and DD have support for laboratory research from Novocure, Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CASE REPORT
published: 26 October 2018
doi: 10.3389/fneur.2018.00919

Somatic SMARCB1 Mutation in Sporadic Multiple Meningiomas: Case Report

Alice S. Wang[1], *Ali O. Jamshidi*[1]*, *Nathan Oh*[1], *Ronald Sahyouni*[1], *Behdokht Nowroozizadeh*[2], *Ronald Kim*[2,3], *Frank P. K. Hsu*[1,3] *and Daniela Bota*[2,3,4]

[1] Department of Neurological Surgery, University of California-Irvine Medical Center, Orange, CA, United States, [2] Department of Pathology and Laboratory Medicine, University of California-Irvine Medical Center, Orange, CA, United States, [3] Chao Comprehensive Cancer Center, University of California-Irvine Medical Center, Orange, CA, United States, [4] Department of Neurology, University of California-Irvine Medical Center, Orange, CA, United States

Background: Multiple intracranial meningiomas account for <10% of all meningiomas. Familial multiple meningiomas have been linked to germline mutations in two genes: *neurofibromatosis type 2* (NF2) and *SWIch/Sucrose Non-Fermentable (SWI/SNF)-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1* (SMARCB1). Sporadic multiple meningiomas have been associated with somatic NF2 mutations and, to date, there has been no case related to somatic SMARCB1 mutations. Here, we describe the first case.

Case Report: A 45-year-old female suffered a head trauma while snowboarding. Subsequent to her injury, she experienced persistent headache, nausea, vomiting, dizziness, and flashing lights in the right eye. Magnetic resonance imaging (MRI) of her brain revealed multiple intracranial meningiomas. She underwent a two-staged craniotomy to remove frontal/parietal/temporal and occipital extra-axial tumors. Pathology confirmed the masses as meningiomas, WHO Grade I. Tumor genetic testing was positive for SMARCB1 mutation but blood genetic testing was negative for SMARCB1 mutation.

Conclusion: In sporadic multiple meningiomas, somatic NF2 mutations are usually the suspected genetic alternations. Our case illustrates that somatic SMARCB1 mutation is another genetic risk factor for sporadic multiple meningiomas, albeit rare.

Keywords: sporadic multiple meningiomas, familial multiple meningiomas, SMARCB1, NF2, somatic mutation, germline mutation

OPEN ACCESS

Edited by:
Marcos Vinicius Calfat Maldaun, Hospital Sírio-Libanês, Brazil

Reviewed by:
Maria Caffo, Università degli Studi di Messina, Italy
Mariko D. DeWire, Cincinnati Children's Hospital Medical Center, United States

***Correspondence:**
Ali O. Jamshidi
aliojam@gmail.com

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *04 August 2018*
Accepted: *10 October 2018*
Published: *26 October 2018*

Citation:
Wang AS, Jamshidi AO, Oh N, Sahyouni R, Nowroozizadeh B, Kim R, Hsu FPK and Bota D (2018) Somatic SMARCB1 Mutation in Sporadic Multiple Meningiomas: Case Report. Front. Neurol. 9:919. doi: 10.3389/fneur.2018.00919

INTRODUCTION

The phenomenon of multiple meningiomas is rare, accounting for <10% of all meningiomas (1). Multiple meningiomas can be categorized as familial or sporadic. Familial multiple meningiomas can manifest due to neurofibromatosis type 2 (NF2) disease, in which the NF2 gene on chromosome 22 mutates the growth inhibitory function of Merlin. Alternatively, familial multiple meningiomas can be inherited in an autosomal dominant fashion without the involvement of the NF2 gene (2). Sporadic multiple meningiomas are usually associated with somatic NF2 mutations (heinrich). Somatic SMARCB1 mutations have been associated with sporadic meningiomas in the literature; however, these were sporadic *solitary* meningiomas (3–5). To date,

there is no documented report of somatic SMARCB1 mutation as the underlying genetic alternation for sporadic *multiple* meningiomas. The authors describe the first case of a somatic SMARCB1 mutation in a patient with sporadic multiple meningiomas who harbors no NF2 mutations.

CASE REPORT

The authors report the case of a 45-year-old female who suffered a snowboarding accident and presented several days following the event complaining of persistent headache, nausea, vomiting, dizziness, and photic auras in the right eye. She visited an urgent care facility twice and during these visits, no imaging was obtained. A neurologist saw her 18 days after the accident. An MRI scan was ordered that showed multiple masses some of which harbored hemorrhagic components: a left frontal parafalcine, calcified 2.0 × 2.2 × 3.3 cm [anteroposterior (AP), transverse (TV), craniocaudal (CC)] mass with associated vasogenic edema, a 4.5 × 2.9 × 4.1 cm (AP, TV, CC) mass in the left frontotemporal convexity with another mass measuring approximately 2.3 × 2.0 × 1.9 cm (AP, TV, CC) located just superiorly, and a 2.6 × 2.9 × 3.9 cm (AP, TV, CC) mass in the left occipital lobe (**Figure 1**). Additionally, there was an 8 mm left to right midline shift (**Figure 1**). Her findings were most consistent with multiple meningiomas. There was also a possible vestibular schwannoma measuring 0.7 × 1.4 × 0.7 cm (AP, TV, CC) in the left internal auditory canal (figure not shown). Initially, she was thought to have NF2. Pre-surgical tumor embolization and a two-staged surgery were recommended. The patient had successful embolization of the left middle meningeal artery and left posterior meningeal artery.

The first surgical stage involved a left-sided craniotomy for resection of the frontal-parietal-temporal meningiomas; pathology reported WHO Grade I meningiomas with a low/moderate proliferation index (percentages of positive Ki-67 tumor nuclei: left occipital mass: 2–3%; midline frontal mass: 3–4%; and left frontal mass: 1–2%; **Figure 1**). NF-2 blood testing (NEUROFIBROMATOSIS TYPE 2 SEQUENCING AND DELETION/DUPLICATION ANALYSIS IN Blood, UAB), which has a mutation detection rate in leukocytes of 93% was negative. This specific study detects truncating mutations (nonsense, frameshift, splicing mutations including deep intronic splice mutations), missense mutations, multi-exon deletions or duplications, and total gene deletions. Post-operative MRIs showed resection of the meningiomas in the left frontal/parietal/temporal convexity (**Figure 2**). Seven months

Abbreviations: SWI/SNF, SWItch/Sucrose Non-Fermentable; SMARCB1, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1; NF2, neurofibromatosis type 2; MRI, magnetic resonance imaging; WHO, World Health Organization; AP, anteroposterior; TV, transverse; CC, craniocaudal; q, long arm of the chromosome.

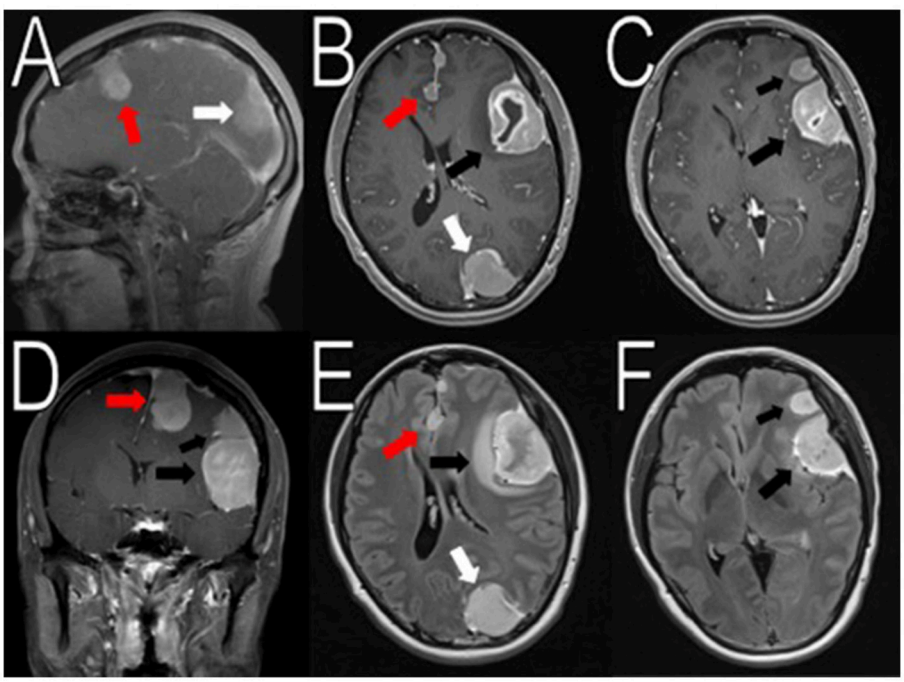


FIGURE 1 | Initial imaging showing multiple menigniomas. Preoperative contrasted T1 and T2 MRI scans reveal multiple meningiomas. The left calcified parafalcine lobulated mass (2 × 2.2 × 3.3 cm, AP, TV, CC) was associated with vasogenic edema (red arrows in **A,B, D–E**). In the left frontal temporal convexity, there was a 4.5 × 2.9 × 4.1 cm (AP, TV, CC) mass with another 2.3 × 2.0 × 1.9 cm (AP, TV, CC) mass located superior to it (black arrows in **B–F**). In the occipital lobe, the mass was measured to be 2.6 × 2.9 × 3.9 cm (AP, TV, CC) (white arrows in **A,B,E**). There was an 8 mm rightward midline shift. The images seemed to suggest neurofibromatosis type 2.

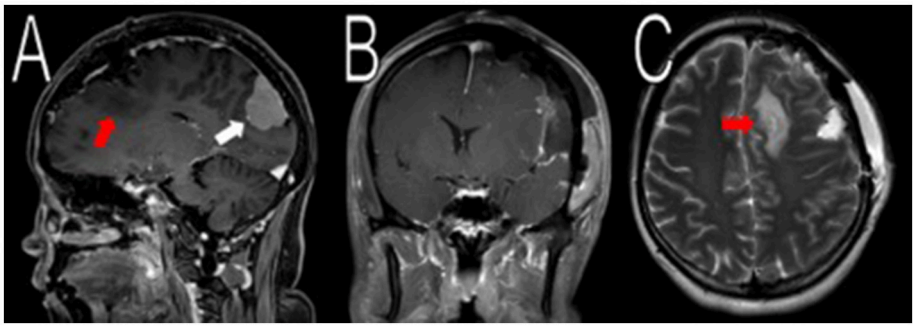


FIGURE 2 | Resection of the frontal/parietal/temporal mass. Post-operative MRI contrasted T1 and T2 scans showed resection of the meningiomas in the left frontal/parietal/temporal convexity with expected post-operative changes (red arrows in **A,C**, not shown in **B**). The occipital lobe mass was visible from the sagittal view (white arrow in **A**).

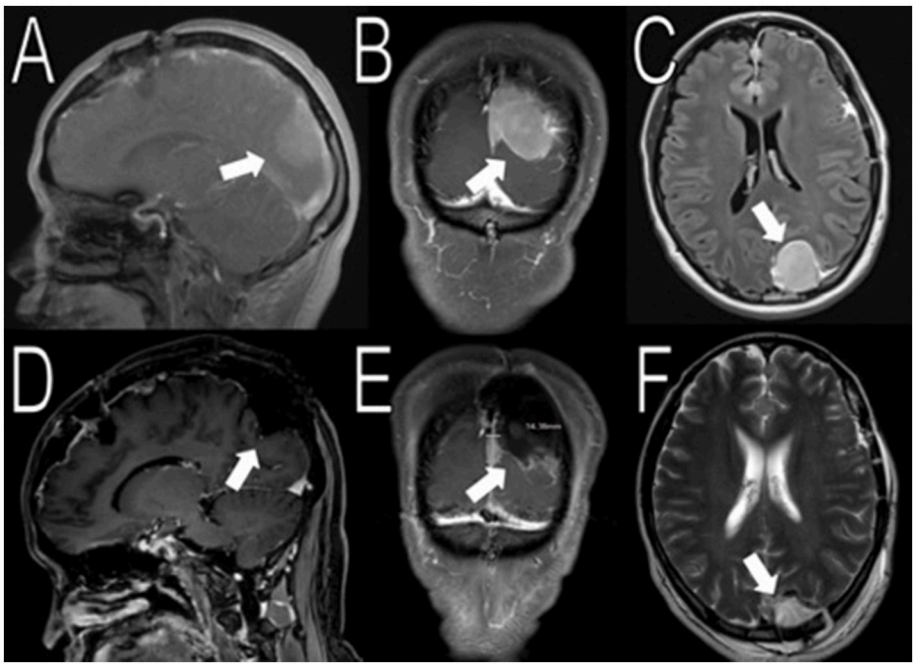


FIGURE 3 | Resection of the occipital mass. Preoperative MRI showed a 2.6 × 2.9 × 3.9 cm (AP, TV, CC) mass in the left occipital convexity (white arrows in **A–C**). Immediate post-operative MRI showed removal of the mass (white arrows in **D–F**).

after her first-stage surgery, she underwent the second surgical stage: left occipital craniotomy for resection of a 2.9 × 2.7 × 4.2 cm (AP, TV, CC) mass (**Figure 3**). A specimen from the left occipital mass was sent to pathology which classified it as meningioma, WHO Grade I with a Ki-67 of 2–3% (**Figure 4**). Her most recent post-operative MRI scans at 16 months of follow up show multiple stable enhancing extra-axial masses compared to her immediate post-operative ones with no new lesions observed (**Figure 5**).

In addition to having multiple meningiomas, she also had a soft tissue mass in her right palm and moles in her left axilla. MRI scans showed the mass to be approximately 11 × 10 × 20 mm (**Figure 6**) with unclear pathology, and the patient was referred to plastic surgery. The patient underwent surgery to excise her cystic mass and pathology found it to be a benign nerve sheath tumor, consistent with Schwannoma with positive immunostain S-100. As for the moles on her left armpit, a shaved biopsy was obtained and pathology confirmed pigmented seborrheic keratosis, consistent with an atypical mole.

Because she was NF2 negative, further genetic testing was pursued for both somatic and germline mutations. Foundation Medicine, Inc. (Cambridge, Massachusetts, USA) tested her tumor tissue positive for SMARCB1 mutation (but not for NF2) while her blood genetic testing was negative for SMARCB1 mutation.

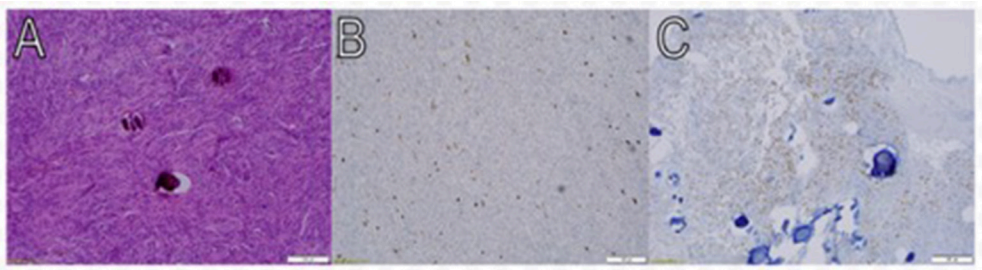


FIGURE 4 | Pathologic findings of meningothelial meningioma. Macroscopic view at low power magnification (10X) shows meningothelial cells that are packed together in fascicles and whorls in a syncytial pattern. The nuclei are round and uniform, and occasional psammoma bodies are noted **(A)**. Approximately 2–3% of tumor cells nuclei are immunoreactive for Ki- 67 (Immunostainx100) **(B)**. Some of the tumor cells are immunoreactive for PR (Immunostainx100) **(C)**.

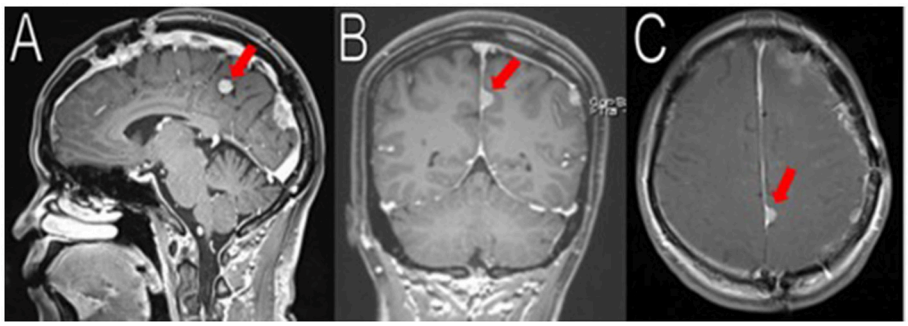


FIGURE 5 | Latest imaging. Her most recent MRIs (16 months after her last surgery) show multiple enhancing extra-axial masses, stable compared to her immediate post-operative MRIs. Here is a stable 1.8 cm (superior-inferior) meningioma arising from the left posterior falx, adjacent to the prior resection cavity (red arrows in **A–C**). No recurrence observed.

DISCUSSION

Multiple meningiomas occur in <10% of patients with meningiomas (1). Multiple meningiomas, whether sporadic or familial, seem to have a clonal origin, rather than an isolated formation of unrelated tumors (6, 7). Cerebrospinal fluid may be the vehicle of transportation for spreading the clonal tumor cells to various locations in the central nervous system (7).

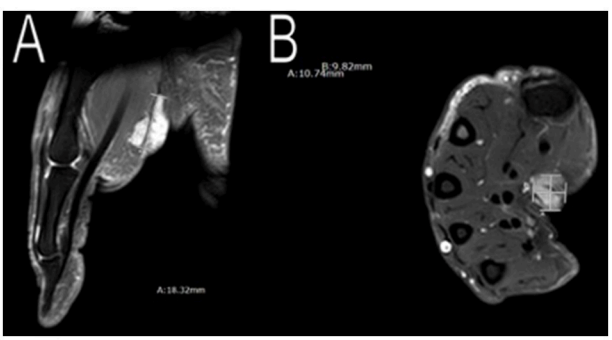


FIGURE 6 | Imaging of her right palm mass. MRI scans showed an approximately 11 × 10 × 20 mm mass in her right palm. Plastic surgery excised the mass and pathology confirmed a benign nerve sheath tumor, consistent with Schwannoma **(A,B)**.

Neurofibromatosis type 2 disease harbors mutations in the NF2 gene, which are well-known risk factors associated with familial multiple meningiomas and sporadic multiple meningiomas (3, 4, 8). The NF2 gene is located at chromosome 22q12.2 and regulates the production of Merlin (schwannomin), a tumor suppressor protein. Approximately 50% of patients with NF2 disease inherit germline NF2 mutations and develop multiple meningiomas (9). The type and position of mutations in the NF2 gene contribute to a differential risk of developing multiple meningiomas. For example, truncating mutations at the proximal 5′ end of the gene pose a higher risk than non-truncating mutations at proximal 3′ end of the gene (10). The most common genetic risk factor is somatic NF2 mutations in sporadic multiple meningiomas (3–5).

Another gene of particular interest is SMARCB1 (aka INI1 and SNF5), which is located on chromosome 22 but at 22q11.23 (4). SMARCB1 is a tumor suppressor protein that is part of the SWI/SNF complex that remodels chromatin structures for transcription (11). For an extensive discussion of the underlying pathophysiological mechanisms, we refer the reader to Kalimuthu et al. (12). Mutations in the SMARCB1 gene have been associated with malignant rhabdoid tumor, schwannomatosis, and meningiomas (11, 13, 14). Bacci et al. found in a family study that germline SMARCB1 mutations, with no somatic SMARCB1 or NF2 mutations, are associated with familial schwannomatosis and multiple meningiomas (14).

In a follow-up study by Hadfield et al., they found no germline SMARCB1 mutations in multiple meningiomas. This study contained both sporadic and familial multiple meningiomas (5:1 ratio in patient proportion); therefore, these sample differences could have contributed to this finding. Additionally, the sample size was small; only 6/47 patients had tumor DNA and blood DNA available for analysis (15). In another family study done by Christiaans et al., germline SMARCB1 mutation and somatic NF2 mutations were found in familial multiple meningiomas. They proposed the four-hit mechanism involving both tumor suppressor genes SMARCB1 and NF2 (13). Interestingly, van den Munckhof et al. found that germline SMARCB1 mutation and somatic NF2 mutations preferentially localized the cranial meningiomas at the falx cerebri (16).

Somatic SMARCB1 mutations have also been studied in meningiomas. Somatic SMARCB1 mutations have been reported in sporadic meningiomas; however, a closer examination of these reports reveals the meningiomas were *solitary* (17, 18). To date, there is no report of somatic SMARCB1 mutations in sporadic *multiple* meningiomas. The authors describe the first case in which somatic SMARCB1 mutation contribute to the development of sporadic multiple meningiomas.

Initially, the authors hypothesized that the patient likely had a founder germline NF2 mutation given that she has no family history of NF2. Once it was determined that she had no NF2 mutations in either blood or the tumor tissue, the authors tested for other mutations. Fountain Medicine, Inc. (Cambridge, Massachusetts, USA) found a mutation in the SMARCB1 gene. Her blood test was negative for SMARCB1 mutation, indicating that she did not harbor known or expected germline SMARCB1 mutations. It is unlikely, although still plausible, that the genetic testing yielded a false negative result, however, based on the family history and her clinical presentation, this is less likely. Therefore, she had a somatic mutation in the SMARCB1 gene. Because she harbored only this mutation and she developed sporadic multiple meningiomas, the authors believe somatic SMARCB1 mutation poses a genetic risk for sporadic multiple meningiomas.

CONCLUSION

Sporadic multiple meningiomas are rare phenomena and germline or somatic NF2 mutations are usually the culprit. Here, the authors describe the first case in which somatic SMARCB1 mutation is responsible for the development of sporadic multiple meningiomas. Somatic SMARCB1 mutation is a genetic risk factor for sporadic multiple meningiomas and should be considered for testing when markers for NF2 are negative in similar clinical situations as it could be a marker for possible future therapeutics.

ETHICS STATEMENT

This study received an exemption from our institutional review board due to the nature of the study and the fact that it is a case report with fewer than 3 subjects.

CONSENT

Written, informed consent was obtained from the participant for the publication of this case report.

AUTHOR CONTRIBUTIONS

AW, AJ, NO, RS, BN, RK, FH, and DB contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

REFERENCES

1. Nahser HC, Grote W, Lohr E, Gerhard L. Multiple meningiomas. Clinical and computer tomographic observations. Neuroradiology (1981) 21:259-63.
2. Wong RH, Wong AK, Vick N, Farhat HI. Natural history of multiple meningiomas. Surg Neurol Int. (2013) 4:71. doi: 10.4103/2152-7806.112617
3. Heinrich B, Hartmann C, Stemmer-Rachamimov AO, Louis DN, MacCollin M. Multiple meningiomas: Investigating the molecular basis of sporadic and familial forms. Int J Cancer (2003) 103:483-88. doi: 10.1002/ijc.10840
4. Lamszus K. Meningioma pathology, genetics, and biology. J Neuropathol Exp Neurol. (2004) 63:275-86. doi: 10.1093/jnen/63.4.275
5. Torres-Martin M, Kusak ME, Isla A, Burbano RR, Pinto GR, Melendez B, et al. Whole exome sequencing in a case of sporadic multiple meningioma reveals shared NF2, FAM109B, and TPRXL mutations, together with unique SMARCB1 alterations in a subset of tumor nodules. Cancer Genet. (2015) 208:327-32. doi: 10.1016/j.cancergen.2015.03.012
6. Larson JJ, Tew JM, Jr., Simon M, Menon AG. Evidence for clonal spread in the development of multiple meningiomas. J Neurosur. (1995) 83:705-9. doi: 10.3171/jns.1995.83.4.0705
7. Stangl AP, Wellenreuther R, Lenartz D, Kraus JA, Menon AG, Schramm J, et al. Clonality of multiple meningiomas. J Neurosur. (1997) 86:853-8. doi: 10.3171/jns.1997.86.5.0853
8. Ruttledge MH, Sarrazin J, Rangaratnam S, Phelan CM, Twist E, Merel P, et al. Evidence for the complete inactivation of the NF2 gene in the majority of sporadic meningiomas. Nature genetics (1994) 6:180-4. doi: 10.1038/ng0294-180
9. Smith MJ. Germline and somatic mutations in meningiomas. Cancer genetics (2015) 208:107-14. doi: 10.1016/j.cancergen.2015.02.003
10. Smith MJ, Higgs JE, Bowers NL, Halliday D, Paterson J, Gillespie J, et al. Cranial meningiomas in 411 neurofibromatosis type 2 (NF2) patients with proven gene mutations: clear positional effect of mutations, but absence of female severity effect on age at onset. J Med Genet. (2011) 48:261-5. doi: 10.1136/jmg.2010.085241
11. Versteege I, Sevenet N, Lange J, Rousseau-Merck MF, Ambros P, Handgretinger R, et al. Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. Nature (1998) 394:203-6. doi: 10.1038/28212
12. Kalimuthu SN, Chetty R. Gene of the month: SMARCB1. J Clin Pathol. (2016) 69:484-9. doi: 10.1136/jclinpath-2016-203650
13. Christiaans I, Kenter SB, Brink HC, van Os TAM, Baas F, van den Munckhof P, et al. Germline SMARCB1mutation and somatic NF2 mutations in familial multiple meningiomas. J Med Genet. (2011) 48:93-7. doi: 10.1136/jmg.2010.082420
14. Bacci C, Sestini R, Provenzano A, Paganini I, Mancini I, Porfirio B, et al. Schwannomatosis associated with multiple meningiomas due to a familial SMARCB1 mutation. Neurogenetics (2010) 11:73-80. doi: 10.1007/s10048-009-0204-2

15. Hadfield KD, Smith MJ, Trump D, Newman WG, Evans DG. SMARCB1 mutations are not a common cause of multiple meningiomas. J Med Genet. (2010) 47:567-8. doi: 10.1136/jmg.2009.075721
16. Van den Munckhof P, Christiaans I, Kenter SB, Baas F, Hulsebos TJ. Germline SMARCB1 mutation predisposes to multiple meningiomas and schwannomas with preferential location of cranial meningiomas at the falx cerebri. Neurogenetics (2012) 13:1-7. doi: 10.1007/s10048-011-0300-y
17. Schmitz U, Mueller W, Weber M, Sevenet N, Delattre O, von Deimling A. INI1 mutations in meningiomas at a potential hotspot in exon 9. Br J Cancer (2001) 84:199-201. doi: 10.1054/bjoc.2000.1583
18. Rieske P, Zakrzewska M, Piaskowski S, Jaskolski D, Sikorska B, Papierz W, et al. Molecular heterogeneity of meningioma with INI1 mutation. Mol Pathol. (2003) 56:299-301. doi: 10.1136/mp.56.5.299

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

CASE REPORT
published: 06 November 2018
doi: 10.3389/fonc.2018.00510

Identification of Novel Genes Involved in the Pathogenesis of an ACTH-Secreting Pituitary Carcinoma: A Case Report and Literature Review

Fuyou Guo, Guoqing Wang, Fang Wang, DingKang Xu and Xianzhi Liu*

Department of Neurosurgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Pituitary carcinomas (PCs) is considerable uncommon entities with a poor prognosis that represents only 0. 1–0.2% of all pituitary tumors. There are fewer than 150 reported cases up to now. In addition, the molecular pathogenesis leading to malignant pituitary transformation remain unclear due to the rarity of PCs. Here we present an uncommon case of ACTH-secreting PCs and explore the gene mutation following pituitary adenoma transformation. Our detailed clinical, histopathological and molecular detection data suggest that novel genes of ATRX and PTEN were implicated in the pathogenesis of PCs by searching Pubmed and the Web of Science databases as well as Cosmic databank. To the best of our knowledge, this is the first documented rare PCs patient with novel gene mutations that included ATRX and PTEN in addition to TP53. Present finding may therefore provide significant information for targeted therapy of PCs.

Keywords: pituitary carcinoma, mutant genes, molecular mechanism, targeted therapy, ATRX, PTEN

OPEN ACCESS

Edited by:
Claudio Tatsui,
University of Texas MD Anderson Cancer Center, United States

Reviewed by:
Brad E. Zacharia,
Penn State Milton S. Hershey Medical Center, United States
Dimitris G. Placantonakis,
New York University, United States

****Correspondence:***
Fuyou Guo
chyou666@hotmail.com

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *03 August 2018*
Accepted: *19 October 2018*
Published: *06 November 2018*

Citation:
Guo F, Wang G, Wang F, Xu D and Liu X (2018) Identification of Novel Genes Involved in the Pathogenesis of an ACTH-Secreting Pituitary Carcinoma: A Case Report and Literature Review. Front. Oncol. 8:510. doi: 10.3389/fonc.2018.00510

INTRODUCTION

Pituitary carcinomas (PCs) constitute an extremely rare clinical entity that represents only 0.1–0.2% of all pituitary tumors, and there are fewer than 150 reported cases (1). PCs usually develop from progressive atypical pituitary adenomas and predominantly consist of hormone-generating tumors, defined by systemic metastases or the presence of disseminations to the cerebrospinal system. However, the molecular pathogenesis leading to malignant pituitary transformation is largely unidentified. A comprehensive understanding of the molecular mechanisms driving malignant pituitary progression would be beneficial for the treatment of pituitary carcinoma. Herein we described an uncommon PCs and the novel genes involved, providing useful evidence for future targeted therapy.

CASE DESCRIPTION

A 55-years-old male presented with progressive deterioration of visual acuity and dizziness for 2 months. A preoperative computed tomographic (CT) scan revealed a large-mass lesion of the sellar region with extreme suprasellar extension (**Figure 1A**). Magnetic resonance imaging (MRI) demonstrated a large lesion located in the sellar region with heterogeneous enhancement and invasion to both cavernous sinuses (**Figures 1B–D**). The size of the tumor upon MRI was ∼3.0 × 2.5 × 4.0 cm. Endocrinologic tests showed that the levels of adrenocorticotropic hormone (ACTH) were significantly elevated to 411.3 pg/ml (range, 7.2–63.3) at 8 a.m. and 352.1 pg/ml

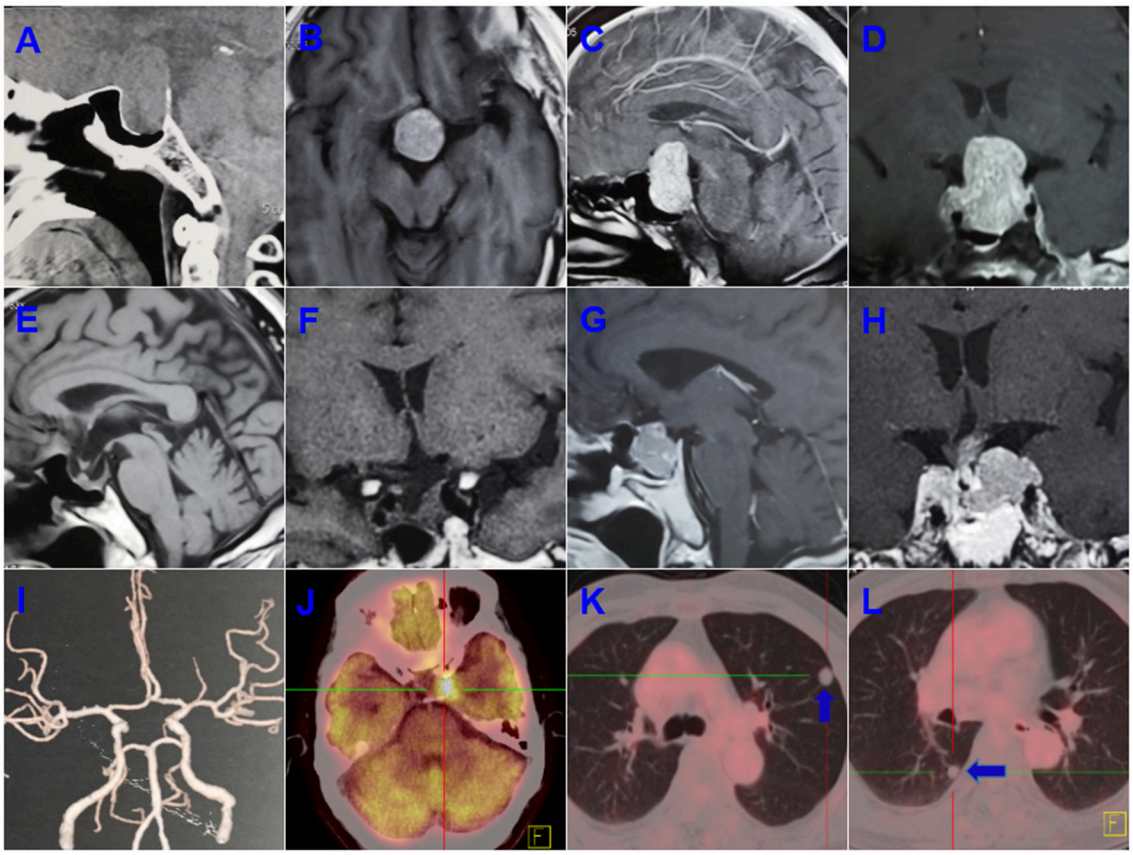


FIGURE 1 | Preoperative computed tomographic (CT) scanning revealed a large mass lesion in the sellar region **(A)**. Magnetic resonance imaging (MRI) also demonstrated a large lesion located in the sellar region, with heterogeneous enhancement and invasion to both cavernous sinuses **(B–D)**. Subtotal resection was obtained after operation **(E,F)**. A recurrent tumor was involved in the saddle fossa and left cavernous sinus **(G,H)**. Computed tomographic angiography (CTA) ruled out a left posterior communicating artery aneurysm **(I)**. The PET-CT showed a residual intracranial tumor in the left cavernous sinus after a second operation **(J)**. Multiple metastatic lesions were found in the lung (**K,L**; blue arrow indicates the metastatic lesion).

(4–32) at 4 p.m. The cortisol concentrations were 1,123.9 ng/ml (171–536) at 8 a.m. and 912.3 ng/ml (64–327) at 4 p.m. Other hormones, such as prolactin, growth hormone, free thyroxine (T3 and T4), and thyroid-stimulating hormone (TSH) were normal. The patient underwent an endonasal transsphenoidal surgery, and subtotal resection was obtained after the operation (**Figures 1E–H**). The postoperative ACTH levels dropped to 96.8 pg/ml at 8 a.m. and 78.3 pg/ml at 4 p.m., and the level of cortisol was reduced to 321.1 ng/ml at 8 a.m. and 165.2 ng/ml at 4 p.m. The residual tumor at the left cavernous sinus was subsequently treated with gamma knife surgery.

The ACTH and cortisol values remained stable during the 4 years of follow-up. However, 5 years after the first surgery, the patient was readmitted with a history of 20 days of left visual disturbance and 10 days of left eyelid ptosis. A MRI scan revealed a recurrent tumor in the sellar region and invasion of the left cavernous sinus. Computed tomographic angiography (CTA) was adopted to rule out an aneurysm of the left posterior communicating artery, and no aneurysm was found on CTA (**Figure 1I**). Hormonal evaluation showed slightly decreased levels of FT3 and FT4 (3.12 pmol/L [3.28–6.47] and 5.22 pmol/L [7.9–18.4], respectively). The ACTH levels were 41.3 pg/ml (7.0–61.1) at 8 a.m. and 38.6 pg/ml (3.5–30.55) at 4 p.m., and the levels of cortisol were 4.9 ug/dl (7–27) at 8 a.m. and 17.6 ug/dl (3.5–13.5) at 4 p.m. A second surgery was performed. The postoperative FT3, FT4, TSH, and cortisol values were significantly decreased compared with respective preoperative hormone levels. The patient was discharged under hormonal replacement therapy with euthyrox (25 ug/d) and cortisone acetate, and adjustment dosages were administrated based on subsequent endocrinologic tests. Postoperative histopathologic examination showed the presence of a PC. PET-CT was used for further evaluation and a residual intracranial tumor was observed in the left cavernous sinus (**Figure 1J**). Multiple metastatic lesions were also found in the lung (**Figures 1K,L**), and biopsy of these lesions revealed a metastatic neuroendocrine tumor.

Initial postoperative histopathologic examination revealed a pituitary adenoma, and microscopic evaluation showed that the tumor consisted of circular cells of uniform morphology

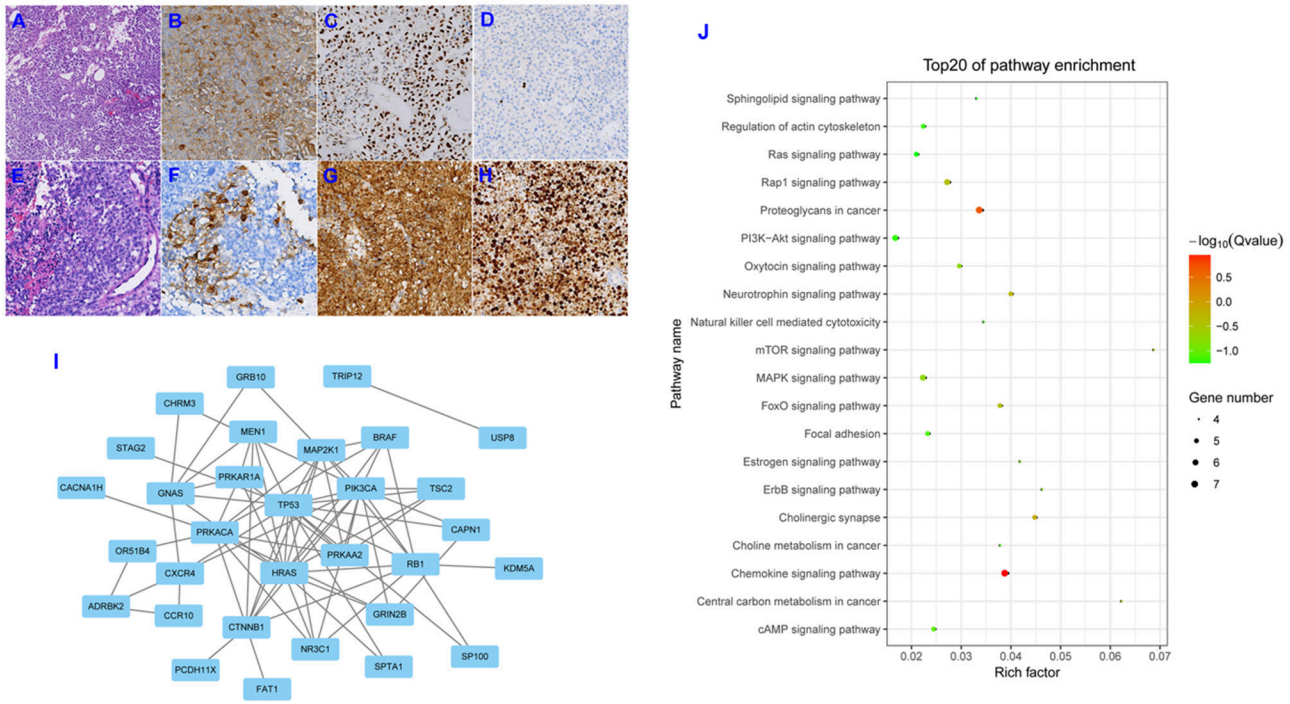


FIGURE 2 | Hematoxylin and eosin (H&E) staining showed circular cells with uniform morphology and no heterotypic cells for the first operation specimen (**A**; original magnification, ×200). Immunohistochemical (IHC) staining revealed positive expression for ACTH and P-53 (**B,C**; original magnification, ×200), and Ki-67 expression was essentially negative (**D**; original magnification, ×200). H&E staining revealed excessive pleomorphic cells and frequent mitoses (**E**; original magnification, ×200). IHC staining was positive for the expression of ACTH (**F**; original magnification, ×200), and strongly positive staining for P53 and Ki-67 was observed (**G,H**; original magnification, ×200). Depiction of the protein-protein interaction (PPI) network for the 44 mutant genes involved in pituitary adenomas **(I)**. Depiction of the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways enriched for the 44 mutant genes **(J)**.

(**Figure 2A**). Immunohistochemical staining was positive for the expression of ACTH and P53 (**Figures 2B,C**), and Ki-67 expression was essentially negative (**Figure 2D**). A second postoperative histopathologic examination showed the presence of a PC. Hematoxylin and eosin staining also revealed the presence of excessive pleomorphic cells and frequent mitoses (**Figure 2E**). Immunohistochemical staining was positive for the expression of ACTH (**Figure 2F**), with strong positive staining for P53 and Ki-67 (**Figures 2G,H**); in fact, Ki-67 expression was up to 80%. In addition, we conducted a systematic review of the literature by searching Pubmed and Web of Science databases, and the Cosmic databank to ascertain all published studies on alterations in gene expression with respect to pituitary adenomas and pituitary carcinomas. Our literature search identified 44 mutant genes in pituitary adenomas. Their protein-protein interaction (PPI) network is shown in **Figure 2I**. Using these 44 genes, we found enrichment of several GO groups using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database (**Figure 2J**). Among these GO groups were signaling pathways involving Ras, mTOR, MAPK, FoxO, ErbB, focal adhesion, and PI3K-Akt. However, we only uncovered limited novel gene expression changes and related clinical features from an isolated case report regarding PC (2–7) (see **Table 1**). In light of the exceeding rareness of PCs, molecular profiles of genes in the current rare case were derived by the Beijing Pangenomics Technology Co., Ltd. Only 3 gene mutations were found among 509 genes examined in the ACTH-producing PC in our study, including mutations in ATRX (alpha thalassemia/mental retardation syndrome X-linked) and P53. In addition, we uniquely identified the novel mutation in PTEN (Phosphatase and tension homolog deleted on chromosome 10) by comparison analysis with published data on PCs. The patient's residual tumor was well-controlled by temozolomide and general radiotherapy for 3 months, and there have been no new lesions or metastases.

DISCUSSION

PCs are considered uncommon entities and exhibit a poor prognosis due to their highly aggressive biology. Unlikely pituitary adenomas, PCs have received little attention, and the malignant transformation process from pituitary adenomas remains unclear. The present case is consistent with the criteria governing PCs as follows: (1) our patient experienced pituitary adenoma resection and subsequent adjuvant radiation as previous management; (2) a second postoperative histopathologic examination showed that the tumor was highly malignant, with Ki-67 expression up to 80%; and (3) multiple metastases into the lungs were

TABLE 1 | Summary of the literature regarding mutant genes involved in PCs cases.

References	Sex	Age	PC type	Metastasis location	Mutation gene	Treatment	Follow-up
Greenman et al. (2)	Female	37 y	Growth hormone secreting	Left neck lymph node	NA	Surgery+ Medicine	NA
Nose-Alberti et al. (3)	Female	22 y	ACTH secreting	Live	c-erbB-2	Surgery	Died after 4 months
Roncaroli et al. (4)					HER-2/neu		
	Male	55 y	FSH secreting	Skull base, nasal sinuses, and larynx, Vertebral bodies and ribs		Surgery	Died after 2 years
	Female	53 y	FSH secreting			Surgery + chemotherapy (cyclophosphamide, vincristine, dacarbazine)	Stable 19 years
Scheithauer et al. (5)	Male	19 y	Thyrotropin secreting	Foramen magnum and cervical 2–3 levels	MEN1	Surgery + chemotherapy (octreotide)	18 years
Wei et al. (6)	Female	50 y	Non-functioning	Multiple intracranial metastases	miR-20a, miR-106b, miR-17-5p	Surgery + radiation + chemotherapy (Temozolomide)	Died after 8 months
Casar-Borota et al. (7)			ACTH secreting	NA		NA	NA
	Male	35 y			ATRX		
	Female	39 y			DAXX		
Present case	Male	60 y	ACTH secreting	Lung	PTEN, ATRX, P53	Surgery + radiation + chemotherapy (Temozolomide)	3-months follow-up remaining

ACTH, adrenocorticotropichormone; ATRX, alpha thalassemia/mental retardation syndrome X-linked; DAXX, death-domain-associated protein; NA, none available; PTEN, phosphatase and tension homolog deleted on chromosome 10; y, years.

observed by PET-CT, and biopsy of lung lesions revealed a metastatic neuroendocrine tumor. In addition, the most common category of PC was ACTH secreting (34.7%), prolactin secreting (23.6%), and null cell (15.3%). The latency period between the presentation of a sellar pituitary adenoma and the manifestation of metastases occupies a surprisingly wide range, from a few months to 18 years (median, 5 years). All accumulating evidence strongly supports the diagnosis of a PC, although it is an extremely rare tumor.

Temozolomide monotherapy is the first-line chemotherapy for pituitary carcinomas based on clinical practice guidelines from the European Society of Endocrinology (8). However, there is a paucity of randomized controlled trials for large-series studies; moreover, this drug is not sensitive and effective for all PCs. In fact, the estimated response rate to temozolomide is 58% in aggressive pituitary adenomas and 55% in PCs (9). Thus, it is necessary to elucidate the precise molecular mechanisms governing malignant transformation, which would then contribute to developing targeted therapy for PCs. Unfortunately, there have only been a few isolated mechanistic studies with respect to PCs described in the recent literature (**Table 1**). We exploited molecular profiles of PCs as they pertain to the pathogenesis of malignant transformation in our rare case; and conducted a comparative study from available data in the Cosmic databank (http://cancer.sanger.ac.uk/cosmic). Evidence showed that the gene mutation frequency for TP53 and HRAS were 33 and 14%, respectively, in PCs using the latest COSMIC databank. In addition, KEGG pathway enrichment analysis showed that the 44 mutant genes were enriched significantly within several signaling pathways, including Ras, mTOR, MAPK, FoxO, ErbB, focal adhesion, and PI3K-Akt. These enriched pathways provided insights into the molecular mechanisms underlying PC initiation and progression, and can therefore be useful in the development of new therapeutic strategies.

Our findings not only detected an uncommon P53 mutation from a total of 509 known genes, but also novel gene mutations in ATRX and PTEN unique to this PC. Mutations in ATRX and PTEN might, then, play vital roles in the malignant transformation of a pituitary adenoma into a PC. Most importantly, PTEN is a tumor suppressor gene that dominates the PTEN/AKT/PI3K pathway, prolonging progression-free survival to 11.4 months on pancreatic neuroendocrine tumors in a sunitinib group compared with 5.5 months in a placebo group (10). We assume that PTEN may be a crucial treatment target for PCs. Thus, we suggest that PTEN inhibitors, such as everolimus be used as an alternative chemotherapy for PCs once treatment failure occurs with temozolomide.

CONCLUSIONS

To our knowledge, this is the first documented PCs patient with novel mutant genes, including ATRX and PTEN. The present findings will therefore contribute to the development of promising targeted therapy based on individual gene assay for uncommon PCs, although further studies of a larger cohort of PC patients are necessary to clarify the precise molecular mechanism(s) underlying the pathogenesis of PCs.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of frontiers in oncology. The protocol was approved by the medical ethical committee of Zhengzhou University. This patient gave written informed consent in

accordance with the Declaration of Helsinki. I currently state that written informed consent was obtained from the participant for the publication of this case report.

AUTHOR CONTRIBUTIONS

FG: study concept and design, acquisition of data and writing paper. GW: study concept, analysis and interpretation of data. FW: study concept and design, data collection. DX: analysis and interpretation of data. XL: critical revision of manuscript for intellectual content.

ACKNOWLEDGMENTS

The authors would like to thank the members of the research group for useful discussions.

REFERENCES

1. Dudziak K, Honegger J, Bornemann A, Horger M, Mussig K. Pituitary carcioma with malignant growth from first presentation and fulminant clinical course-case report and review of the literature. *J Clin Endocrinol Metab.* (2011) 96:2665–9. doi: 10.1210/jc.2011-1166
2. Greenman Y, Woolf P, Coniglio J, O'Mara R, Pei L, Said JW, et al. Remission of acromegaly caused by pituitary carcinoma after surgical excision of growth hormone-secreting metastasis detected by 111-indium pentetreotide scan. *J Clin Endocrinol Metab.* (1996) 81:1628–33.
3. Nose-Alberti V, Mesquita MI, Martin LC, Kayath MJ. Adrenocorticotropin-producing pituitary carcinoma with expression of c-erbB-2 and high PCNA index: a comparative study with pituitary adenomas and normal pituitary tissues. *Endocr Pathol.* (1998) 9:53–62. doi: 10.1007/BF02739952
4. Roncaroli F, Nosé V, Scheithauer BW, Kovacs K, Horvath E, Young WF Jr., et al. Gonadotropic pituitary carcinoma: HER-2/neu expression and gene amplification. Report of two cases. *J Neurosurg.* (2003) 99:402–8. doi: 10.3171/jns.2003.99.2.0402
5. Scheithauer BW, Kovacs K, Nose V, Lombardero M, Osamura YR, Lloyd RV, et al. Multiple endocrine neoplasia type 1-associated thyrotropin-producing pituitary carcinoma: report of a probable *de novo* example. *Hum Pathol.* (2009) 40:270–8. doi: 10.1016/j.humpath.2008.06.013
6. Wei Z, Zhou C, Liu M, Yao Y, Sun J, Xiao J, et al. MicroRNA involvement in a metastatic non-functioning pituitary carcinoma. *Pituitary* (2015) 18:710–21. doi: 10.1007/s11102-015-0648-3
7. Casar-Borota O, Botling J, Granberg D, Stigare J, Wikström J, Boldt HB, et al. Serotonin, ATRX, and DAXX expression in pituitary adenomas: markers in the differential diagnosis of neuroendocrine tumors of the Sellar region. *Am J Surg Pathol.* (2017) 41:1238–46. doi: 10.1097/PAS.0000000000000908
8. Raverot G, Burman P, McCormack A, Heaney A, Petersenn S, Popovic V, et al. European Society of Endocrinology. Clinical practice guidelines for the management of aggressive pituitary tumours and carcinomas. *Eur J Endocrinol.* (2018) 178:G1–24. doi: 10.1530/EJE-17-0796
9. Lin AL, Sum MW, Deangelis LM. Is there a role for early chemotherapy in the management of pituitary adenomas? *Neuro Oncol.* (2016) 18:1350–6. doi: 10.1093/neuonc/now059
10. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med.* (2011) 364:501–13. doi: 10.1056/NEJMoa1003825

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

ORIGINAL RESEARCH
published: 20 November 2018
doi: 10.3389/fonc.2018.00509

The Comparative Treatment of Intraventricular Chemotherapy by Ommaya Reservoir vs. Lumbar Puncture in Patients With Leptomeningeal Carcinomatosis

Mariano Montes de Oca Delgado[1], *Bernardo Cacho Díaz*[2], *José Santos Zambrano*[1], *Vicente Guerrero Juárez*[1], *Manuel Salvador López Martínez*[1], *Elvira Castro Martínez*[1], *Javier Avendaño Méndez-Padilla*[3,4], *Sonia Mejía Pérez*[3,4], *Ignacio Reyes Moreno*[5], *Axayacatl Gutiérrez Aceves*[5,6] *and Alberto González Aguilar*[1,3,4,5]*

[1] Emergency Department, National Institute of Neurology and Neurosurgery "Manuel Velasco Suárez" (INNN), Mexico City, Mexico, [2] Neuroscience Unit, National Cancer Institute, Mexico City, Mexico, [3] Neurosurgery Department, National Institute of Neurology and Neurosurgery "Manuel Velasco Suárez" (INNN), Mexico City, Mexico, [4] Neurooncology Department, National Institute of Neurology and Neurosurgery "Manuel Velasco Suárez" (INNN), Mexico City, Mexico, [5] Neurological Service, The American British Cowdray Medical Center, Mexico City, Mexico, [6] Radioneurosurgery Department, National Institute of Neurology and Neurosurgery "Manuel Velasco Suárez" (INNN), Mexico City, Mexico

Object: Leptomeningeal Carcinomatosis (LCM) represents a state of systemic malignant disease with poor prognosis. The purpose of this study is to compare overall survival (OS) between intraventricular chemotherapy through Ommaya reservoir (OR) and chemotherapy through lumbar puncture (LP) in LCM.

Patients and Methods: Forty adult patients with LCM were included. All patients underwent lumbar puncture and Magnetic resonance imaging (MRI). Thirty patients received chemotherapy through LP and 10 undergone colocation of Ommaya reservoir for intraventricular chemotherapy.

Results: The most common symptom was headache (Present in 50%). The cranial nerves most affected were VI and VII. Leptomeningeal enhancement was the most frequent finding in MRI. The OS in the LP group was 4 months and Ommaya group was 9.2 months ($p = 0.0006$; CI:1.8-3), with statistical differences in favor to Intraventricular treatment. Proportional hazard regression showed that receiving chemotherapy through Ommaya reservoir was a protective factor (Hazard ratio = 0.258, Standard Error = 0.112, $p = 0.002$ and 95% CI 0.110-0.606). Using KPS as a factor did not affect the hazard ratio of Ommaya reservoir itself.

Conclusions: OS was significantly higher in patients with Ommaya reservoir in spite of Karnofsky Performance Status (KPS) previous to chemotherapy. Therefore, intraventricular chemotherapy should be preferred over lumbar puncture chemotherapy administration if there are resources available.

Keywords: leptomeningeal carcinomatosis, overall survival, chemotherapy, ommaya reservoir, lumbar puncture, karnofsky performance status, intraventricular

Edited by:
Luis Souhami,
McGill University, Canada

Reviewed by:
Yoshua Esquenazi,
University of Texas Health Science Center at Houston, United States
Maria Caffo,
Università degli Studi di Messina, Italy

***Correspondence:**
Alberto González Aguilar
albertogonzalez@neurocirugia-innn.com

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *24 July 2018*
Accepted: *17 October 2018*
Published: *20 November 2018*

Citation:
Montes de Oca Delgado M, Cacho Díaz B, Santos Zambrano J, Guerrero Juárez V, López Martínez MS, Castro Martínez E, Avendaño Méndez-Padilla J, Mejía Pérez S, Reyes Moreno I, Gutiérrez Aceves A and González Aguilar A (2018) The Comparative Treatment of Intraventricular Chemotherapy by Ommaya Reservoir vs. Lumbar Puncture in Patients With Leptomeningeal Carcinomatosis. Front. Oncol. 8:509. doi: 10.3389/fonc.2018.00509

INTRODUCTION

LCM is a rare complication of advanced cancer, which consists in infiltration of the meninges and Cerebrospinal fluid (CFS) space by malignant cells (1). Any cancer can metastasize to meninges but is mainly detected in association with breast cancer, lung cancer, melanoma, and in fewer occasions with other types of cancer (Gastrointestinal, prostate, lymphoma, leukemia, unknown primary cancer) (2). It has an incidence of ∼5% of the patients with cancer but because of the asymptomatic patients or late-onset symptomatology, it may increase even to 20% as biopsies studies have demonstrated (3, 4). The median survival is around 4–6 weeks when untreated but it may improve as well as neurological status because of chemotherapy regimens (2, 4, 5). Karnofsky Performance Status (KPS) is the most reliable prognostic factor in patients with diagnosis of LCM (3, 4, 6). The gold standard remains the identification of malignant cells in CSF cytological study (7). The treatment goals are to improve the neurological status and to prolong survival. Different treatments are used (Radiotherapy and Neurosurgery) but the chemotherapy is essential in the management of LCM. Traditionally the method of election was the lumbar puncture (Intrathecal), but currently there are other options such as the Ommaya reservoir (Intraventricular) that might have better outcomes for patients (8). There is not a standard route of administration and both are recommended taking into consideration that chemotherapy needs good distribution and penetration; Intraventricular chemotherapy acts directly in CSF and probably it is superior to lumbar administration but there is not a trial that confirms this hypothesis completely. The present article is a retrospective study that compares the Intraventricular vs. the lumbar administration of chemotherapy in LCM.

PATIENTS AND METHODS

We conducted a retrospective study collecting and analyzing data from patients diagnosed with LCM between 1980 and 2016 at National Institute of Neurology and Neurosurgery. We obtained clinical, imaging, histological, and treatment outcome data from electronic database such as gender, age, Karnofsky Performance Status (KPS), overall survival in months (OS, established with date of decease), symptomatology, primary tumor, localization of lesion by neuroimaging, treatment received, date of histological diagnosis, lumbar puncture (Glucose, proteins, cells, malignant cells), HIV status, and type of treatment (Intraventricular and Intrathecal). Diagnosis was established by presence of malignant cells in CSF and by neuroimaging findings in patients with histological diagnosis of cancer. Statistical analysis was performed using Stata/MP 14.1. In an effort to identify potential bias we stablished mean and *t*-test for scalar variables. Survival was established by Kaplan-Meier method taking on account impact of primary tumor and KPS. We used log-rank test to establish the statistical significance of difference in overall survival.

Chemotherapy Protocol

The chemotherapy regimen administered was Methotrexate 15 mg (MTX) monotherapy, and IT triple therapy (IT-triple; 15 mg MTX, 30 mg/m^2 Cytarabine and 15 mg/m^2 Hydrocortisone) or Cytarabine (Ara-C) alone 30 mg/m^2. The regimen was administered up to twice a week, according to the condition of the patient, until negative cytology (Induction phase), followed by once weekly for 4 weeks (Consolidation phase) and the last maintenance phase was once a month until progression, maximal doses or death.

RESULTS

We identified 40 patients; ten patients had undergone installation of an intraventricular Ommaya reservoir (Between 2000 and 2014) and received chemotherapy for LCM while 30 patients received intrathecal chemotherapy through lumbar puncture. We obtained the following data: 26 patients were male (65%) and 14 were female (35%) with a ratio of 1.8:1. The median age was 52 years range of 18–76 (**Table 1**).

The KPS range was 40–100, with median of 70. Neurological examination and clinical symptoms were as follows: Headache was the most common symptom, present in 20 patients (50%). The rest of signs and cranial nerves (CN) most affected as well as KPS previous treatment are resumed in **Table 2**.

TABLE 1 | Patients characteristics.

	All patients	Ommaya	LP	*p*
Gender	*n* = 40 %(n)	10 (25)	30 (75)	0.251
Male	26 (65)	5 (50)	21(70)	
Female	14 (35)	5 (50)	9 (30)	
Age in years, median (range)	52 (18-76)	50 (18-64)	54.5 (20-76)	0.168 (Xi2) 0.033 (Fisher)
KPS, median (range)	70 (40-100)	70 (50-100)	70 (40-100)	0.580
PRIMARY TUMOR				
• Breast	10 (25)	3 (30)	7 (23.33)	
• Lung	7 (17.5)	0 (0)	7 (23.33)	
• Leukemia	7(17.5)	2 (20)	5 (16.67)	
• Melanoma	5 (12.5)	0 (0)	5 (16.67)	
• Ovary	4 (10)	2 (20)	2 (6.67)	
• Prostate	3 (7.5)	1 (10)	2 (6.67)	
• Lymphoma	2 (5)	1 (10)	1 (3.33)	
• Unknown	2 (5)	1 (10)	1(3.33)	
TREATMENT REGIMEN				
• Ara-C	7 (17.5)	1 (10)	6 (20)	0.846
• Mtx	5 (12.5)	1(10)	4 (13.33)	
• Mtx/Ara	28 (70)	8 (80)	20 (66.67)	
Overall survival (OS in months)	0.4 – 10	3-10	0.4-7.1	0.0006

KPS, Karnofsky Performance Status; LP, Lumbar puncture; Ara-C, Citarabine; Mtx: Methotrexate.

TABLE 2 | Clinical symptoms and cranial nerves affected.

Clinical features	No. patients	Percentage
Headache	20	50
Seizures (Tonic-clonic)	5	12.5
Nausea or vomit	8	20
Cognitive disorders	6	15
Altered state of consciousness	5	12.5
Motor	12	30
Sensitive	6	15
Cerebellum	5	12.5
Ataxia	5	12.5
Diplopia	8	20
Dysphagia	2	5
Dysarthria	3	7.5
Radicular pain	3	7.5
Cranial nerve affection	18	45
Cranial nerves affection	**No. patients**	**Percentage**
None	20	50
IX, X	3	7.5
VI	4	10
VI, III	3	7.5
VI, IX, X	2	5
VII	5	12.5
VIII	3	7.5
KPS previous treatment	**LP (%)**	**Ommaya (%)**
40	1 (3.3)	0
50	4 (13.3)	3 (30)
60	7 (23.3)	2 (20)
70	8 (26.6)	2 (20)
80	2 (6.6)	0
90	4 (13.3)	2 (20)
100	4 (13.3)	1 (10)
Total	30 (100)	10 (100)

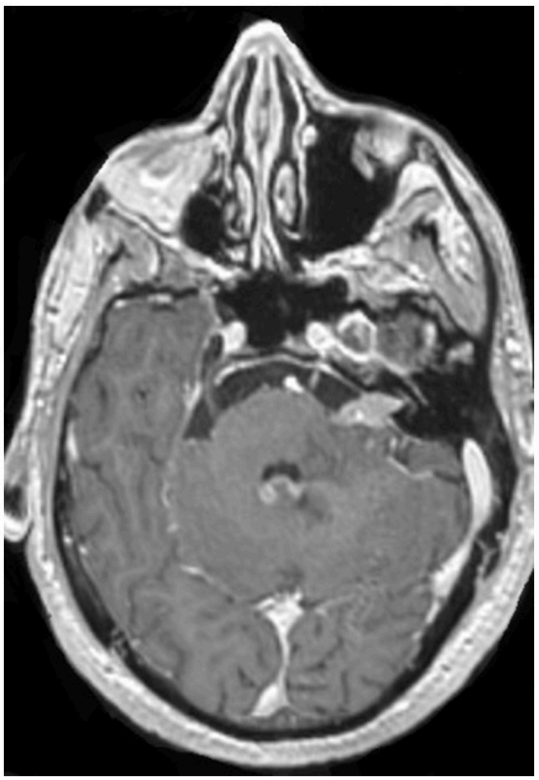


FIGURE 1 | Axial MRI with nodular contrast enhancement in VII cranial nerve and enhancement in fourth ventricle, patient with diagnosis of lung cancer.

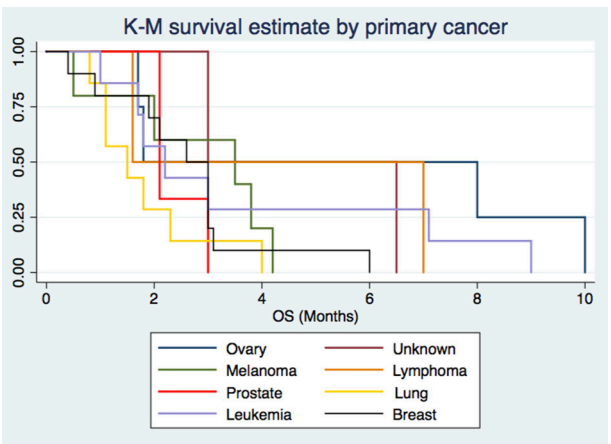
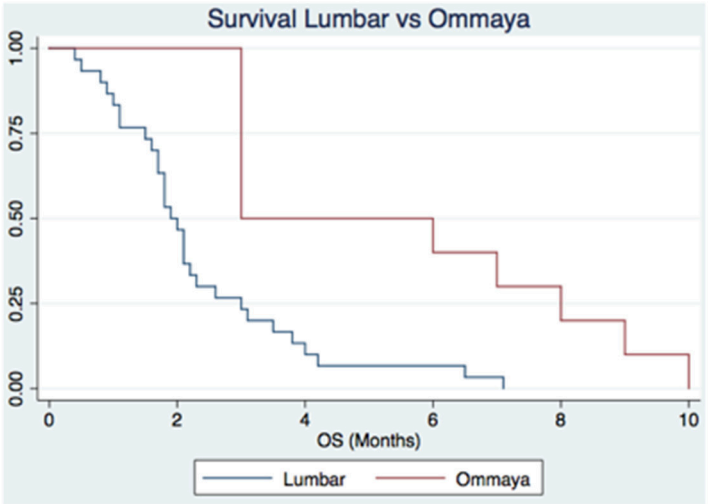


FIGURE 2 | The origin of Leptomeningeal Carcinomatosis by primary cancer.

The most affected CN were VI and VII. Neuroimaging findings were: meningeal enhancement (especially in cerebellum 21/40 patients) and nodular lesions 15/40 patients (**Figure 1**), in the 30% of patients the Magnetic Resonance Imaging (MRI) was normal.

The most common site of primary tumor was breast with 10 patients (25%), followed by lung (7 patients, 17.5%) and Leukemia (7 patients, 17.5%), then melanoma with 5 patients (12.5%), ovary with 4 patients (10%), then prostate with 3 patients (7.5%) and at last but not least lymphoma and unknown with 2 patients (5%, respectively) (**Figure 2**).

The classic pattern of LCM is Hypoglycorrhachia, hyperproteinorrhachia, and malignant cells present. We analyzed the percentage of patients that presented this classic pattern and those who present different pattern. Referent to proteins in CSF, all patients presented values >45 (Range of 53–245), mean of 101.8. Glucose outcomes were divided in: Normal (8 patients, 20%), hypoglycorrhachia (30 patients, 75%) and hyperglycorrhachia (2 patients, 5%). Cellularity was present in all patients, with a range of 5–985, mean of 55.3. Classic pattern was present in 30 patients of the sample (75%).



Log-rank test for equality of survival between Ommaya and Lumbar puncture		
Chemotherapy	**Events observed**	**Events expected**
Lumbar	30	20.46
Ommaya	10	19.54
Total	40	40.00
	Xi2 = 11.70	**p=0.0006**

FIGURE 3 | The Overall Survival by Lumbar chemotherapy vs. Intraventricular with Ommaya reservoir in patients with Leptomeningeal Carcinomatosis.

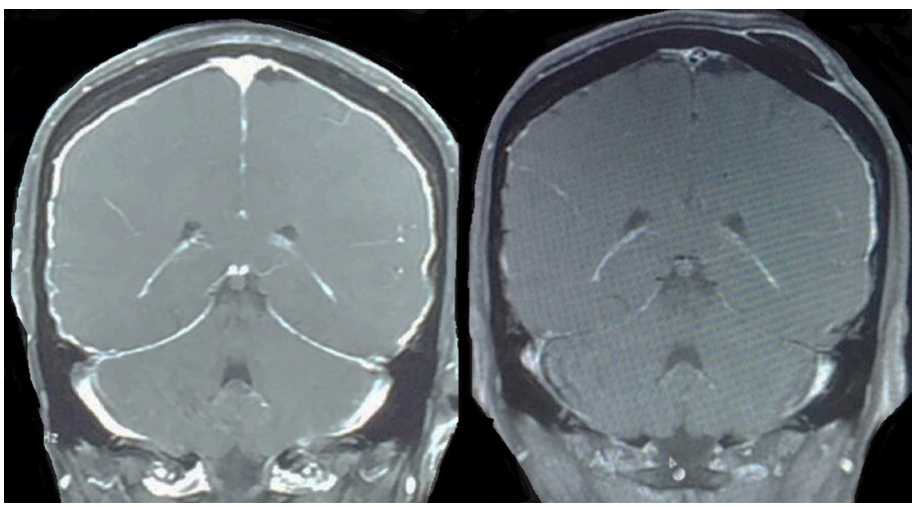


FIGURE 4 | 45 yr old female patient with diagnosis of breast cancer and leptomeningeal disease with complete radiological response after treatment with Mtx/Ara-C by Ommaya reservoir.

The Overall survival in the group with chemotherapy by LP was 4 months and Ommaya group was 9.2 months (p = 0.0006; CI:1.8-3), significantly higher in patients who received chemotherapy through Ommaya reservoir (see **Figure 3**).

Cox model for proportional-hazard regression showed that receiving chemotherapy through Ommaya reservoir was a protective factor (Hazard ratio = 0.258, Standard Error = 0.112, p = 0.002 and 95% CI 0.110-0.606). Using KPS as a factor did not affect the hazard ratio of Ommaya reservoir itself.

Overall survival by primary cancer had a median of 1.5 months for lung cancer, 2.1 months for prostate, 2.2 months for leukemia, 2.8 months for breast cancer, 3 months for melanoma,

4.3 months for lymphoma, 4.7 months for unknown primary, and 4.9 months for ovary cancer. Cox regression method showed breast and lung cancer as risk factors for poor prognosis with statistical significance ($p = 0.069$ and $p = 0.012$, respectively) (see **Figure 4**).

Regarding complications, two patients were reported with neuroinfectious disease with isolation and identification of *Klebsiella pneumoniae* in both cases. According to CTR (Common Toxicity Criteria) chemotherapy related complications noted were: Two patients with toxicity grade 2 in platelets count, two patients with toxicity grade 2 in WBC count, and one patient with toxicity grade 4 in platelet count.

We analyzed the prognostic factors (age, KPS, Chemotherapy and Intraventricular chemotherapy) without statistical differences (see **Table 3**).

TABLE 3 | Favorable prognostic factor in Leptomeningeal carcinomatosis by Cox regression method.

Cox regression						
No. subjects = 40			**No. observations = 40**			
No. failures = 40						
Variable	**Hazard ratio**	**Standard error**	**z**	***p***	**95% Conf. Interval**	
KPS	1.013	0.121	1.10	0.270	0.989	1.037
Ommaya	0.259	0.112	−3.11	0.002	0.111	0.607
Triple chemotherapy	1.230	0.134	1.32	0.906	0.896	1.506

DISCUSSION

LCM is a rare complication of advanced cancer, which consists in infiltration of the meninges and CFS space by malignant cells and with the presence of new treatments that increase survival it is likely that its frequency increases. We have reported and analyzed the outcomes obtained with chemotherapy through lumbar puncture vs. Ommaya reservoir in patients with diagnosis of LCM. There are numerous topics to underline. Some of our results were consistent with those reported on previous clinical trials.

As we mentioned before, headache was the most common symptom, present in 20 patients (50%), which is concordant with studies that described clinical features in LCM (9, 10). Cranial nerves are usually affected in patients with LCM, our patients presented mainly affection of VI and VII nerves alone or in combination with other cranial nerves (35% in total). Some reviews have noted that indeed, VI is the cranial nerve most affected (8, 11).

Previous studies showed abnormalities in CSF in more than 90% of the cases (11–13). It is necessary to have in mind that the most frequent pattern profile in lumbar puncture in patients with LCM began to be well identified since the 50's, nowadays CSF analysis has great importance in the approach of LCM (14–16). All of our patients presented abnormalities in CSF and 75% of them presented the classic pattern that we had discussed.

LCM involves the entire axis of CNS, therefore MRI takes great relevance. Contrast enhancement is necessary when obtaining a neuroaxis image. The principal site of lesion in our study was by far cerebellum, but it is clear that sites affected were variable and did not follow a pattern. However, bulky lesions are not always observable and diffuse pattern can be present as well as multiple lesions (17–19).

There are only three drugs available to administer intra-CSF: Methotrexate (MTX), Cytarabine (Ara-C) and less often Thiotepa. Effectiveness of these drugs is demonstrated in LCM, nevertheless is limited in some solid tumors associated to LCM (Melanoma and lung cancer). There was not significant difference between the three distinct types of chemotherapy employed in our study (Methotrexate, Liposomal Cytarabine and MTX/Ara-C). Until now, effectivity of these drugs remains similar (3, 20). In addition, combination vs. single agent therapy neither has shown overwhelming superiority so it remains controversial, but it can be associated to less tolerance (14, 21). OS was significantly higher in the Ommaya reservoir group. The patient with the highest OS was a young woman with low KPS, nevertheless the log-rank showed no significance to this point. Concerning to Intraventricular chemotherapy administration, there is adequate drug distribution within the leptomeningeal space. Even when CSF flow is unimpeded, the normal CSF circulation carries fluid preferentially to the ventricles (22, 23). As a result, the delivery of drug administered into the lumbar Intrathecal space is unlikely to achieve clinically relevant drug concentrations within the cerebral ventricles, where malignant cells are known to reside (24–27).This may explain the observation that there is better response in patients who receive Intraventricular chemotherapy, in contrast to Intrathecal chemotherapy.

On the other hand, a recent clinical phase II trial (28), demonstrates that disturbances in the CSF flow makes chemotherapy ineffective as it may hinder the drug distribution and increase intracranial pressure. Same authors have pointed that ventroculolumbar chemotherapy showed improvement of increased intracranial pressure, altered mental status and cauda echina symptoms. It must be noted that this trial only includes Methotrexate in evaluation, however is a reliable study about perfusion rate, adverse effects and toxicity.

About primary tumors, results were similar to the rest of literature. Confirming that breast cancer, lung cancer and melanoma are the solid tumors with major association to LCM (16).

OS was affected by primary cancer as other studies have demonstrated (3, 29, 30).

Data regarding complications related to placement of Ommaya reservoir was limited to those noted on database.

CONCLUSIONS

In our study, OS was determined by the factors previously mentioned, which is consistent with reports on similar trials. LCM represents an advanced stage of cancer and therefore

it is a pathology of poor prognosis. Analysis of CSF and MRI to identify sites of lesions are fundamental to achieve diagnosis and to establish management. Recent research indicates that the future in the treatment of LCM is in the study of molecular targeted therapies such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) (31).

Another diagnostic studies like rare cell capture technology should be taken into consideration to the approach of LCM on the future. As well as the detection of CSF malignant cells through CellSearch (32, 33).

Chemotherapy is the cornerstone of the treatment and Intraventricular administration through Ommaya reservoir or other dispositive, have shown similar outcomes and also have demonstrated to be the best option when available.

We should mention that our results stablish intraventricular chemotherapy as a better option of treatment in this group of patients, nevertheless, due to the retrospective design and extended time of study, result should be taken cautiously. Further studies must include bigger sample size with data about complications related to the procedures such as increased intracranial pressure and ventriculitis.

A prospective randomized study would be ideal to set conclusions but we consider it particularly difficult to select a homogeneous sample in patients with leptomeningeal disease.

Is important always having in mind that the objective of chemotherapy is to improve neurological status and quality of life more than prolonging survival. Next trials should be focused on improving diagnostic and therapeutic options that may reduce costs, avoid delayed processing, exempt patients from invasive procedures and allow a more precise diagnosis and prognosis.

ETHICS STATEMENT

Ethical review process was not required due to the retrospective design of study and anonymized data of patients included, in accordance with the local legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

MM and AGo: design of study, data collection, manuscript writing, analysis of results, discussion. BC, JS, VG, ML, EC, JA, SM, IR, and AGu: manuscript writing, analysis of results.

REFERENCES

1. Eberth CJ. Zur Entwicklung des Epitheliomas (Cholesteatomas) dur Pia under der Lungs. *Virchow's Arch.* (1870) 49:51–63. doi: 10.1007/BF02214196
2. Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. *Cancer* (1982) 49:759–72.
3. Grossman SA, Krabak MJ. Leptomeningeal carcinomatosis. *Cancer Treat Rev.* (1999) 25:103–19. doi: 10.1053/ctrv.1999.0119
4. Le Rhun E, Taillibert S, Chamberlain MC. Carcinomatous meningitis: leptomeningeal metastases in solid tumors. *Surg Neurol Int*. (2013) 4:S265–88. doi: 10.4103/2152-7806.111304
5. Leal T, Chang JE, Mehta M, Robins HI. Leptomeningeal metastasis: challenges in diagnosis and treatment. *Curr Cancer Ther Rev*. (2011) 7:319–27. doi: 10.2174/157339411797642597
6. Jaeckle KA. Neoplastic meningitis from systemic malignancies: diagnosis, prognosis and treatment. *Semin Oncol.* (2006) 33:312–23. doi: 10.1053/j.seminoncol.2006.04.016
7. Clarke JL, Perez HR, Jacks LM, Panageas KS, Deangelis LM. Leptomeningeal metastases in the MRI era. *Neurology* (2010) 74:1449–54. doi: 10.1212/WNL.0b013e3181dc1a69
8. Gwak HS, Joo J, Kim S, Yoo H, Shin SH, Han JY, et al. Analysis of treatment outcomes of intraventricular chemotherapy in 105 patients for leptomeningeal carcinomatosis from non–small-cell lung cancer. *J Thorac Oncol.* (2013) 8:599–605. doi: 10.1097/JTO.0b013e318287c943
9. Lara-Medina F, Crismatt A, Villareal-Garza C, Alvarado-Miranda A, Flores-Hernández L, González-Pinedo M, et al. Clinical features and prognostic factors in patients with carcinomatous meningitis secondary to breast cancer. *Breast J.* (2012) 18:233–41. doi: 10.1111/j.1524-4741.2012.01228.x
10. Palma JA, Fernandez-Torron R, Esteve-Belloch P, Fontes-Villalba A, Hernandez A, Fernandez-Hidalgo O, et al. Leptomeningeal carcinomatosis: prognostic value of clinical, cerebrospinal fluid, and neuroimaging features. *Clin Neurol Neurosurg.* (2013) 115:19–25. doi: 10.1016/j.clineuro.2012.03.048
11. Chamberlain MC. Leptomeningeal Metastasis. *Curr Opin Oncol.* (2010) 22:627–35. doi: 10.1097/CCO.0b013e32833de986
12. Kim YS, Resnick JS. Hypoglycorrhachia with meningeal carcinomatosis: report of two cases. *Ann Intern Med.* (1965) 63:115–21. doi: 10.7326/0003-4819-63-1-115
13. Glantz MJ, Hall WA, Cole BF, Chozick BS, Shannon CM, Wahlberg L, et al. Diagnosis, management, and survival of patients with leptomeningeal cancer based on cerebrospinal fluid-flow status. *Cancer* (1995) 75:2919–31. doi: 10.1002/1097-0142(19950615)75:12<2919::AID-CNCR2820751220>3.0.CO;2-9
14. Kim DY, Lee KW, Yun T, Park SR, Jung JY, Kim DW, et al. Comparison of intrathecal chemotherapy for leptomeningeal carcinomatosis of a solid tumor: methotrexate alone versus methotrexate in combination with cytosine arabinoside and hydrocortisone. *Jpn J Clin Oncol.* (2003) 33:608–12. doi: 10.1093/jjco/hyg118
15. Little JR, Dale AJ, Okazaki H. Meningeal Carcinomatosis. *Arch Neurol.* (1974) 30:138–43. doi: 10.1001/archneur.1974.00490320026003
16. Shim Y, Gwak HS, Kim S, Joo J, Shin SH, Yoo H. Retrospective analysis of cerebrospinal fluid profiles in 228 patients with leptomeningeal carcinomatosis: differences according to the sampling site, symptoms, and systemic factors. *J Korean Neurosurg Soc.* (2016) 59:570–6. doi: 10.3340/jkns.2016.59.6.570
17. Chamberlain MC. Comprehensive neuraxis imaging in leptomeningeal metastasis: a retrospective case series. *CNS Oncol.* (2013) 2:121–8. doi: 10.2217/cns.12.45
18. Dietemann JL, Correia Bernardo R, Bogorin A, Abu Eid M, Koob M, Nogueria T, et al. Normal and abnormal meningeal enhancement: MRI features. *J Radiol.* (2005) 86:1659–83. doi: 10.1016/S0221-0363(05)81507-0
19. Singh SK, Leeds NE, Ginsberg LE. MR imaging of leptomeningeal metastases: comparison of three sequences. *Am J Neuroradiol.* (2002) 23:817–21.
20. Glantz MJ, Van Horn A, Fisher R, Chamberlain MC. Route of intracerebrospinal fluid chemotherapy administration and efficacy of therapy in neoplastic meningitis. *Cancer* (2010) 116:1947–52. doi: 10.1002/cncr.24921
21. Hitchins RN, Bell DR, Woods RL, Levi JA. A prospective randomized trial of single-agent versus combination chemotherapy in meningeal carcinomatosis. *J Clin Oncol.* (1987) 5:1655–2. doi: 10.1200/JCO.1987.5.10.1655

22. Chamberlain MC, Kormanik PA. Prognostic significance of 111indium-DTPA CSF flow studies in leptomeningeal metastases. *Neurology* (1996) 46:1674–77. doi: 10.1212/WNL.46.6.1674
23. Glantz MJ, Jaeckle KA, Chamberlain MC, Phuphanich S, Recht L, Swinnen LJ, et al. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. *Clin Cancer Res.* (1999) 5:3394–402.
24. Bleyer WA, Drake JC, Chapner BA. Neurotoxicity and elevated cerebrospinal-fluid methotrexate concentration in meningeal leukemia. *N Engl J Med.* (1973) 289:770–3. doi: 10.1056/NEJM197310112891503
25. Bleyer WA. Clinical pharmacology of intrathecal methotrexate: I. Pharmacokinetics in nontoxic patients after lumbar injection. *Cancer Treat Rep*. (1977) 61:703–8.
26. Bleyer WA. Clinical pharmacology of intrathecal methotrexate: II. An improved dosage regimen derived from age-related pharmacokinetics. *Cancer Treat Rep*. (1977) 61:1419–75.
27. Mason WP, Yeh SD, DeAngelis LM. 111Indium-diethylenetriamine pentaacetic acid cerebrospinal fluid flow studies predict distribution of intrathecally administered chemotherapy and outcome in patients with leptomeningeal metastases. *Neurology* (1998) 50:438–44. doi: 10.1212/WNL.50.2.438
28. Gwak HS, Joo J, Shin SH, Yoo H, Han JY, Kim HT, et al. Ventriculolumbar perfusion chemotherapy with Methotrexate for treating Leptomeningeal carcinomatosis – A phase II study. *Oncologist* (2014) 19:1044–5. doi: 10.1634/theoncologist.2014-0199
29. Bruna J, González L, Miró J, Velasco R, Gil M, Tortosa A. Leptomeningeal carcinomatosis: prognostic implications of clinical and cerebrospinal fluid features. *Cancer* (2009) 115:369–81. doi: 10.1002/cncr.24041
30. Taillibert S, Laigle-Donadey F, Chodkiewicz C, Sanson M, Hoang-Xuan K, Delattre JY. Leptomeningeal metastases from solid malignancy: a review. *J. Neurooncol.* (2005) 75:85–99. doi: 10.1007/s11060-004-8101-x
31. Lee DW, Lee KH, Kim JW, Keam B. Molecular targeted therapies for the treatment of leptomeningeal carcinomatosis: current evidence and future directions. *Int J Mol Sci.* (2016) 17(Suppl. 7):E1074. doi: 10.3390/ijms17071074
32. Le Rhun E, Tu Q, De Carvalho Bittencourt M, Farre I, Mortier L, Cai H, et al. Detection and quantification of CSF malignant cells by the CellSearch technology in patients with melanoma leptomeningeal metastasis. *Med Oncol.* (2013) 30(Suppl. 2):538. doi: 10.1007/s12032-013-0538-3
33. Nayak L, Fleisher M, Gonzalez-Espinoza R, Lin O, Panageas K, Reinr A, et al. Rare cell capture technology for the diagnosis of leptomeningeal metastasis in solid tumors. *Neurology* (2013) 80:1598–605. doi: 10.1212/WNL.0b013e31828f183f

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

TECHNOLOGY REPORT
published: 03 December 2018
doi: 10.3389/fonc.2018.00576

Advanced Ultrasound Imaging in Glioma Surgery: Beyond Gray-Scale B-mode

Massimiliano Del Bene[1,2], *Alessandro Perin*[1], *Cecilia Casali*[1], *Federico Legnani*[1], *Andrea Saladino*[1], *Luca Mattei*[1], *Ignazio Gaspare Vetrano*[1], *Marco Saini*[1], *Francesco DiMeco*[1,3,4] *and Francesco Prada*[1,5,6*]

[1] Department of Neurosurgery, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, [2] Department of Experimental Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy, [3] Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy, [4] Department of Neurological Surgery, Johns Hopkins Medical School, Baltimore, MD, United States, [5] Department of Neurological Surgery, University of Virginia, Charlottesville, VA, United States, [6] Focused Ultrasound Foundation, Charlottesville, VA, United States

Introduction: Glioma surgery is aimed at obtaining maximal safe tumor resection while preserving or improving patient's neurological status. For this reason, there is growing interest for intra-operative imaging in neuro-oncological surgery. Intra-operative ultrasound (ioUS) provides the surgeon with real-time, anatomical and functional information. Despite this, in neurosurgery ioUS mainly relies only on gray-scale brightness mode (B-mode). Many other ultrasound imaging modalities, such as Fusion Imaging with pre-operative acquired magnetic resonance imaging (MRI), Doppler modes, Contrast Enhanced Ultrasound (CEUS), and elastosonography have been developed and have been extensively used in other organs. Although these modalities offer valuable real-time intra-operative information, so far their usage during neurosurgical procedures is still limited.

Purpose: To present an US-based multimodal approach for image-guidance in glioma surgery, highlighting the different features of advanced US modalities: fusion imaging with pre-operative acquired MRI for Virtual Navigation, B-mode, Doppler (power-, color-, spectral-), CEUS, and elastosonography.

Methods: We describe, in a step-by-step fashion, the applications of the most relevant advanced US modalities during different stages of surgery and their implications for surgical decision-making. Each US modality is illustrated from a technical standpoint and its application during glioma surgery is discussed.

Results: B-mode offers dynamic morphological information, which can be further implemented with fusion imaging to improve image understanding and orientation. Doppler imaging permits to evaluate anatomy and function of the vascular tree. CEUS allows to perform a real-time angiosonography, providing valuable information in regards of parenchyma and tumor vascularization and perfusion. This facilitates tumor detection and surgical strategy, also allowing to characterize tumor grade and to identify residual tumor. Elastosonography is a promising tool able to better define tumor margins, parenchymal infiltration, tumor consistency and permitting differentiation of high grade and low grade lesions.

OPEN ACCESS

Edited by:
Marcos Vinicius Calfat Maldaun, Hospital Sírio-Libanês, Brazil

Reviewed by:
Sunit Das, St. Michael's Hospital, Canada
Edjah K. Nduom, National Institutes of Health (NIH), United States

****Correspondence:***
Francesco Prada
francesco.prada@istituto-besta.it

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *15 September 2018*
Accepted: *16 November 2018*
Published: *03 December 2018*

Citation:
Del Bene M, Perin A, Casali C, Legnani F, Saladino A, Mattei L, Vetrano IG, Saini M, DiMeco F and Prada F (2018) Advanced Ultrasound Imaging in Glioma Surgery: Beyond Gray-Scale B-mode. Front. Oncol. 8:576. doi: 10.3389/fonc.2018.00576

Conclusions: Multimodal ioUS represents a valuable tool for glioma surgery being highly informative, rapid, repeatable, and real-time. It is able to differentiate low grade from high grade tumors and to provide the surgeon with relevant information for surgical decision-making. ioUS could be integrated with other intra-operative imaging and functional approaches in a synergistic manner to offer the best image guidance for each patient.

Keywords: Glioma, intra-operative ultrasound, contrast enhanced ultrasound, Doppler, B-mode, elastography, fusion imaging, navigated ultrasound

INTRODUCTION

Extent of resection (EOR) together with brain function sparing represent the most critical aspects of glioma surgery. A growing body of literature and evidences firmly supports gross total removal (GTR), instead of subtotal (STR) or biopsy (1, 2), defining GTR as the complete resection of contrast-enhancing regions in high grade glioma (HGG) on T1 weighted Gd-enhanced magnetic resonance imaging (MRI), and of hyper-intense areas on T2/FLAIR MRI in non-enhancing low grade glioma (LGG).

In diffuse LGG, GTR is able to improve progression free survival (PFS), overall survival (OS) and the time needed for malignant transformation (1–5). In HGG, GTR is nowadays considered the first phase of the standard multimodal therapeutic approach in order to extend PFS and OS (1, 2).

Surgeon's perception of gross total removal in glioma surgery is commonly inaccurate (6): portions of intra-axial tumor may resemble healthy brain parenchyma thus leading to sub-optimal resection and subsequently influencing patient's prognosis.

With these premises a growing interest for intra-operative imaging has led to the development of new technologies to localize tumors in order to ultimately help surgeons achieving GTR (7).

Numerous intra-operative approaches have been proposed: computed tomography (ioCT), magnetic resonance imaging (ioMRI), ultrasound (ioUS), fluorescence guided surgery (FGS) [e.g., 5-ALA, fluorescein, second window idocyanine green (ICG)] and other experimental techniques (e.g., optical coherence tomography and Raman spectroscopy) (7–14).

Among all these techniques ioUS is still one of the most employed, studied and developed, despite being the most dated since its first report was in 1978 with Reid (15).

US application in brain is especially favored by cerebral mechanical properties which allow an excellent US propagation and by the absence of superficial layers such as skin and subcutaneous connective which can distort US waves (16).

The main value of ioUS is the possibility to study the surgical scenario in real-time, every time it is needed, without the interruption of surgical work flow and, in specific condition, permitting to operate under direct guidance (17).

Continuous research and development led to US probes and scanners able to provide images with superb temporal and spatial resolution, comparable, or even superior to volumetric MRI (18).

Numerous studies have also investigated the diagnostic properties of ioUS in terms of sensitivity, specificity and ability to increase EOR and subsequently PFS and OS (9, 19–22).

In general ioUS demonstrated to own high diagnostic value in glioma surgery, in particular in low grade lesions, allowing to maximize the extent of resection and consequently to improve prognosis and quality of life of patients (9, 19–25).

It has to be said that in most of the cases ioUS application is limited to standard brightness mode (B-mode) with or without co-registration to pre-operative MRI. B-mode alone, being an anatomical representation of the echo wave for each point in the space, is a truncated application for ioUS. Indeed one pivotal adjunct of this technology is the possibility to implement different modalities to broaden the amount of different information.

The aim of our work is to review and describe different ioUS modalities in glioma surgery underlying the potential implications of standard b-mode and other advanced techniques such as fusion imaging, Doppler (power-, color-, spectral-), CEUS, and elastosography.

INTRAOPERATIVE ULTRASOUND IN GLIOMA SURGERY

US Equipment

US scanner should include the predisposition for different US modalities, a tracking system, the possibility to support different probes, the option to modify imaging presets through a complete access to all the US parameters. In general a specific designation for neurosurgery application is not required, as in most of cases a last generation general radiology US scanner with different presets is sufficient (10).

The scanner should provide a tracking system to allow fusion imaging with pre-operative MRI, to correct brain shift, and also to acquire a 3D US scan to obtain an updated neuronavigation volume.

The system should be equipped with different probes: a linear multifrequency (3–11 MHz) probe for deep-seated lesion, an high frequency (10–22 MHz) for small superficial lesions and a mini-convex to study the surgical field from inside the surgical cavity, overcoming the limitations of surgical artifacts in the final stages of tumor resection (10, 26).

Another issue is represented by imaging presets: in most US scanner designed for neurosurgery, imaging preset is standardized in order to provide highly contrasted image with few modifiable parameters. US is a demanding technique, with a steep learning curve and high operator dependency, but the only way to obtain the maximum in every situation is to became accustomed to this imaging modality and consequently being able to master the settings accordingly to the scenario (27).

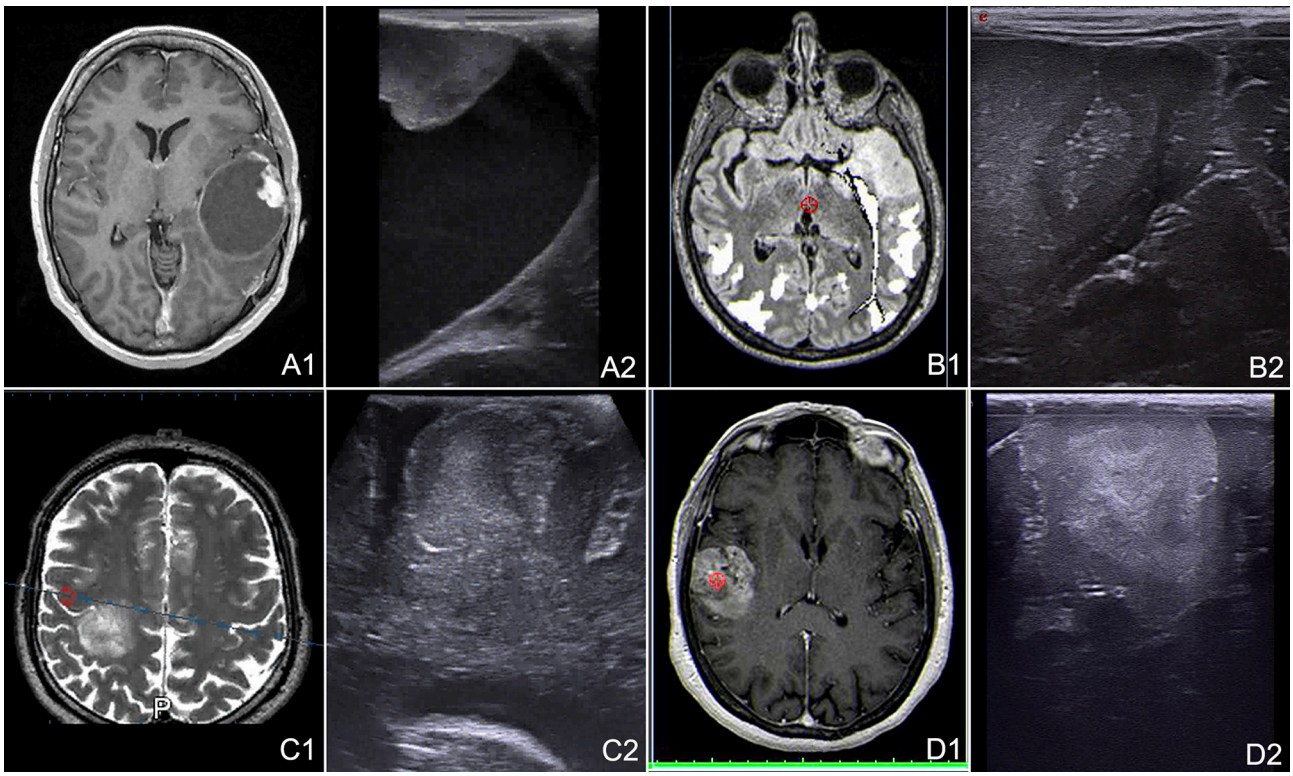


FIGURE 1 | B-mode representation of different glioma grades. **(A)** Left temporal pilocytic astrocytoma. **(B)** Left temporal diffuse astrocytoma. **(C)** Right parietal anaplastic astrocytoma. **(D)** Right temporo-parietal glioblastoma. (1) pre-operative volumetric MRI. (2) Intra-operative trans-dural US scan. Note the different lesion appearances and in particular the different degree of margins definition.

The typical workflow at our Institution comprise the use of a last generation US scanner (MyLab, Esaote, Italy) with an integrated magnetic tracking system allowing for virtual navigation (MedCom GmbH, Germany). Typically the patient is registered in the 3D frame to the pre-operative MRI volume, permitting fusion imaging between ioUS and MRI and also to navigate with a pointer (as with a standard navigation system), to plan the surgical strategy and designing craniotomy site and shape (28). After bone flap removal the probes (usually a linear multifrequency and a mini-convex) are wrapped in plastic sterile sheath with coupling sterile US gel (Civco, USA) and a first direct trans-dural insonation is performed. The field is continuously irrigated with saline solution to allow US coupling and to improve imaging, reducing air or blood clots between probe and brain/dura. In every case the first US modality applied is B-mode, usually followed by Doppler, CEUS, elastography, depending on which information is necessary to achieve.

Indeed B-mode provides anatomical information requisite in order to understand and exploit the other modalities. Furthermore, B-mode permits to correct the brain-shift and brain deformation that naturally take place as resection advances (29, 30). Multiple US scans are performed throughout the whole surgery. Once tumor resection is completed, the final multimodal scan is conducted to evaluate potential hidden residual tumor and hypothetical tissue and vessels damages.

B-mode ioUS

B-mode is the most simple and diffuse modality of US imaging, such that in some cases "US" and "B-mode" are erroneously used as synonyms. Literally, B-mode stands for Brightness mode, a two-dimensional US imaging modality formed by bright dots, which represent the amplitude of each reflected eco-wave in a specific point in the space. B-mode permits to visualize and characterize anatomical structures relying on their capacity to reflect, refract, absorb or transmit US beam (31, 32) (**Figures 1**–**3**). The brightness of a structure of interest (e.g., tumor) is evaluated in comparison to surrounding healthy tissue and consequently a structure can be hyperechoic, hypoechoic, or isoechoic. It has to be said that neurosurgical US semiotics is demanding especially for an un-experienced user. In general, structures defined as hyperechoic are: ependyma, choroid plexus, arachnoid interfaces, dural structures, skull, most tumors and their margins. Cisterns, ventricles, cerebro-spinal fluid, and some tumors tend to be hypoechogenic. Gray matter, white matter (typically gray matter is brighter than white matter) and some tumors appear as isoechoic (33, 34) (**Figures 1**–**3**).

Glioma appearance in ioUS B-mode is dependent on lesion grading and consequently biological behavior (**Figure 1**). HGG own an explosive growth, with high proliferation and areas of cysts, bleedings, necrosis, high-cells-density, and invasive zones. All these features lead to an heterogeneous representation in

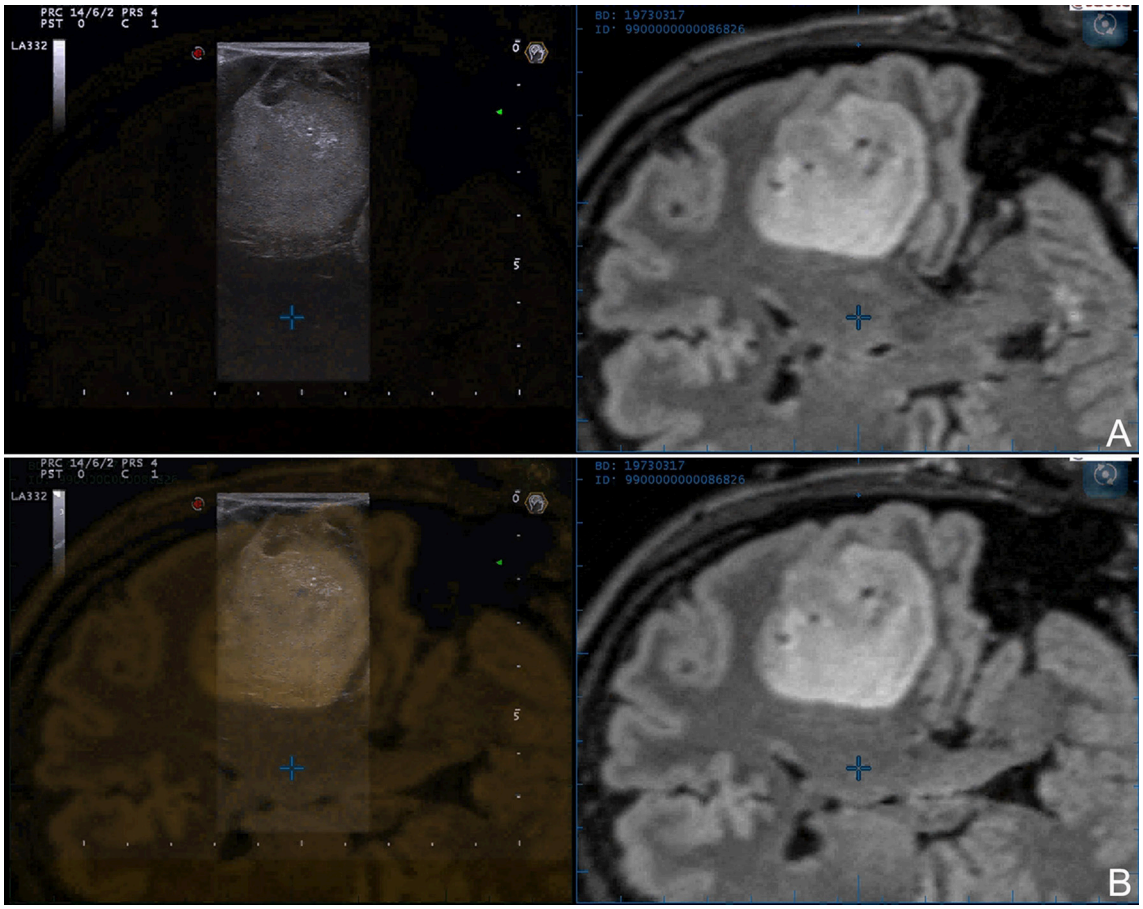


FIGURE 2 | Navigated intra-operative B-mode US in a case of left temporo-insular low-grade glioma. Two different configurations of navigated ioUS are displayed: **(A)** side-by-side or **(B)** superimposition. The continuous comparison between the two modalities aid in orientation and understanding of ioUS images.

which is possible to identify the different areas of the lesion. In general, it is possible to say that HGG appear heterogeneously echogenic with hyperechoic margins and iso-hypoechoic central necrotic areas. In general, the margins are more identifiable than in LGG even if is difficult to differentiate between tumor boundaries and peri-lesional edema (10, 23, 33, 35–39) (**Figure 1**). On the other hand, LGG appear slightly hyperechoic if compared to healthy brain, with homogeneous aspect and blurred margins particularly where they merge with healthy white matter (**Figure 1**). In most of cases B-mode imaging overlap pre-operative FLAIR MRI scan in LGG (**Figure 2**). The main difficulty in these tumors is to identify the margins/areas of invasion from peri-lesional edema (23, 33, 35–38).

Numerous studies have reported on the applications of B-mode in oncological neurosurgery and in particular in glioma resection (9, 10, 19–26). Several reviews and meta-analyses have addressed the value of ioUS in glioma surgery even if it is still not available a randomized controlled trial as pointed out in the last version of Cochrane review on intra-operative imaging technologies to enhance EOR in glioma (7).

In his meta-analysis Guangying Zhang found that B-mode provides an high sensitivity and specificity (0.75 and 0.88) in identifying tumor residual in glioma surgery operation, especially in LGG. In their study the Authors also confirmed the difficulty in distinguishing edema from infiltrating zone in particular for HGG and the ability of B-mode to display tumor presence also in areas with preserved blood brain barrier (21).

Bodil Karoline Ravn Munkvold performed a review on the diagnostic properties of ioUS in glioma surgery and analyzed factors influencing EOR. He found an overall specificity of 85% while sensitivity was 46% even if the residual tumor was small (median 1.05 ml) in cases with false-negative ioUS. Specificity was higher in LGG than in HGG (94 and 77%) and lowest in patients who undergone previous radiotherapy. The Authors conclude their analysis stating that ioUS specificity is high while the sensitivity for small residue is lower than post-operative MRI (22).

Syed Mahboob conducted a meta-analysis of the existing literature on the application of ioUS B-mode in glioma surgery. He analyzed 739 cases of LGG an HGG glioma operated under ioUS B-mode guidance in which gross total resection was achieved in 77% of patients (HGG 71.9% and LGG 78.1%). The Authors also examined, through a multivariate analysis, the factors implied in GTR finding that ioUS image quality is

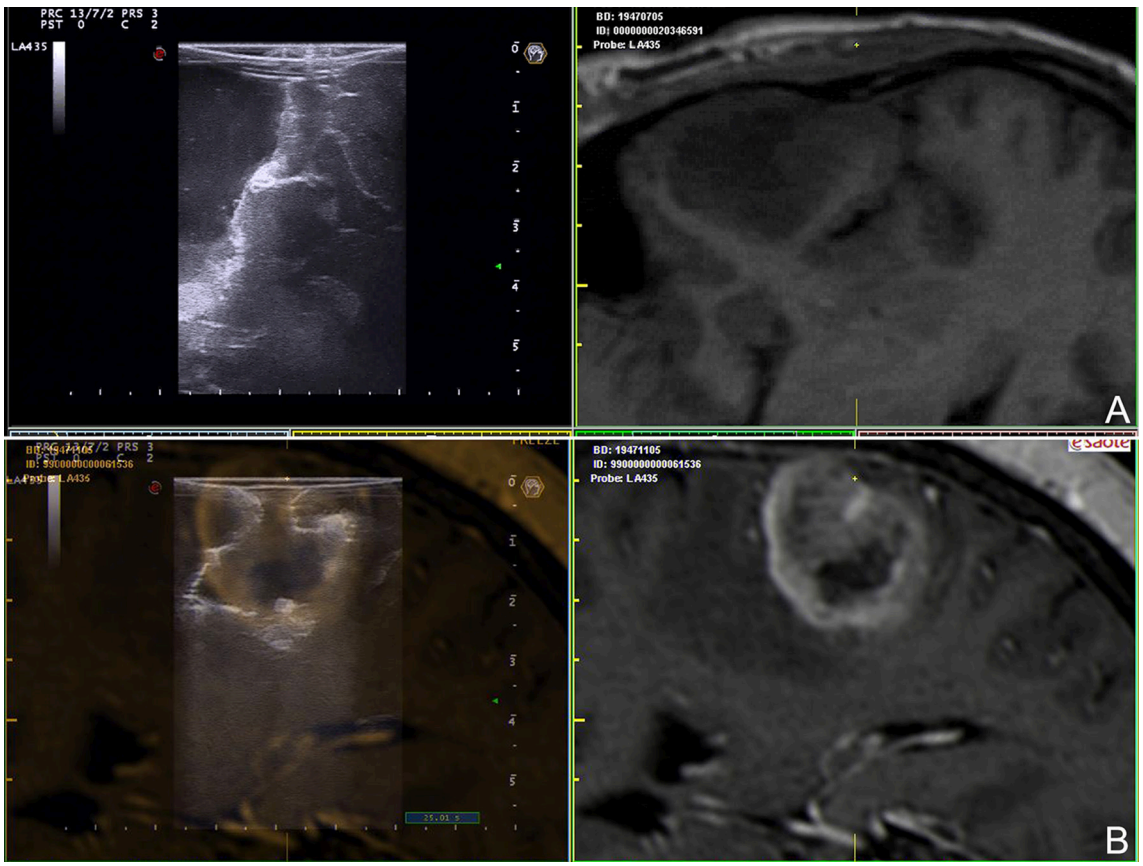


FIGURE 3 | Navigated intra-operative B-mode US in the final stages of surgery. **(A)** Left temporal anaplastic astrocytoma. **(B)** Right fronto-temporal glioblastoma. The comparison between ioUS and corresponding pre-operative MRI aid in identifying residual tumor and understanding ioUS semiotics: **(A)** side-by-side view, **(B)** superimposition.

one of those and in turn it is influenced by previous surgery and radiotherapy. The Authors conclude that ioUS is able to improve EOR, especially in conjunction with other technologies to enhance anatomic orientation (9).

Jia Wang in his study investigated the role of ioUS in improving the survival time of patients who underwent resection of cerebral gliomas. He compared the survival rate at 6 months, 1-year, and 2-year in LGG and HGG patients operated with and without ioUS. He observed that in those patients in which ioUS was used survival rate at 1 and 2 year were significantly better than the survival rates of the controls (19). Their results were confirmed by Saether et al. in another retrospective study (40).

In our experience B-mode is extremely helpful in each phase of surgery. Before dural opening, it permits to find the lesion, to study its extension and if necessary to modify the craniotomy accordingly (**Figure 1**). Once dura is opened, brain shift take place, and consequently anatomy could be importantly modified. In this context B-mode allows to find the lesion, neighbor anatomical landmarks and vital structures (**Figure 1**). Furthermore, B-mode provides information on which gyrus is infiltrated and which is spared thus allowing to tailor the corticectomy according to lesion extension. Notably, being ioUS real-time, in case of discordance between US and neuronavigation, B-mode provide the most reliable and updated information (28). If the lesion is deep-seated, B-mode permits to plan the surgical corridor and if necessary to select the appropriate sulcus for a trans-sulcal approach. During surgical removal B-mode is repeated several times, to understand the dynamic surgical anatomy (e.g., inform on the distance to ventricles or vital structures) and to guide other ioUS modalities such as Doppler, CEUS, and elastography. In our experience repeated ioUS scan permits to be more confident in surgical resection and at the same time to be more efficient and safer.

At the end of surgical resection, a last scan is performed to identify potential residual tumor (10) (**Figure 3**). In case of doubt, more advanced imaging such as CEUS can be employed.

It has to be said that as surgical resection advances the ioUS image quality decrease (**Figures 1**, **3**). The sensitivity, specificity and derived values (positive predictive value, negative predictive value) are optimal before surgical resection and deteriorate as surgery proceeds (41). This is mainly due to surgical induced artifacts and edema and as a consequence several approaches have been proposed to overcome this limitation.

Navigating the US probe it is possible to compare the location of an hyperechoic area in ioUS with the tumor extension on pre-operative MRI; if the suspected tumor is outside the tumor area in the pre-operative imaging it is likely to be an artifact (25, 28, 37, 42–47) (**Figures 2**, **3**). Notably this approach can be only suggestive because even correcting the brain shift it is still not possible to correct brain deformation.

Selbekk et al. in 2013 proposed the use of a special coupling fluid to fill the surgical cavity. The hypothesis is that surgical artifacts are related to different acoustic coefficients of saline water and brain parenchyma thus inducing a bright artifact in surgical cavity wall. In order to overcome this limitation the Authors proposed a fluid with the same attenuation coefficient of human brain (48). Even if really interesting this approach is still experimental and is far from being routinely used in clinical practice.

Šteno et al. identified the cause of brightness artifacts in the column of water in the surgical cavity and as a consequence in the distance between probe and surgical bed (26, 36, 43). They proposed the application of miniature high frequency probes to scan the border of the surgical cavity from inside. The main limitation of this approach is the physical characteristics of these probes that are limited in field of view, lateral resolution, and US penetration.

In our experience the most reliable solution to overcome surgical induced artifacts and to discriminate between them, residual tumor and tumor induced edema is CEUS and we will analyze this application in the specific section below.

Tumor recognition in different phases of surgical resection is only one of the limitations of B-mode.

ioUS has to pay the steep learning curve and operator dependency mainly related to orientation and semiotics interpretation. Usually, neurosurgeons are accustomed to standard orthogonal planes (axial, coronal, and sagittal) while ioUS provides oblique planes dependent on probe location and orientation. In our experience fusion imaging with pre-operative MRI is extremely helpful to overcome this issue especially in case of an un-experienced operator (**Figures 2**, **3**). The continuous comparison with a familiar imaging allows to understand the orientation and the specific US semiotics, which is dynamic and influenced by surgical resection (10, 25, 28, 42–44, 46, 49). Another solution is 3D ioUS which allows to scan the surgical field obtaining a 3D volume in which is possible to navigate through a pointer in the standard planes (axial, coronal and sagittal) (10, 24, 25, 40–44). In our opinion this represent a really useful solution that can facilitates ioUS understanding and permits to navigate in an update 3D volume. At the same time, US scan, being a volumetric acquisition, bears less information than 2D US. Indeed 3D US does not allow to take advantage from the proprioceptive feedback and eye-hand coordination to reconstruct a real-time mental representation of the surgical field, as it is performed by sonologists in other corporeal regions to explore different relationships between structures (26).

Navigated ioUS

Cerbral US is not a familiar imaging for neurosurgeons. This is due to the impossibility to use US in pre- and post-surgical phases, whereas the opposite is true for diagnostic imaging such as MRI and CT, which own specific semiotics and orientation in three orthogonal planes. Furthermore, ioUS is peculiar for several reasons. Image orientation depends on the plane of insonation and consequently on probe orientation and position (**Figures 1**–**3**). Semiotics is specific and dynamic among the different phases of surgical resection. US does not permit to study intracranial space before bone removal and to plan craniotomy because of bone shielding (28) (**Figures 1**–**3**).

Fusion imaging permits to co-register ioUS and pre-operative MRI for a continuous comparison of the two imaging modalities, enhancing US understanding and orientation. MRI provides known anatomical details and superimposing or visualizing side-by-side the modalities permits to interpret US orientation, semiotics and to understand its changes during time (**Figures 2**–**4**). Furthermore, different MRI datasets can be uploaded such as functional MRI, DTI, perfusion MRI, positron emission tomography in order to understand the location of vital structures, white matter tracts, or more aggressive areas in relation to tumor and real-time surgical situation (24, 25, 28, 41–44, 46). Brain shift can also be corrected relying on real-time US, updating neuronavigation for the most part of surgery while standard neuronavigation can be used to plan the surgical approach (28, 41, 43, 44, 46, 49, 50). Some groups have also demonstrated the possibility to correct brain shift and brain deformation in an automatic fashion through a software analysis taking into account landmarks position in ioUS and deforming MRI images accordingly (50–53).

Numerous Authors have demonstrated the clinical utility of navigated ioUS in glioma surgery allowing to maximize extent of resection and improving patients outcome (10, 19, 25, 40).

In our experience fusion imaging has demonstrated to be a reliable, accurate and useful technique especially for novice US users but also in complex cases and in experimental settings to compare or validate different US modalities in relation to MRI (**Figure 4**).

Doppler ioUS

Doppler US differs from standard B-mode not providing strictly anatomical but rather functional information. It relies on the Doppler effect. When a mechanical wave is reflected by a moving object this generates modifications of frequency and wavelength of echo-waves that can be studied allowing to infer information in regard of vessels blood flow (31). In routine practice, different sub-modalities of doppler are available, depending on which analysis is conducted it is possible to characterize blood flow in specific features (**Figure 5**). Color Doppler studies the presence of flow, its direction and velocity through the setting of a region of interest (ROI) (**Figure 5**). US scanners provides these information as color scale superimposed to standard B-mode (31, 54). Power Doppler is more sensitive to the amplitude of flow rather than direction and velocity (**Figure 5**). The image in encoded in a color scale depicting the total amount of Doppler signal, which in turn is dependent on the number of scattering molecules (in case of blood vessels mainly erythrocytes). This technique is extremely sensitive also to slow flow, typical of capillary district,

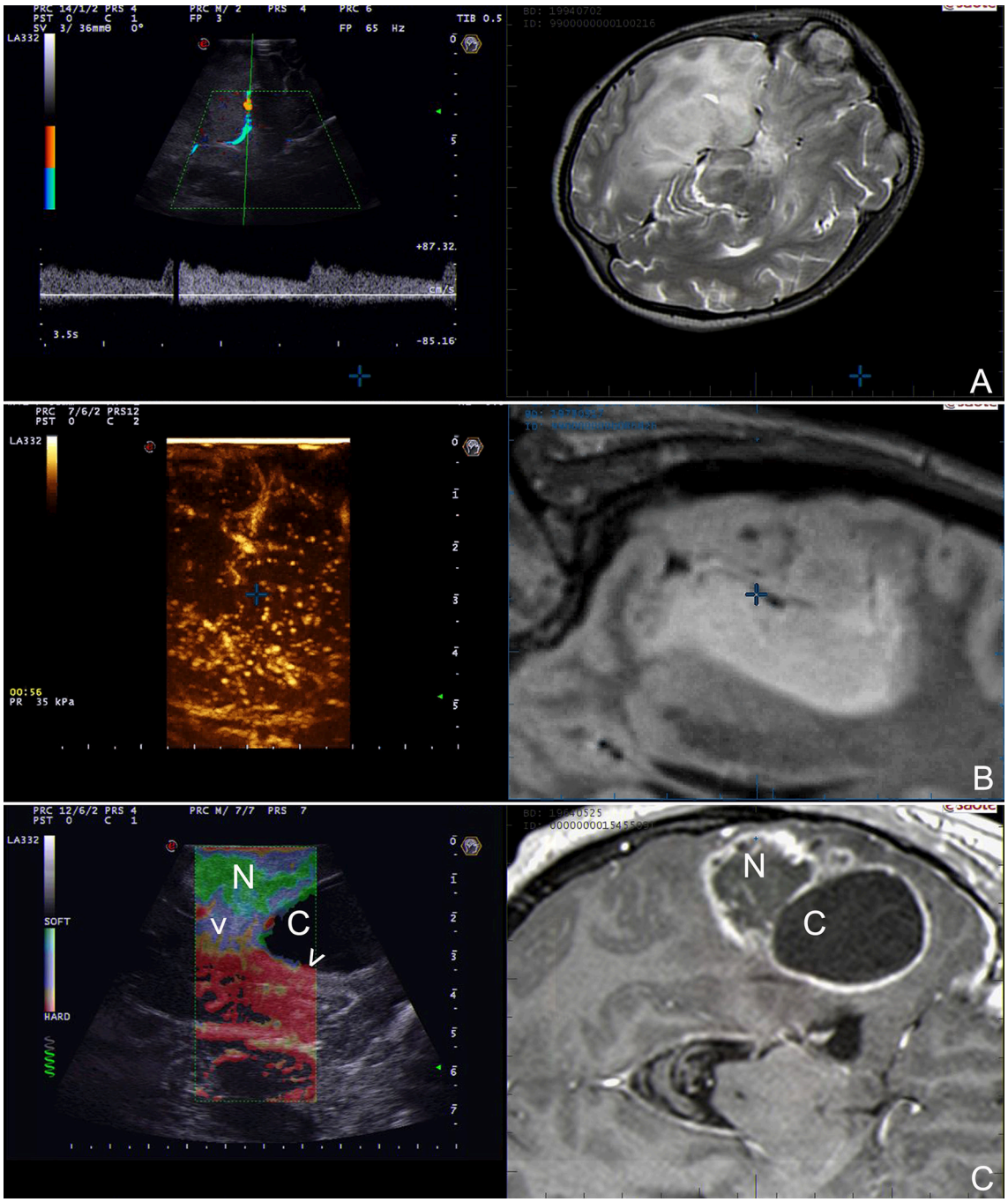


FIGURE 4 | Navigated ioUS (advanced modalities). **(A)** Color and spectral Doppler in a case of left temporo-insular anaplastic oligodendroglioma. **(B)** Contrast enhanced ultrasound in a case of left insular anaplastic astrocytoma. **(C)** Strain elastography in a case of left temporal glioblastoma; note the differences between the necrotic and the cystic areas and the interface with surrounding brain. Exploiting the continuous comparison between ioUS an pre-operative MRI is possible to understand US images and to infer about US and MRI correspondences. Legends are as follow: arrow heads: interface between tumor and brain; N: necrotic part of the tumor; C: cystic part of the tumor.

thus allowing, in some circumstances, to visualize also flow in sub-millimetric vessels (10, 31, 39, 54, 55) (**Figure 5**). Spectral Doppler requires identification of vessel of interest in B-mode through the setting of a proper ROI and indicating the vessel orientation. This analysis provides a detailed flow-velocity over time graph allowing to characterize vessels nature (e.g., artery, vein) and modification of flow during surgery (31, 54, 55) (**Figure 5**).

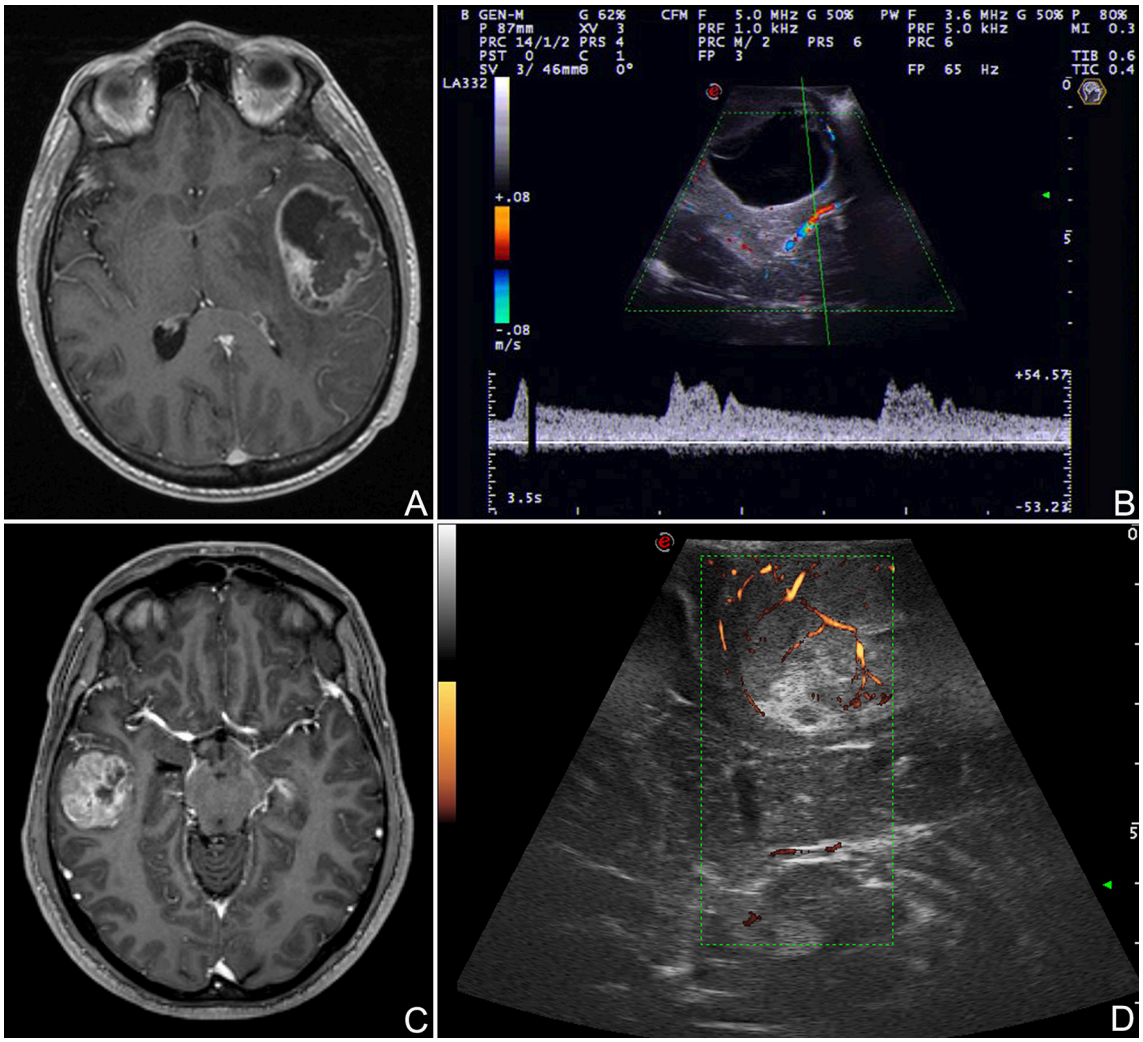


FIGURE 5 | Doppler modalities. **(A,B)** Color Doppler and spectral doppler in a case of left temporal glioblastoma. **(C,D)** Power Doppler in a case of right temporal glioblastoma. Color Doppler informs on presence of flow, its direction and velocity through the setting of a region of interest. Spectral Doppler allows for a systematic analysis of flow-velocity over time thus permitting to characterize vessels nature. Power Doppler provides information on amplitude of flow depicting the number of scattering molecules (mainly erythrocytes).

Each of these modalities has its specific indications and drawbacks. Color Doppler is informative in regard of vessels location and flow direction/velocity but at the same time it provides low spatial and temporal resolution and is severely limited by angle of insonation (**Figure 5**). Power Doppler is less dependent on angle of insonation and provides higher spatial resolution permitting to study also sub-millimetric vessels (**Figure 5**). On the other hand it is not informative on velocity and direction and suffers from low temporal resolution related to Doppler signal analysis. Lastly, spectral Doppler produces analyses with high temporal resolution allowing to characterize flow velocity pattern and changes in great detail while the drawbacks are the need to set a ROI, the absence of anatomical information and the important influence of angle of insonation (31, 54) (**Figure 5**).

In glioma surgery, probably, vessels study has less relevance if compared to extra-axial tumor such as skull base meningiomas. In any case, in specific condition this could be very helpful in orienting in the surgical field and in preventing post-operative deficits. Doppler imaging can aid in planning the surgical corridor and dura opening in case of medially located glioma (e.g., midline) according to bridging veins and sinus location (55). In case of deep seated gliomas surfacing on the basal cortex, Doppler allows to identify vessels position and to avoid undesirable damages (e.g., pericallosal arteries or middle cerebral artery branches (10, 49, 55). In specific conditions a vessel can represent a natural landmark for tumor margins location; if this situation is identified on pre-operative MRI, intra-operative Doppler could inform on vessel position thus aiding in achieving GTR avoiding unsafe excesses in eloquent areas (39). In this

regard, Steno et al. reported on the feasibility to visualize lenticolo-striatal arteries in insular low grade glioma surgery. The Authors were able to visualize and preserve these small perforators thanks to last generation power Doppler (39).

In our experience Doppler imaging own several indications in glioma surgery, such as vessels flow characterization with spectral Doppler and repeated power Doppler scans in approaching vital structures (e.g., Sylvian vessels). At the same time, we are convinced that in most of the aforementioned applications contrast enhanced ultrasound is more informative and in our routine practice has replaced Doppler imaging.

Contrast Enhanced ioUS

For other imaging methods such as CT and MRI the use of contrast media is almost mandatory while it is less recognized for ioUS.

The use of CEUS during neuro-oncological procedures has been recently included in the guidelines from the European Federation of the Societies for Ultrasound in Medicine and Biology (EFSUMB), representing a paradigm shift for the use of US in neurosurgery (56).

Contrast enhanced ultrasound (CEUS) is an US modality which exploits a contrast agent (UCA) and a specific algorithm to study the cerebral vasculature down to the capillary bed (**Figures 4**, **6**–**8**). Nowadays, second-generation UCA are suspensions for venous administration of gas filled micro-bubbles stabilized by a phospholipid shell (MB) allowing for a dynamic and continuous imaging (10, 35, 55–59) (**Figure 7**). US scanner must be set to low-mechanical index acoustic power in order to induce MB oscillation (minimizing disruption) and consequently to produce a non-linear harmonic echo. Exploiting this feature, CEUS algorithm suppresses the linear US echo from tissue and display only the non-linear harmonic echo of MB thus producing a specific representation of MB distribution (10, 56, 59–62) (**Figures 4**, **6**–**8**).

Furthermore, MBs, being micron-sized, are not able to extravasate from vessels and behave as a purely intravascular contrast agent, allowing to study all districts of the vascular tree: arterial, venous, and capillary (10, 55–59) (**Figures 4**, **6**–**8**). CEUS is a dynamic modality which permits to visualize tumors by virtue of degree of vascularization, sharing features with other organs with a terminal circulation such as the kidney (**Figures 4**, **6**–**8**). It is possible to identify four phase of contrast enhancement (CE): arterial phase, peak of CE, parenchymal phase and venous phase (58, 59) (**Figure 7**). These phases are dependent on tumor vascularization and perfusion pattern and consequently are extremely informative on tumor biology. Our group has extensively studied CEUS application in neurosurgery with a special attention to glioma surgery (35, 37, 45, 55, 57, 58, 63–69). In our experience CEUS demonstrated to be able to (1) highlight tumors and their phases compared to brain parenchyma (35, 57, 69) (**Figures 4**, **6**–**8**), (2) characterize glioma grade (35) (**Figure 6**), (3) inform on vascularization and degree of perfusion (57, 69) (**Figures 4**, **6**–**8**), (4) show vascular rearrangement that take place with tumor removal (37, 55, 69) (**Figure 8**), (5) highlight residual tumor (37) (**Figure 8**), (6) aid surgical decision making through serial imaging assessment of surgical anatomy (10) (**Figures 4**, **6**–**8**).

GBM usually demonstrate a rapid contrast enhancement (CE) with an impetuous arterial phase (2–3 s), a prompt CE peak (3–5 s) followed by a short parenchymal phase and rapid venous phase (5–10 s). It is almost always possible to identify several feeders, which give a centripetal chaotic transit of MB. Venous phase highlights a diffuse drainage system with multiple medullary veins directed toward ventricles. After tumor removal, we observed with CEUS that medullary veins disappear and in some cases it is possible to see arterialized veins to change flow direction after resection (37, 57, 69). Characteristically it is possible to identify two CE patterns in GBM: (1) heterogeneous with nodular high CE spots interspersed by low-CE areas of necrosis and (2) peripheral rim CE surrounding a central core of necrosis without CE. In all cases GBM show a clearly demarcated border after UCA administration due to the different vascularization of tumor and healthy brain parenchyma (35, 57, 69) (**Figures 4**, **6**–**8**). We also demonstrated that CEUS is able to highlight the same tumor volume of pre-operative MRI with the same CE pattern thus permitting to visualize residual tumor among all surgical phases (37, 69) (**Figure 6**).

Anaplastic astrocytoma (AA) demonstrated a slower UCA dynamics with longer phases and CE duration. Even in AA, arterial feeders and venous drainage are visible in most of cases but in general less defined than in GBM. CE pattern is usually diffuse with in some cases few scattered areas of higher CE mixed with small hypoperfused areas. Tumor borders are visible but less sharply than in GBM (35, 57) (**Figure 6**).

LGG are characterized by two behaviors. Astrocytomas tend to resemble AA CE but with phases even slower. Arterial feeders are usually not identifiable, MB transit is organized and regular while venous drainage is diffuse through numerous capillaries and consequently not discernible. CE is diffuse with dotted appearance, only slightly higher than surrounding parenchyma and with blurred margins (35, 57) (**Figure 6**). On the other hand, oligodendroglioma CE has a tendency to be more rapid than in astrocytoma, owing faster arterial and venous phases which in any case are slower than in AA. CE pattern in homogeneous with sporadic intralesional cysts and calcification. Margins are better defined than in astrocytoma (35, 57).

Lastly, CEUS permits to identify neighbor vascular structures (both arterial and venous) allowing to follow their localization even at the end of the surgery when resection is on the margins and brain shift has made navigation inaccurate thus assuring a safer dissection (10, 55) (**Figures 4**, **6**, **7**).

Intra-Operative Elastosonography

Finger palpation has always been used in medicine. US elastography (ESG) represents the evolution of this approach. Applying a force to a tissue is possible to obtain a deformation that is related to its intrinsic mechanical characteristic, namely Young's E modulus (measure of the stiffness of a solid material) (70, 71). There are several techniques to measure and represent the elastic property of a tissue (70–72). Outside of the liver the most employed elastographic techniques are shear wave elastograhy (SWE) and strain elastography (SE). SWE belongs to

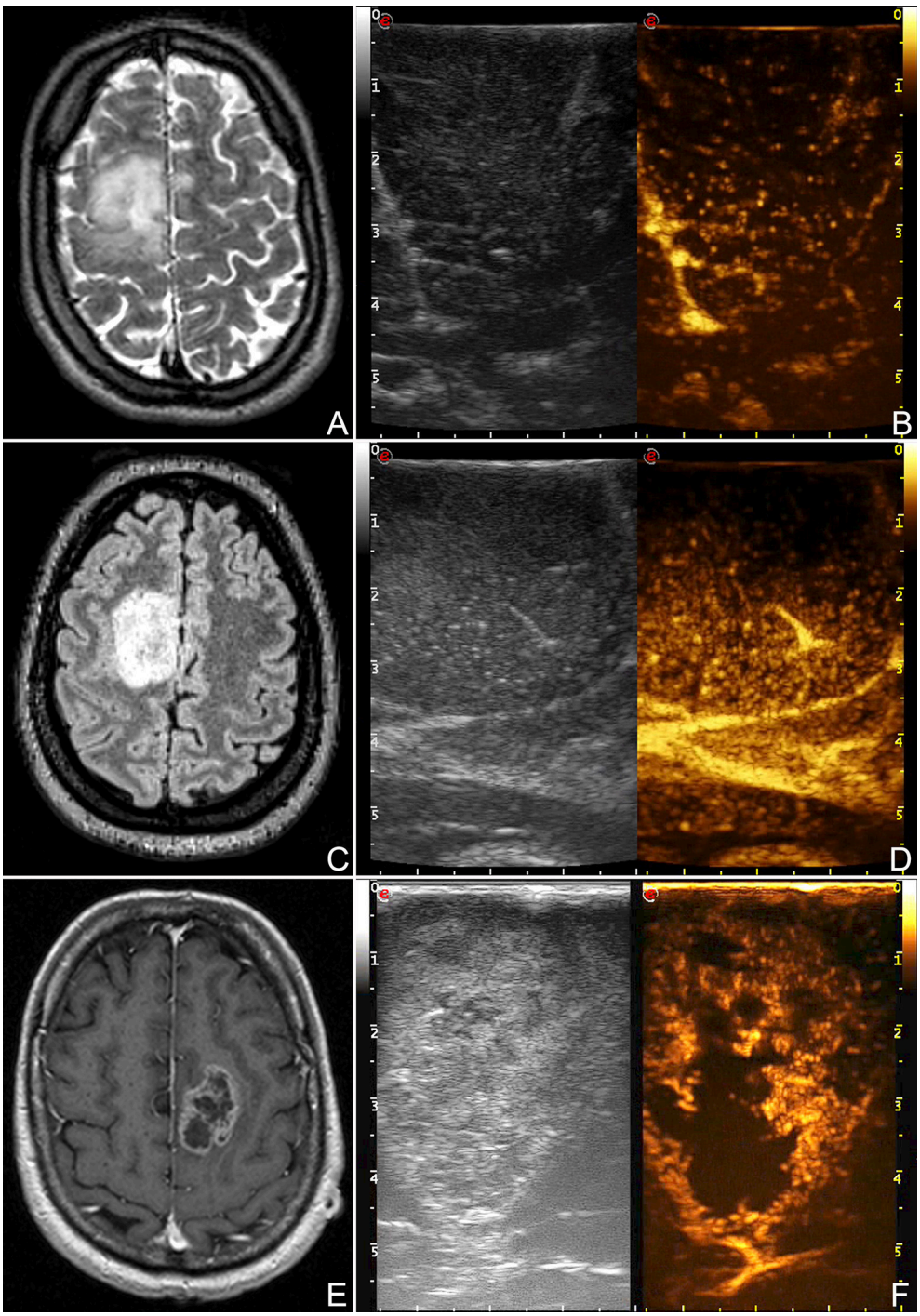


FIGURE 6 | CEUS representation of different glioma grades. **(A,B)** Right frontal low-grade glioma, **(C,D)** right frontal anaplastic astrocytoma, **(E,F)** left frontal glioblastoma. These images demonstrate the different degree and pattern of contrast enhancement among different glioma grades.

dynamic elastosonography and involves a focused US stimulus to induce a micrometric displacement to obtain share waves, which propagate orthogonally in the tissue (72). SWE provides both quantitative and qualitative information on tissue stiffness. SE is a quasi-static elastographic modality based on a mechanical stimulus to induce a tissue deformation which is measured by a high-frequency serial US acquisitions (70–72) (**Figures 4**, **9**). SE is more diffuse than SWE but again is capable only of qualitative measures.

Our group has focused the attention on SE demonstrating the feasibility in large-scale cohort of oncological-neurosurgery patients with the aims of lesions discrimination and

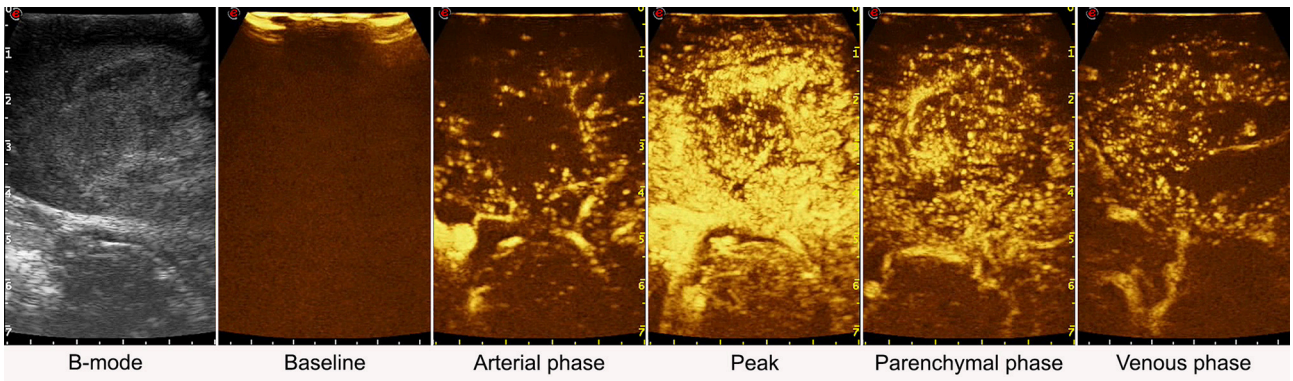


FIGURE 7 | Time-frame of contrast enhancement in a case of right temporal glioblastoma. GBM have a rapid arterial and venous phase. MBs transit is chaotic and the peak is extremely intense. The major arterial supplies and draining veins are clearly visible. Contrast enhancement pattern is irregular and heterogeneous CE with both nodular high-enhanced and hypoperfused areas. Tumor borders are better defined than in B-mode.

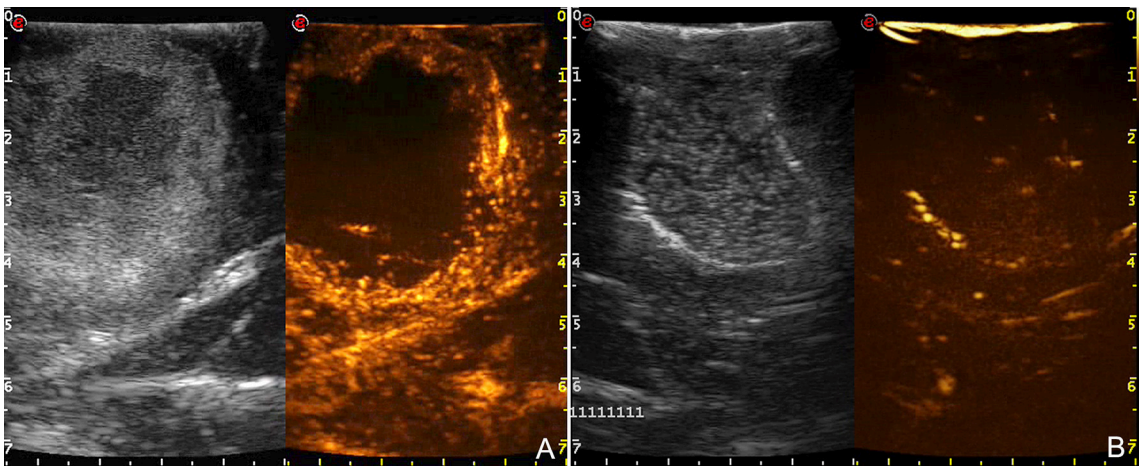


FIGURE 8 | Comparison between pre- **(A)** and post-resection **(B)** CEUS scans in a case of right temporo-parietal glioblastoma. After tumor removal, B-mode became difficult to understand because of surgical-induced artifacts whereas CEUS clearly demonstrates the presence of potential residual tumor.

characterization. Our SE exam is usually conducted before dura opening, maintaining the probe stationary and exploiting brain pulsatility as described by other Authors (73). In 64 patients we did not observed damage or adverse effect and we were able to discriminate lesion volume. In glioma subgroup we observed that in most of cases SE provide a lesion representation superimposable to standard B-mode but with a sharper margins visualization (**Figures 4**, **9**). More importantly, SE demonstrated of being able to discriminate between LGG and HGG with a 85.7% of sensitivity and 94.7% of specificity (**Figure 9**). Indeed in most of cases LGG appear stiffer while HGG softer than surrounding brain parenchyma thus allowing to differentiate these tumor through an intra-operative US scan (**Figure 9**).

Our findings are aligned with the results obtained from other groups with SE and with SWE (10, 73–77). In any case, even if these results are really encouraging, elastosonography still must be considered an experimental technique.

CONCLUSION

ioUS represents a pivotal adjunct to the existing surgical armamentarium, especially for a delicate application such as glioma surgery. ioUS is a polyvalent real-time imaging technique able to provide a great amount of information both anatomical and functional. Exploiting the advantages of each modality (B-mode, fusion imaging, Doppler-, CEUS, Elastography) it is possible to overcome several limitations of ioUS and to study glioma under various aspects. However, ioUS is an imaging technique that is rather demanding, requiring a specific training for each modality and in general for US semiotics, US physics and "knobology."

In our opinion ioUS should be part of a multimodal comprehensive approach for surgical guidance in glioma resection also encompassing other imaging and functional modalities in a synergistic and complementary fashion.

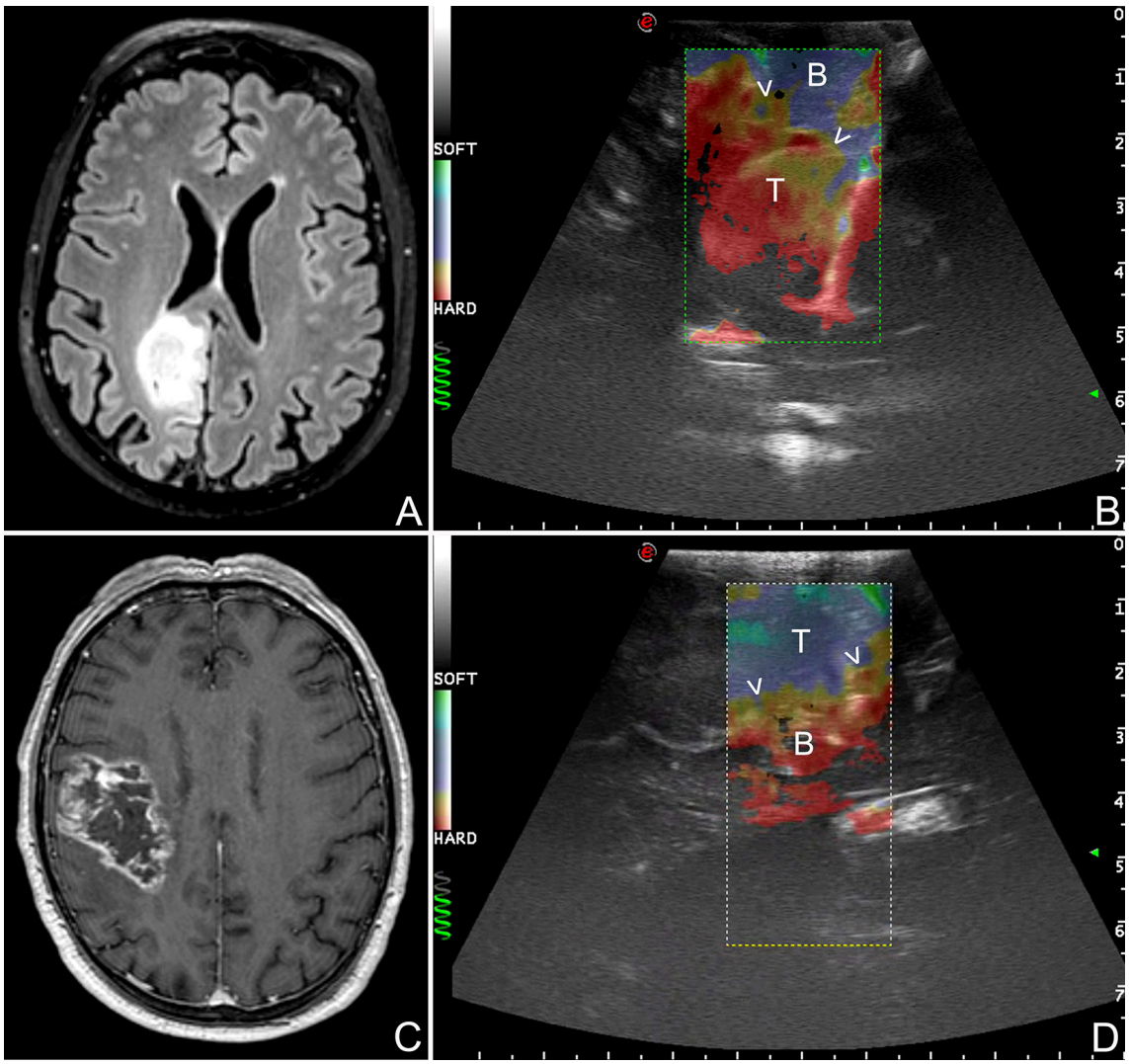


FIGURE 9 | Strain elastography (SE) scans in different glioma grades. **(A,B)** SE in a case of right parietal low grade glioma. **(C,D)** SE in a case of right fronto-parietal glioblastoma. SE is able to differentiate between LGG and HGG relying on their stiffness. LGG appear stiffer than brain whereas HGG softer. Furthermore, SE aid in identifying tumor borders and in distinguishing tumor and edema. (T: tumor, B: brain, arrow heads: interface between tumor and surrounding brain).

AUTHOR CONTRIBUTIONS

MD, FP: study concept and design. FP, MD, and FD critical revision of the manuscript for intellectual content. FP, MD, CC, MS, FL, AP, LM, AS, IV, and FD acquisition of data, data analysis, and interpretation. FP, MD, and FD: study supervision.

REFERENCES

1. Network NCC. *Central Nervous System Cancers (Version 1.2016)*. Clinical Practice Guidelines in Oncology (2016).
2. D'Amico RS, Englander ZK, Canoll P, Bruce JN. Extent of resection in glioma-a review of the cutting edge. *World Neurosurg.* (2017) 103:538–49. doi: 10.1016/j.wneu.2017.04.041
3. Aghi MK, Nahed BV, Sloan AE, Ryken TC, Kalkanis SN, Olson JJ. The role of surgery in the management of patients with diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. *J Neurooncol.* (2015) 125:503–30. doi: 10.1007/s11060-015-1867-1
4. Duffau H. The role of surgery in low-grade gliomas: do timing and extent of resection matter? *CNS Oncol.* (2017) 6:179–83. doi: 10.2217/cns-2017-0009
5. Jakola AS, Skjulsvik AJ, Myrmel KS, Sjavik K, Unsgard G, Torp SH, et al. Surgical resection versus watchful waiting in low-grade gliomas. *Ann Oncol.* (2017) 28:1942–8. doi: 10.1093/annonc/mdx230
6. Orringer D, Lau D, Khatri S, Zamora-Berridi GJ, Zhang K, Wu C, et al. Extent of resection in patients with glioblastoma: limiting factors, perception of resectability, and effect on survival. *J Neurosurg.* (2012) 117:851–9. doi: 10.3171/2012.8.JNS12234
7. Jenkinson MD, Barone DG, Bryant A, Vale L, Bulbeck H, Lawrie TA, et al. Intraoperative imaging technology to maximise extent of

resection for glioma. *Cochrane Database Syst Rev.* (2018) 1:Cd012788. doi: 10.1002/14651858.CD012788.pub2
8. Kut C, Chaichana KL, Xi J, Raza SM, Ye X, McVeigh ER, et al. Detection of human brain cancer infiltration *ex vivo* and *in vivo* using quantitative optical coherence tomography. *Sci Transl Med.* (2015) 7:292ra100-292ra100. doi: 10.1126/scitranslmed.3010611
9. Mahboob S, McPhillips R, Qiu Z, Jiang Y, Meggs C, Schiavone G, et al. Intraoperative ultrasound-guided resection of gliomas: a meta-analysis and review of the literature. *World Neurosurg.* (2016) 92:255–63. doi: 10.1016/j.wneu.2016.05.007
10. Prada FE, Solbiati LE, Martegani AE, DiMeco FE (editors). Intraoperative Ultrasound (IOUS) in Neurosurgery. In: *From Standard B-mode to Elastosonography*. Springer International Publishing (2016).
11. Coburger J, Nabavi A, Konig R, Wirtz CR, Pala A. Contemporary use of intraoperative imaging in glioma surgery: a survey among EANS members. *Clin Neurol Neurosurg.* (2017) 163:133–41. doi: 10.1016/j.clineuro.2017.10.033
12. Senders JT, Muskens IS, Schnoor R, Karhade AV, Cote DJ, Smith TR, et al. Agents for fluorescence-guided glioma surgery: a systematic review of preclinical and clinical results. *Acta Neurochir.* (2017) 159:151–67. doi: 10.1007/s00701-016-3028-5
13. Suero Molina E, Schipmann S, Stummer W. Maximizing safe resections: the roles of 5-aminolevulinic acid and intraoperative MR imaging in glioma surgery-review of the literature. *Neurosurg Rev*. (2017) doi: 10.1007/s10143-017-0907-z. [Epub ahead of print].
14. Zhang J, Fan Y, He M, Ma X, Song Y, Liu M, et al. Accuracy of Raman spectroscopy in differentiating brain tumor from normal brain tissue. *Oncotarget* (2017b) 8:36824–31. doi: 10.18632/oncotarget.15975
15. Reid MH. Ultrasonic visualization of a cervical cord cystic astrocytoma. *AJR Am J Roentgenol.* (1978) 131:907–8. doi: 10.2214/ajr.131.5.907
16. Makuuchi M, Torzilli G, Machi J. History of intraoperative ultrasound. *Ultrasound Med Biol.* (1998) 24:1229–42. doi: 10.1016/S0301-5629(98)00112-4
17. Dohrmann GJ, Rubin JM. History of intraoperative ultrasound in neurosurgery. *Neurosurg Clin N Am.* (2001) 12:155–66, ix. doi: 10.1016/S1042-3680(18)30074-3
18. Ng A, Swanevelder J. Resolution in ultrasound imaging. *Cont Educ Anaesth Critic Care Pain* (2011) 11:186–92. doi: 10.1093/bjaceaccp/mkr030
19. Wang J, Liu X, Ba YM, Yang YL, Gao GD, Wang L, et al. Effect of sonographically guided cerebral glioma surgery on survival time. *J Ultrasound Med.* (2012) 31:757–62. doi: 10.7863/jum.2012.31.5.757
20. Sastry R, Bi WL, Pieper S, Frisken S, Kapur T, Wells W. III, et al. Applications of ultrasound in the resection of brain tumors. *J. Neuroimaging* (2017) 27:5–15. doi: 10.1111/jon.12382
21. Zhang G, Li Z, Si D, Shen L. Diagnostic ability of intraoperative ultrasound for identifying tumor residual in glioma surgery operation. *Oncotarget* (2017) 8:73105–14. doi: 10.18632/oncotarget.20394
22. Munkvold BKR, Jakola AS, Reinertsen I, Sagberg LM, Unsgard G, Solheim O. The diagnostic properties of intraoperative ultrasound in glioma surgery and factors associated with gross total tumor resection. *World Neurosurg.* (2018) 115:e129–36. doi: 10.1016/j.wneu.2018.03.208
23. Solheim O, Selbekk T, Jakola AS, Unsgard G. Ultrasound-guided operations in unselected high-grade gliomas–overall results, impact of image quality and patient selection. *Acta Neurochir.* (2010) 152:1873–86. doi: 10.1007/s00701-010-0731-5
24. Moiyadi AV, Shetty PM, Mahajan A, Udare A, Sridhar E. Usefulness of three-dimensional navigable intraoperative ultrasound in resection of brain tumors with a special emphasis on malignant gliomas. *Acta Neurochir.* (2013) 155:2217–25. doi: 10.1007/s00701-013-1881-z
25. Moiyadi A, Kannan S, Shetty P. Navigated intraoperative ultrasound for resection of gliomas: predictive value, influence on resection and survival. *Neurol India* (2015) 63:727–35. doi: 10.4103/0028-3886.166549
26. Steno A, Matejcik V, Steno J. Letter to the editor: identification of residual glioma using ultrasound miniprobes. *Neurosurg Focus* (2016) 41:E15. doi: 10.3171/2016.5.FOCUS16180
27. Enriquez JL, Wu TS. An introduction to ultrasound equipment and knobology. *Crit Care Clin.* (2014) 30:25–45, v. doi: 10.1016/j.ccc.2013.08.006
28. Prada F, Del Bene M, Mattei L, Lodigiani L, DeBeni S, Kolev V, et al. Preoperative magnetic resonance and intraoperative ultrasound fusion imaging for real-time neuronavigation in brain tumor surgery. *Ultraschall Med.* (2015) 36:174–86. doi: 10.1055/s-0034-1385347
29. Stieglitz LH, Fichtner J, Andres R, Schucht P, Krahenbuhl AK, Raabe A, et al. The silent loss of neuronavigation accuracy: a systematic retrospective analysis of factors influencing the mismatch of frameless stereotactic systems in cranial neurosurgery. *Neurosurgery* (2013) 72:796–807. doi: 10.1227/NEU.0b013e318287072d
30. Gerard IJ, Kersten-Oertel M, Petrecca K, Sirhan D, Hall JA, Collins DL. Brain shift in neuronavigation of brain tumors: a review. *Med Image Anal.* (2017) 35:403–20. doi: 10.1016/j.media.2016.08.007
31. Gibbs V, Cole D, Sassano A. *Ultrasound Physics and Technology: How, Why and When*. London: Churchill Livingstone/Elsevier (2009).
32. Sconfienza LM, Mauri G, Secchi F. Ultrasound system setup and general semeiology. In: Prada F, Solbiati L, Martegani A, and DiMeco F, editors. *Intraoperative Ultrasound (IOUS) in Neurosurgery: From Standard B-Mode to Elastosonography*. Cham: Springer International Publishing (2016). p. 21–8.
33. Coburger J, König RW. Intraoperative findings in brain tumor surgery. In: Prada F, Solbiati L, Martegani A, and DiMeco F, editors. *Intraoperative Ultrasound (IOUS) in Neurosurgery: From Standard B-Mode to Elastosonography*. Cham: Springer International Publishing (2016). p. 41–58.
34. Prada F, Del Bene M, Moiraghi A, DiMeco F. Echographic brain semeiology and topographic anatomy according to surgical approaches. In: Prada F, Solbiati L, Martegani A and DiMeco F, editors. *Intraoperative Ultrasound (IOUS) in Neurosurgery: From Standard B-Mode to Elastosonography.* Cham: Springer International Publishing (2016).p. 29–39.
35. Prada F, Mattei L, Del Bene M, Aiani L, Saini M, Casali C, et al. Intraoperative cerebral glioma characterization with contrast enhanced ultrasound. *Biomed Res Int.* (2014) 2014:484261. doi: 10.1155/2014/484261
36. Steno A, Matejcik V, Steno J. Intraoperative ultrasound in low-grade glioma surgery. *Clin Neurol Neurosurg.* (2015) 135:96–9. doi: 10.1016/j.clineuro.2015.05.012
37. Prada F, Bene MD, Fornaro R, Vetrano IG, Martegani A, Aiani L, et al. Identification of residual tumor with intraoperative contrast-enhanced ultrasound during glioblastoma resection. *Neurosurg Focus* (2016) 40:E7. doi: 10.3171/2015.11.FOCUS15573
38. Šteno A, Giussani C, Riva M. Multimodal imaging in glioma surgery. In: Prada F, Solbiati L, Martegani A, and DiMeco F, editors. *Intraoperative Ultrasound (IOUS) in Neurosurgery: From Standard B-Mode to Elastosonography*. Cham: Springer International Publishing (2016). p. 81–97.
39. Steno A, Jezberova M, Holly V, Timarova G, Steno J. Visualization of lenticulostriate arteries during insular low-grade glioma surgeries by navigated 3D ultrasound power Doppler: technical note. *J Neurosurg.* (2016) 125:1016–23. doi: 10.3171/2015.10.JNS151907
40. Saether CA, Torsteinsen M, Torp SH, Sundstrom S, Unsgard G, Solheim O.. Did survival improve after the implementation of intraoperative neuronavigation and 3D ultrasound in glioblastoma surgery? A retrospective analysis of 192 primary operations. *J Neurol Surg A Cent Eur Neurosurg.* (2012) 73:73–8. doi: 10.1055/s-0031-1297247
41. Lindner D, Trantakis C, Renner C, Arnold S, Schmitgen A, Schneider J, et al. Application of intraoperative 3D ultrasound during navigated tumor resection. *Minim Invasive Neurosurg.* (2006) 49:197–202. doi: 10.1055/s-2006-947997
42. Rygh OM, Selbekk T, Torp SH, Lydersen S, Hernes TA, Unsgaard G. Comparison of navigated 3D ultrasound findings with histopathology in subsequent phases of glioblastoma resection. *Acta Neurochir.* (2008) 150:1033–41; discussion 1042. doi: 10.1007/s00701-008-0017-3
43. Steno A, Karlik M, Mendel P, Cik M, Steno J. Navigated three-dimensional intraoperative ultrasound-guided awake resection of low-grade glioma partially infiltrating optic radiation. *Acta Neurochir.* (2012) 154:1255–62. doi: 10.1007/s00701-012-1357-6
44. Coburger J, Konig RW, Scheuerle A, Engelke J, Hlavac M, Thal DR, et al. Navigated high frequency ultrasound: description of technique and clinical comparison with conventional intracranial ultrasound. *World Neurosurg.* (2014) 82:366–75. doi: 10.1016/j.wneu.2014.05.025

45. Prada F, Del Bene M, Moiraghi A, Casali C, Legnani FG, Saladino A, et al. From grey scale b-mode to elastosonography: multimodal ultrasound imaging in meningioma surgery—pictorial essay and literature review. *Biomed Res Int.* (2015) 2015:925729. doi: 10.1155/2015/925729
46. Moiyadi AV, Unsgård G. Navigable ultrasound, 3D ultrasound and fusion imaging in neurosurgery. In: Prada F, Solbiati L, Martegani A, and DiMeco F, editors. *Intraoperative Ultrasound (IOUS) in Neurosurgery: From Standard B-Mode to Elastosonography*. Cham: Springer International Publishing (2016). p. 135–45.
47. Selbekk T, Solheim O, Unsgard G. Ultrasound-guided neurosurgery: experiences from 20 years of cross-disciplinary research in Trondheim, Norway. *Neurosurg Focus* (2016) 40:E2. doi: 10.3171/2015.12.FOCUS15582
48. Selbekk T, Jakola AS, Solheim O, Johansen TF, Lindseth F, Reinertsen I, et al. Ultrasound imaging in neurosurgery: approaches to minimize surgically induced image artefacts for improved resection control. *Acta Neurochir.* (2013) 155:973–80. doi: 10.1007/s00701-013-1647-7
49. Unsgard G, Rao V, Solheim O, Lindseth F. Clinical experience with navigated 3D ultrasound angiography (power Doppler) in microsurgical treatment of brain arteriovenous malformations. *Acta Neurochir.* (2016) 158:875–83. doi: 10.1007/s00701-016-2750-3
50. Reinertsen I, Lindseth F, Askeland C, Iversen DH, Unsgard G. Intra-operative correction of brain-shift. *Acta Neurochir.* (2014) 156:1301–10. doi: 10.1007/s00701-014-2052-6
51. Comeau RM, Sadikot AF, Fenster A, Peters TM. Intraoperative ultrasound for guidance and tissue shift correction in image-guided neurosurgery. *Med Phys.* (2000) 27:787–800. doi: 10.1118/1.598942
52. Arbel T, Morandi X, Comeau RM, Collins DL. Automatic non-linear MRI-ultrasound registration for the correction of intra-operative brain deformations. *Comput Aided Surg.* (2004) 9:123–36. doi: 10.1080/10929080500079248
53. Reinertsen I, Descoteaux M, Siddiqi K, Collins DL. Validation of vessel-based registration for correction of brain shift. *Med Image Anal.* (2007) 11:374–88. doi: 10.1016/j.media.2007.04.002
54. Caldiera V, Caputi L, Ciceri E. Doppler imaging: basic principles and clinical application. In: Prada F, Solbiati L, Martegani A, and DiMeco F, editors. *Intraoperative Ultrasound (IOUS) in Neurosurgery: From Standard B-Mode to Elastosonography*. Cham: Springer International Publishing (2016) 101–20.
55. Prada F, Del Bene M, Mauri G, Lamperti M, Vailati D, Richetta C, et al. Dynamic assessment of venous anatomy and function in neurosurgery with real-time intraoperative multimodal ultrasound: technical note. *Neurosurg Focus* (2018) 45:E6. doi: 10.3171/2018.4.FOCUS18101
56. Sidhu PS, Cantisani V, Dietrich CF, Gilja OH, Saftoiu A, Bartels E, et al. The EFSUMB guidelines and recommendations for the clinical practice of Contrast-Enhanced Ultrasound (CEUS) in non-hepatic applications: update 2017 (Long Version). *Ultraschall Med.* (2018) 39:e2–e44. doi: 10.1055/a-0586-1107
57. Prada F, Perin A, Martegani A, Aiani L, Solbiati L, Lamperti M, et al. Intraoperative contrast-enhanced ultrasound for brain tumor surgery. *Neurosurgery* (2014) 74:542–52; discussion 552. doi: 10.1227/NEU.0000000000000301
58. Prada F, Del Bene M, DiMeco F. Contrast-Enhanced Ultrasound (CEUS) in neurosurgery. In: Prada F, Solbiati L, Martegani A, and DiMeco F, editors. *Intraoperative Ultrasound (IOUS) in Neurosurgery: From Standard B-Mode to Elastosonography*. Cham: Springer International Publishing (2016).p. 159–69.
59. Dietrich CF, Averkiou M, Nielsen MB, Barr RG, Burns PN, Calliada F, et al. How to perform Contrast-Enhanced Ultrasound (CEUS). *Ultrasound Int Open* (2018) 4:E2–e15. doi: 10.1055/s-0043-123931
60. Schrope BA, Newhouse VL. Second harmonic ultrasonic blood perfusion measurement. *Ultrasound Med Biol.* (1993) 19:567–79. doi: 10.1016/0301-5629(93)90080-8
61. Simpson DH, Chin CT, Burns PN. Pulse inversion Doppler: a new method for detecting nonlinear echoes from microbubble contrast agents. *IEEE Trans Ultrason Ferroelectr Freq Control* (1999) 46:372–82. doi: 10.1109/58.753026
62. Greis C. Technology overview: SonoVue (Bracco, Milan). *Eur Radiol.* (2004) 14(Suppl. 8):P11–5. doi: 10.1007/s10406-004-0076-3
63. Prada F, Del Bene M, Casali C, Saladino A, Legnani FG, Perin A, et al. Intraoperative navigated angiosonography for skull base tumor surgery. *World Neurosurg.* (2015) 84:1699–707. doi: 10.1016/j.wneu.2015.07.025
64. Prada F, Del Bene M, Saini M, Ferroli P, DiMeco F. Intraoperative cerebral angiosonography with ultrasound contrast agents: how I do it. *Acta Neurochir.* (2015) 157:1025–9. doi: 10.1007/s00701-015-2412-x
65. Vetrano IG, Prada F, Erbetta A, DiMeco F. Intraoperative ultrasound and Contrast-Enhanced Ultrasound (CEUS) features in a case of intradural extramedullary dorsal schwannoma mimicking an intramedullary lesion. *Ultraschall Med.* (2015) 36:307–10. doi: 10.1055/s-0035-1552129
66. Vetrano IG, Prada F, Nataloni IF, Bene MD, Dimeco F, Valentini LG. Discrete or diffuse intramedullary tumor? Contrast-enhanced intraoperative ultrasound in a case of intramedullary cervicothoracic hemangioblastomas mimicking a diffuse infiltrative glioma: technical note and case report. *Neurosurg Focus* (2015) 39:E17. doi: 10.3171/2015.5.FOCUS15162
67. Prada F, Del Bene M, DiMeco F. Image guidance in skull base tumor resection: a synergistic approach using intraoperative navigated angiosonography for real-time vessel visualization. *Surg Neurol Int.* (2016) 7:82. doi: 10.4103/2152-7806.190437
68. Prada F, Del Bene M, Farago G, DiMeco F. Spinal dural arteriovenous fistula: is there a role for intraoperative contrast-enhanced ultrasound? *World Neurosurg* (2017) 100:712.e715–8. doi: 10.1016/j.wneu.2017.01.045
69. Prada F, Vitale V, Del Bene M, Boffano C, Sconfienza LM, Pinzi V, et al. Contrast-enhanced MR imaging versus contrast-enhanced US: a comparison in glioblastoma surgery by using intraoperative fusion imaging. *Radiology* (2017) 285:242–9. doi: 10.1148/radiol.2017161206
70. Bamber J, Cosgrove D, Dietrich CF, Fromageau J, Bojunga J, Calliada F, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: basic principles and technology. *Ultraschall Med.* (2013) 34:169–84. doi: 10.1055/s-0033-1335205
71. Shiina T, Nightingale KR, Palmeri ML, Hall TJ, Bamber JC, Barr RG, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: part 1: basic principles and terminology. *Ultrasound Med Biol.* (2015) 41:1126–47. doi: 10.1016/j.ultrasmedbio.2015.03.009
72. Cosgrove D, Piscaglia F, Bamber J, Bojunga J, Correas JM, Gilja OH, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: Clinical applications. *Ultraschall Med.* (2013) 34:238–53. doi: 10.1055/s-0033-1335375
73. Selbekk T, Bang J, Unsgaard G. Strain processing of intraoperative ultrasound images of brain tumours: initial results. *Ultrasound Med Biol.* (2005) 31:45–51. doi: 10.1016/j.ultrasmedbio.2004.09.011
74. Uff CE, Garcia L, Fromageau J, Dorward N, Bamber JC. Real-time ultrasound elastography in neurosurgery. In: *2009 IEEE International Ultrasonics Symposium* (2009). p. 467–70.
75. Selbekk T, Brekken R, Solheim O, Lydersen S, Hernes TA, Unsgaard G. Tissue motion and strain in the human brain assessed by intraoperative ultrasound in glioma patients. *Ultrasound Med Biol.* (2010) 36:2–10. doi: 10.1016/j.ultrasmedbio.2009.05.007
76. Selbekk T, Brekken R, Indergaard M, Solheim O, Unsgard G. Comparison of contrast in brightness mode and strain ultrasonography of glial brain tumours. *BMC Med Imaging* (2012) 12:11. doi: 10.1186/1471-2342-12-11
77. Chauvet D, Imbault M, Capelle L, Demene C, Mossad M, Karachi C, et al. *In vivo* measurement of brain tumor elasticity using intraoperative shear wave elastography. *Ultraschall Med.* (2016) 37:584–90. doi: 10.1055/s-0034-1399152

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

PERSPECTIVE
published: 17 December 2018
doi: 10.3389/fonc.2018.00593

A Time-Tested Information System in Neurosurgical Oncology

Dima Suki, David M. Wildrick and Raymond Sawaya*

Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

The Brain and Spine Center at The University of Texas MD Anderson Cancer Center is a leading multidisciplinary referral center for patients with nervous system (NS) tumors. It has a wealth of clinical experience and an internationally recognized leadership role in the management of NS cancers. In that context, an informatics infrastructure that allows the archiving of both the prospective and retrospective characterization of patients, diseases, treatments, and outcomes is invaluable. We describe our experience with the Neurosurgical Oncology Database, a database that has provided valuable, extensive, and readily searchable data on multifaceted patient, tumor, and treatment characteristics for many years, successfully serving as an administrative and operational resource and as a resource for retrospective and prospective research endeavors.

Keywords: neurosurgical oncology, database, informatics, data management, information systems

OPEN ACCESS

Edited by:
Marcos Vinicius Calfat Maldaun, Hospital Sírio-Libanês, Brazil

Reviewed by:
Carsten Friedrich, University of Rostock, Germany
Yoshua Esquenazi, University of Texas Health Science Center at Houston, United States

****Correspondence:***
Dima Suki
dsuki@mdanderson.org

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *27 August 2018*
Accepted: *26 November 2018*
Published: *17 December 2018*

Citation:
Suki D, Wildrick DM and Sawaya R (2018) A Time-Tested Information System in Neurosurgical Oncology. Front. Oncol. 8:593. doi: 10.3389/fonc.2018.00593

INTRODUCTION

The Brain and Spine Center at The University of Texas MD Anderson Cancer Center (MD Anderson) is a major referral center for patients with nervous system (NS) tumors. It has a wealth of clinical experience and an internationally recognized leadership role in the management of NS cancers, both common and rare (1). As such, the department's leaders were keenly aware of their obligation to learn from their experience, and to apply this knowledge to improve disease classification, come up with novel therapy and management, and supply benchmark data that supports innovative experimental protocols (**Figure 1**). To meet this obligation, it was essential to have an informatics infrastructure that allowed us to archive and readily query both prospective and retrospective characterization of patients, diseases, treatments, and outcomes. The repository was intended to serve as an administrative and operational resource and as a resource for quality improvement, benchmarking, and educational purposes. It was also intended to serve as a valuable resource for research studies encompassing the epidemiology, natural history, characterization, and treatment of NS tumors and the multifaceted outcomes of patients with these tumors. The repository was endorsed as a top priority from day 1 and was afforded significant resources over time.

Establishing a database such as this one is a complex endeavor whose success and longevity necessitate a wide range of skills and resources on a long-term basis. This manuscript discusses the features of such a database and elements that are key to its success and longevity (**Table 1**).

METHODS

The initial step in the development of the database was the formation of a multidisciplinary multilevel database task force. The task force was charged with identifying the uses of the database,

FIGURE 1 | Department of Neurosurgery tree, showing the Database as a fundamental element near the base of the tree [reproduced with permission from Lang et al. (1)].

the various data items to be collected, the format and level of detail of these items, and resolving various multidisciplinary issues. The task force included:

1 An institutional programming group. Members of this group had extensive experience in the development of complex clinical databases.
2 Committed faculty members in the various areas encompassed by the database.
3 Clinical research staff with knowledge in the NS tumor field and clinical research.
4 Data management staff that are actively involved in the data collection, verification, analysis, and reporting process.
5 A task force chairperson with extensive experience in database development and management, research protocol design and conduct, statistical analysis, regulatory compliance, as well as a strong understanding of the field of neurosciences.

A strong line of communication was secured among various team members. With the support of the task force, we applied a user-centered method to analyze tasks, workflow, and optimal interfaces for data entry, review, and mining. We then designed prototypes to map the results of user, task, and representation (interface) analyses and evaluated these prototypes. These steps were critical and fundamental to the final product.

TABLE 1 | Important considerations in planning, developing and maintaining a successful database.

1. Purpose/objectives of database
2. Stakeholders/subject matter experts/users
   a. Intra- or interdisciplinary
   b. Commitment/involvement
3. Scope of database
   a. Target patient population
   b. Volume
   c. Disease-, site- or treatment-specific
   d. Cross-sectional vs. longitudinal
   e. Database lifetime
   f. Core dataset
4. Sources of data/links to other databases
5. Available infrastructure
6. Choice of database program/housing issues (interdependent with infrastructure available, issues of staffing, maintenance/enhancements/upgrades and cost)
7. Staffing
   a. Background/training
   b. Exact role
   c. Retention
   d. Cost
8. Governance plan
9. Quality assurance
   a. The ALCOA data integrity test (Attributable, Legible, Contemporaneous, Original and Accurate)
   b. Standardized data sources/definitions
   c. Oversight plan
10. Compliance
   a. Institutional review/ethical board approval
   b. Issues of consent/authorization vs. waiver
   c. Applicable policies and regulations at all levels (e.g., Code of Federal Regulations; Good Clinical Practice; Health Insurance Portability and Accountability Act [HIPAA] and/or other applicable privacy laws; institutional information security policies; other policies and regulations)
11. Assessment of initial feasibility and long-term viability (baseline and maintenance costs being major considerations)

HARDWARE/SOFTWARE AND SYSTEM DESIGN (FIGURE 2)

The database is web based, which ensures easy access to users from various physical locations within the MD Anderson firewall. The software used has many of the features of other currently used data management programs, including (but not limited to) allowing complex data structures and complex logical checks. In addition, the software has superior security features and easy to navigate user and statistical software interfaces. It is backed by a premiere company and is periodically updated, thereby assuring the users state-of-the-art technology.

DATABASE STRUCTURE (FIGURES 3–5)

The database is relational, as depicted in **Figure 3**, and is organized into screens of varying lengths and numbers of

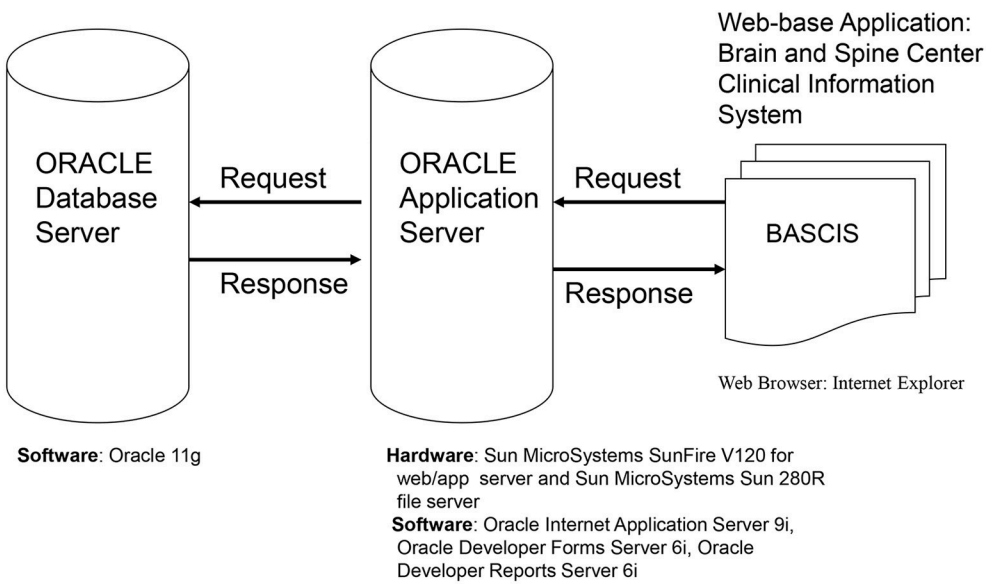


FIGURE 2 | Database hardware/software and system design.

fields. The main data entry screens are accessed through a tab at the top of the screen. Key tabs are the Demographics tab (with details on the patients' demographic information); Tumor History (with longitudinal details on the patients' tumor history, including radiographic and pathologic diagnoses, histology, grade, and metastases); Surgery (with specific sub-screens depending on the type of case (brain, skull base, spine, peripheral, pain, other; metastasis vs. primary NS; and details on all procedures related to the nervous system tumor, hospital stay, symptomatology, complications); Chemotherapy; Radiation; and Imaging. **Figure 4** shows an example schema of brain procedure-related tables, and **Figure 5**, an example of the brain procedure interface. The database allows for additions/modifications as needed via an approved process.

PATIENT ELIGIBILITY

All patients undergoing a neurosurgery at MD Anderson, irrespective of diagnosis, have their data collected and stored in the database. The requirement for patient consent was waived by the institutional review board (IRB). The waiver relied on justifications that the research (in this case strictly data collection and storage) involves no more than minimal risk to the subjects, that the waiver would not adversely affect the rights and welfare of subjects, that the collection could not be practicably carried out without the waiver, and that whenever appropriate, the subjects will be provided with additional pertinent information.

DATA COLLECTION

The patient is registered in the database at the time of their MD Anderson neurosurgery. Registration triggers the beginning of the review/data collection process for a given patient. Dictated notes for all patient encounters (clinic visits; surgery or other procedure; testing; or other reason), scanned documents, images, and other components of the patient's electronic medical record (EMR) are reviewed after registration and until postoperative day 30 or until events and treatments during the 30 days can be captured, whichever is later. Variables entered into the database include but are not limited to: patient demographic data; clinical parameters, such as Karnofsky Performance Scale score (and other functional measures), neurologic status, symptoms, diagnosis date, cancer site(s), tumor histology (and other pathology-specific characteristics), and imaging characteristics; treatments, such as surgery details (procedures, indications, intraoperative adjuncts used, blood loss and transfusions, and extent of resection, where applicable), radiotherapy details (type, date, dose, schedule), chemotherapy details (type, date, dose, schedule); and treatment outcomes including length of hospital and rehabilitation stay, complications/toxicities, and survival time. In addition to the imaging data obtained from the patients' medical records, a qualitative visual review of the image is performed to assess for entities such as presence or absence of tumor necrosis, contrast enhancement, cysts, hemorrhage, gliomatosis cerebri, and others, as well as confirmation of tumor location and tumor functional grade. A quantitative assessment of preoperative/postoperative necrosis, tumor, and cyst volumes and extent of resection is also performed using the Vitrea software.

All patients are uniquely identified in the database. An identifier is assigned, allowing information to be retrieved without any traceable link to the actual identity of the patient (except, of course, by the database administrator/users with permission). There are multiple levels of user privilege so that various classes of users only have access to information appropriate for their roles.

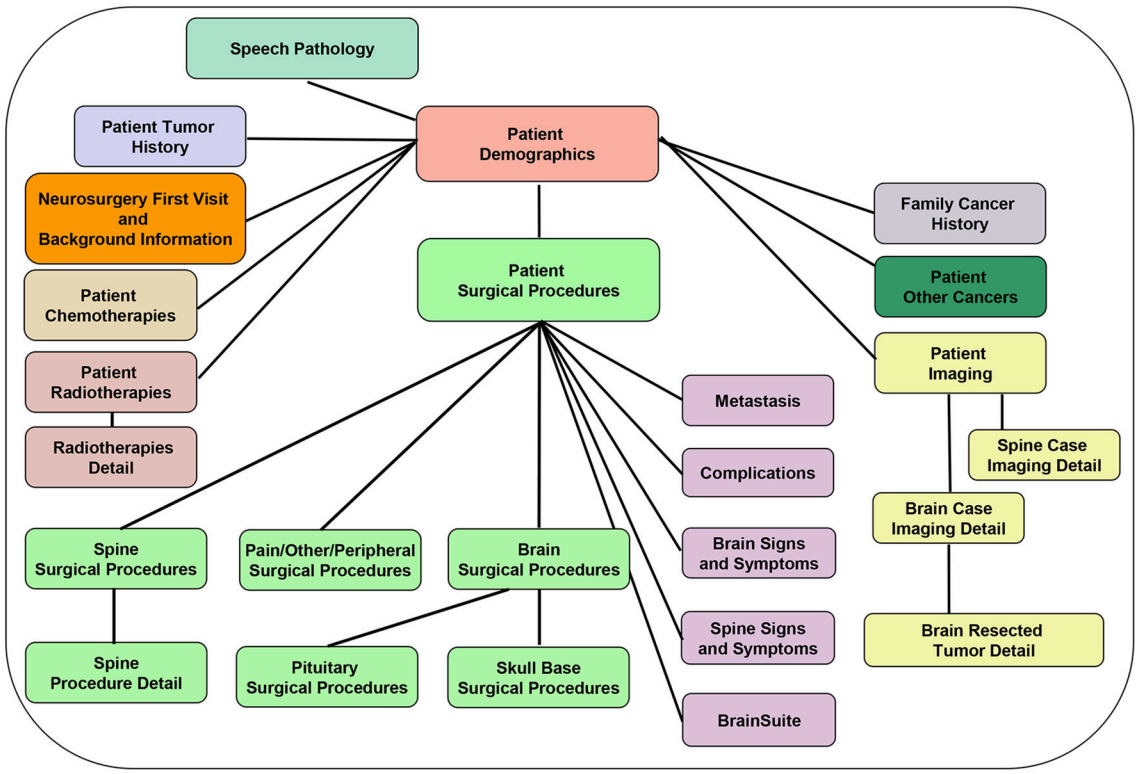


FIGURE 3 | Database back-end structure, showing the various database tables and depicting the table relationships (one-to-one: e.g., Patient Demographics and Cancer Family History tables; and one-to-many: e.g., Patient demographics and Patient Surgical Procedures table).

Every attempt is made to collect the data in a prospective fashion, e.g., operating room findings are documented by the neurosurgeons as soon as possible after the surgery. Also, whenever possible, data acquisition from other hospital sources (e.g., hospital registration database) is automated to decrease duplication of effort, reduce error level, and ensure a quick download. Other manual downloads include data from the MD Anderson Tumor Registry, Surgical Indexing, and others. Evaluation of data from additional sources for suitability for potential download is performed on a regular basis, though not always achievable.

DATA ENTRY

The database contains a minimal number of text fields. Most fields are coded for consistency and ease of entry and to enhance search and retrieval capabilities. Data are entered through a point-and-click approach with drop-down menus. Entries are standardized by precise inclusion criteria and precise definitions noted in a data and database dictionary. The coding structures used have been designed for a maximum flexibility and precision of searches and data analysis. Where applicable, data on a given entity are recorded from an expandable hierarchical set of codes and linked to a number of relevant descriptors. For clarity and ease of data entry, the system was designed to show specific fields on a given screen only when applicable (e.g., fields related to the primary non-NS cancer history only appear for patients with a NS metastasis) or to automatically fill in fields in a hierarchy where appropriate. Standard diagnostic and procedural coding schemes (Systematized Nomenclature of Medicine [SNOMED] and Current Procedural Terminology [CPT] Systems) are also included as an additional coding methodology.

DATA DICTIONARY

An extensive database dictionary has been developed to serve as a reference guide for database coordinators and other database users. The dictionary includes all details on all data collected, including a description of the fields, their source, definition, and allowable responses. As a simple example: "**Any Treatment field:** Pull Down Menu options are Yes; No; Unk. This field refers to any treatment to the primary cancer at any time up to the patient's first visit to the BTC neurosurgeon. Does not include treatment to the systemic metastases. Get information from history of present illness and past medical history in neurosurgeon's dictation or previous relevant patient dictations/scan documents/or medical chart." Additional notes or unique scenarios are highlighted as a guide for the staff. As an example: "**Note:** A family member with a primary outside the CNS that metastasized to the CNS should not be coded as one with a history of CNS cancer."

The dictionary ensures the consistency and validity of the data stored and of their interpretation. The complete version of the

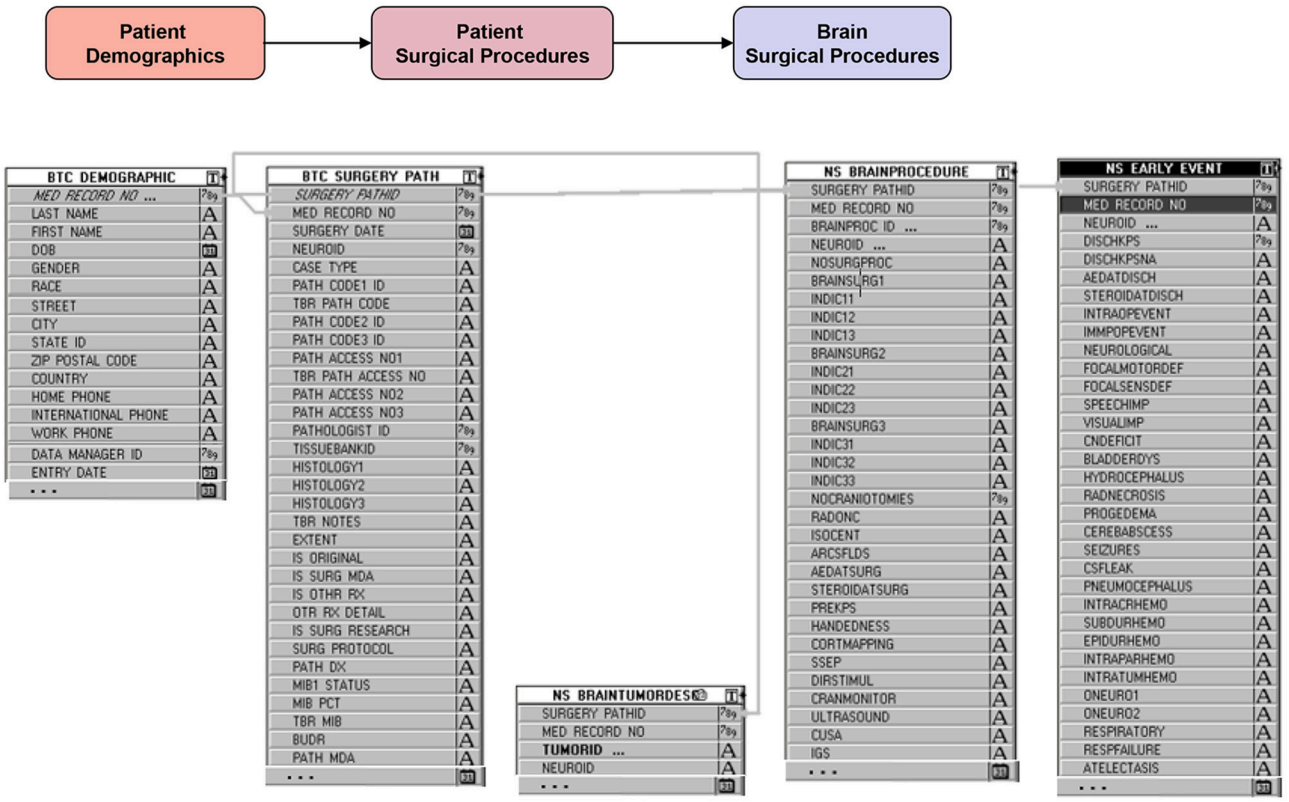


FIGURE 4 | Example backend schema of brain procedure information (starting with demographic table), followed by general details of the surgery (surgery date, pathology findings, etc…), specific details of the procedures performed during the surgery and the intraoperative adjuncts used, and finally events or complications during and after surgery.

dictionary is accessible within the database for easy access and is constantly updated to reflect changes.

DATABASE GOVERNANCE

Strict written policies and procedures and standard forms are in place to govern every database-related aspect including database access and maintenance, data collection, entry, extracting, and quality assurance (**Table 2**). These are reviewed on a regular basis and modified as necessary. All requests for data are tracked and their status is documented.

DATA QUERIES AND RETRIEVAL (FIGURE 6)

The database includes some built-in reports that are routinely generated from the data. An example of such a report is the number of surgical cases during a given time frame, stratified by surgical procedure, tumor site (brain, skull base, spine, and other), surgeon, or other. The database allows the direct e-mailing of such reports to designated individuals on specified dates. Non-routine or complicated queries are performed by the departmental database programmer on an as needed basis. Reports are formatted for viewing or analysis according to the needs of the user. The database has interfaces with commonly used statistical and data management software. This allows the quick export of pertinent patient data in a standard format. Approval by designated individuals is required for all data extractions. Data to be used for research purposes will only be retrieved and distributed according to a protocol approved by the IRB.

DATA QUALITY

The most important and most difficult aspect of having a clinical database is ensuring the veracity of the data and its meeting of all applicable quality assurance (QA) standards. This issue is addressed at multiple levels:

1 Hiring of highly-qualified staff members for data extraction and coding. Given the complexity of medical data in general, and data related to the nervous system in particular, close attention was paid to the selection of the staff members, most of whom are non-practicing medical doctors, and to their training on aspects relevant to the database and data collection and coding. The database team includes 4.5 full time equivalents (FTEs) handling clinical data collection and

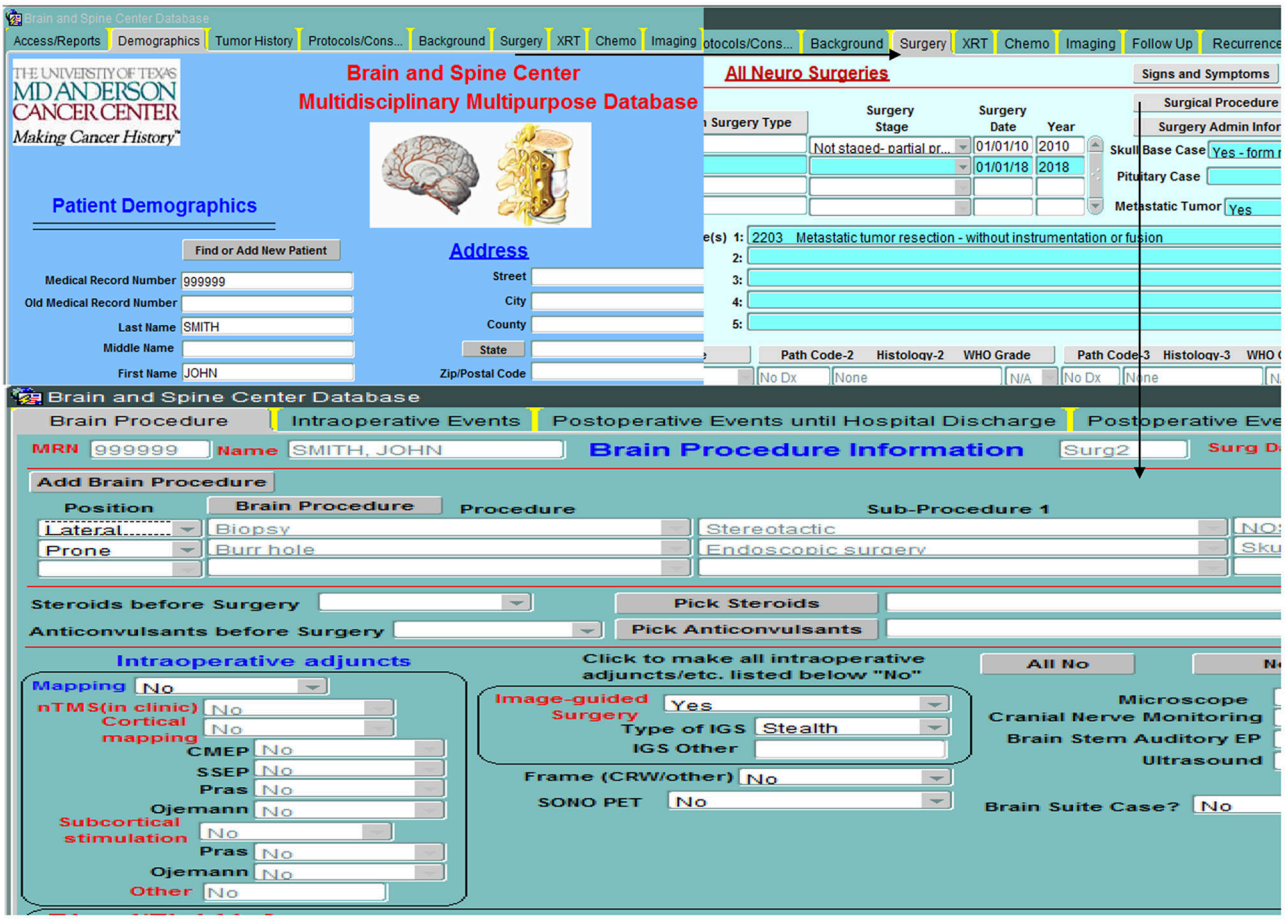


FIGURE 5 | Example of brain procedure information front-end interfaces used to input data.

entry, imaging, data and database management, and general oversight.

2 The data and database dictionary mentioned in the previous section, ensuring standardized and well-communicated data sources and definitions.

3 A QA standard operating procedure (SOP) detailing every aspect of the QA process as noted below. The SOP is regularly reviewed to ensure that it remains up to date and covers the following areas:

   a. A check of the daily database census against clinic and operating room schedules allows the capture of data on all eligible patients.
   b. Complex built-in logic checks and validation rules limit a large number of data entry errors/missing data at the time of entry (**Figure 7**).
   c. Multiple internal consistency checks of the data by designated quality assurance staff reveal missing and erroneous information not detected by the logic checks and validation rules.
   d. A dedicated "to be resolved" sub-screen on all screens allows for flagging of questionable data and signaling the need for further review by appropriate staff. (**Figure 8**)
   e. Comparison of a random sample of the data with the entries in the patient's medical record reveals additional errors and improves the external consistency of the data.
   f. An audit trail ensures that all entries (new or revisions) into the database are documented and traced to the individual who made the entry and the time the entry was made (**Figure 9**).
   g. Finally, regular staff meetings intended to go over problematic issues, determine needs for change, provide continuous training, and positively impact overall performance and outcome.

SECURITY AND REGULATORY COMPLIANCE

The database is governed by an IRB-approved protocol. Issues of patient consent and authorization are addressed as appropriate. The database meets all applicable policies and regulations at various levels (Code of Federal Regulations; Good Clinical Practice; the Health Insurance Portability and Accountability Act [HIPAA, a United States law that sets privacy standards for the protection of patients' medical records and other health

TABLE 2 | Examples of database policies and procedures in place.

- Account creation, deletion, modification policy and its related forms
  - Account creation, deletion, modification policy
  - Account creation form
  - Account modification form
  - Account inactivation form
- Change/correction process policy and form
  - Change/correction process policy
  - Change/correction request form
- Password change guideline
- Technical support procedure
- Neurosurgery database data capture-entry-reporting SOP
- Neurosurgery database QA SOP
- Request for data retrieval policy and its related forms
  - Request for individual data retrieval–research purposes
  - Request for data counts–research purposes
  - Request for data counts/retrieval–non-research purposes
  - Request for individual data retrieval–non-research purposes
  - Request for data retrieval–preparation for research purposes

information]; information security policies; other institutional policies). Particularly with regard to HIPAA compliance, the following measures are taken:

1 Access to the database is restricted to individuals with explicit permission. Users have a level of permission necessary to perform their respective jobs. Passwords need to be changed every 90 days. Application system lockout is enabled after 3 bad tries.
2 As noted above, an audit trail ensures that all entries (new/revised) into the database are documented and traced to the individual who made the entry.
3 The database contains a database-specific unique identifier that is independent of patient personal identifiers. For all requests that do not require patient identifiers, the anonymous database ID is used to identify the records. When the data are to be used for research purposes rather than for patient care or administrative reports, release of patient identifiers necessitates IRB approval. Published results obtained from any analysis are not linked to any patient identifiers.
4 The database undergoes regular check by the institutional information security department.

RESULTS

At the time of preparation of this manuscript, the database had spanned a period of 25 years, with the latest structure being in place for 14 years. It currently houses historical and demographic data; data on disease, tumor, and patient characteristics; and perioperative and other treatment data on close to 27,000 patients [over 34,000 neurosurgical cases with a current annual accrual of around 1,800 cases. Since its inception, the database has been highly utilized within and outside the Department of Neurosurgery for various research, administrative, educational, and other purposes. It has been the source of data for numerous publications and presentations at scientific meetings. These publications and presentations encompass areas of epidemiology, tumor characterization, treatments, and treatment outcomes. As an example, the study by Lacroix et al. (2) evaluated the outcome of 416 patients undergoing varying degrees of glioblastoma resection and required extensive use of the Neurosurgery database. It confirmed the survival advantage of a near total resection (98% or more) compared with a lesser resection. This seminal study has resulted in renewed interest in advancing neurosurgical techniques for the treatment of malignant brain tumors. In 2014, Marko et al. (3) used data from this database to study 721 patients newly diagnosed with glioblastoma (from 1993 to 2010) to construct a mathematical model of factors affecting personalized survival. Their findings argued against a surgical management strategy based on rigid extent-of-resection thresholds and instead provided the first explicit evidence supporting a maximum safe resection approach to glioblastoma surgery. These findings were further bolstered by a study by Li et al. (4), who employed our database to study the influence of maximum safe glioblastoma resection in 1,229 patients. In what is probably the largest single-center series of glioblastoma patients with extensive tumor resections, their study supported the established association between extent of resection and survival and moreover, showed that going beyond a conventional 100% resection (of all contrast-enhancing tumor) by also removing a significant portion of the fluid-attenuated inversion recovery (FLAIR) abnormality region, when safely feasible, may prolong survival without significantly increasing overall or neurological postoperative morbidity. More recently, Al-Holou et al. (5) drew data from our database on 1204 patients with glioblastoma to show that relative to piecemeal resection of these tumors, circumferential perilesional resection is significantly and independently associated with improved outcomes. Clearly, studies such as these on a scale this large would have been impossible without a patient database as robust and extensive as ours, and one that ensured that data typically inconsistently recorded in the medical records, such as method of tumor removal, or data not typically available, such as volumetric perioperative analyses of all brain tumors is regularly and consistently documented. Other select publications are listed in **Table 3**].

Meetings with the data management team members are held regularly as well as on an *ad-hoc* basis. The meetings serve as a platform for dealing with problematic issues and identifying needs for modification. They aim at encouraging good data management practices and keeping communication open in a friendly unthreatening environment.

Initially, for the first few years, both an informed consent and a HIPAA authorization document needed to be signed by patients, but the IRB later approved waivers for these, given that waiver justifications for both consent and authorization were met.

Funding for the database over the years was provided by departmental funds, two MD Anderson Cancer Center institutional database grants, as well as by designated and undesignated philanthropic donor funds.

DEPARTMENT OF NEUROSURGERY REPORT: Monthly Cases Summary

Report from: 05/01/2018 To: 05/31/2018

A- ALL COUNTS BELOW REFLECT CASES PERFORMED BY NEUROSURGEONS REGARDLESS OF PRIMARY SERVICE

Total Cases by Primary Neurosurgeon:

Surgeon	
Cole	8
Hank	22
Holmes	9
Lee	13
Ling	1
Mike	24
Newman	8
Parker	25
Roberts	7
Smith	2
White	13
Total	132

Total Brain/Skullbase OR & Stereotactic Radiosurgery Cases by Primary Neurosurgeon:

Surgeon	
Cole	8
Hank	15
Holmes	8
Lee	13
Ling	1
Mike	17
Parker	25
Roberts	1
Smith	2
White	13
Total	103

FIGURE 6 | Example of basic canned (pre-programmed) data queries and retrieval interfaces: Monthly summary of cases.

DISCUSSION

Information management is the creation and application of processes directed toward the collection and review of data in a structured and effective manner (13). The ready accessibility of patient, disease, treatment, and outcome data from an informatics infrastructure repository is a major catalyst for the advancement of medical knowledge, as it helps in the rapid translation of clinical and laboratory discoveries into new and better treatments and therapies. As noted under the Methods section, the database is web based, which ensures easy access to users from various physical locations protected by the MD Anderson firewall. It is sufficiently flexible to support multiple tumor and treatment types, and multiple clinical case scenarios. It incorporates elements of a prospective data collection process as well as elements of a point-of-care data entry process (including ease of access and navigation). It provides the necessary and compatible backbone for downloading data from other MD Anderson Cancer Center institutional sources. This relational database allows for user-centered, screen-driven, structured, and efficient data entry, review, and mining, and a role-based security system. It ensures the highest data quality through a large number of external and internal consistency checks, complex built-in logic checks and validation rules, dedicated "to be resolved" fields on every screen, an audit trail, a detailed data dictionary, and extensive training of qualified data management staff, a crucial prerequisite to a high quality product (14–17). It is HIPAA-compliant.

The database task force was valuable to the success of the project. Task force members brought important clinical knowledge and expertise to the group. Traditionally, clinicians may have had little or no control over the development and implementation of patient information systems. Many databases are developed by programmers with a somewhat limited understanding of the clinical issues involved. A closer look at the traditional "*Build it and they will come*" approach reveals major limitations and an inherent risk of failure. A high level of input in the development process by intended users leads

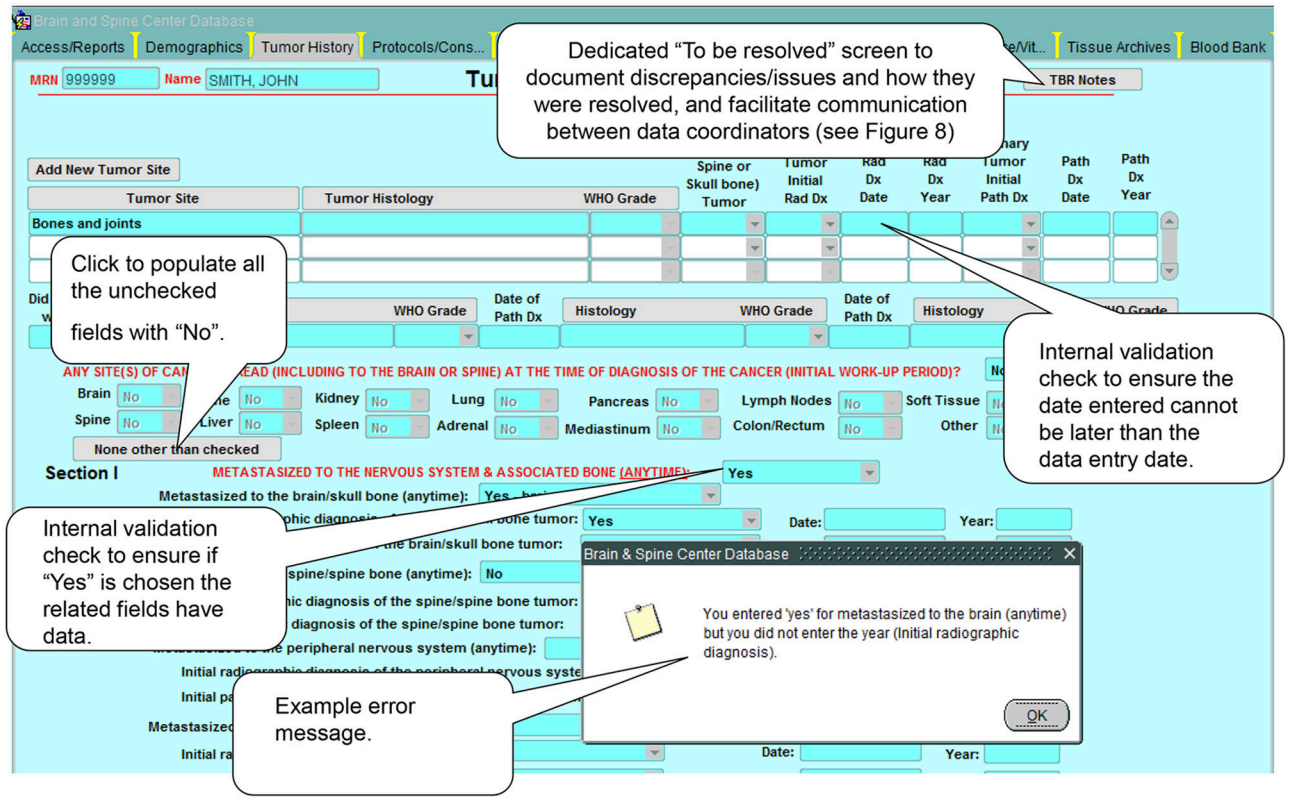


FIGURE 7 | Example of built-in logic checks and validation rules. These internal consistency checks and rules help control the quality of the data in the database by preventing the input of erroneous data.

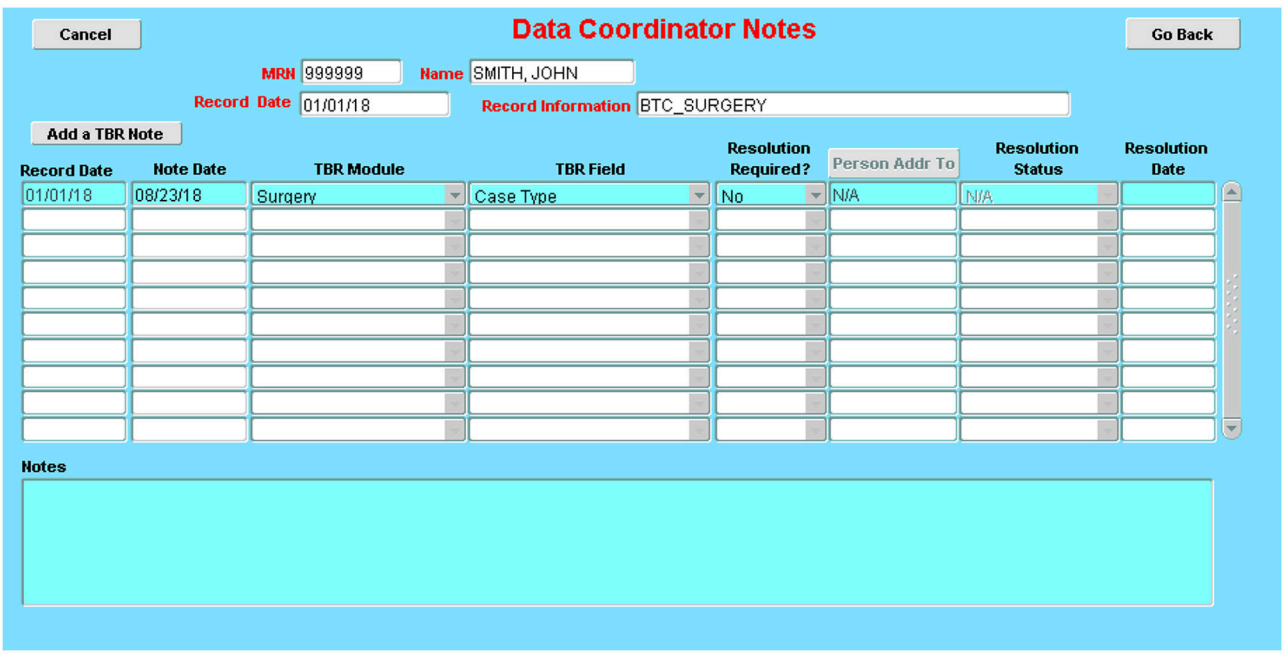


FIGURE 8 | Issue-tracking sub-screen: These sub-screens, which are accessible on every database screen, allow the documentation of issues encountered during data collection and how they were resolved (e.g., error in a dictation; discrepancies between two dictations; missing details on a required field).

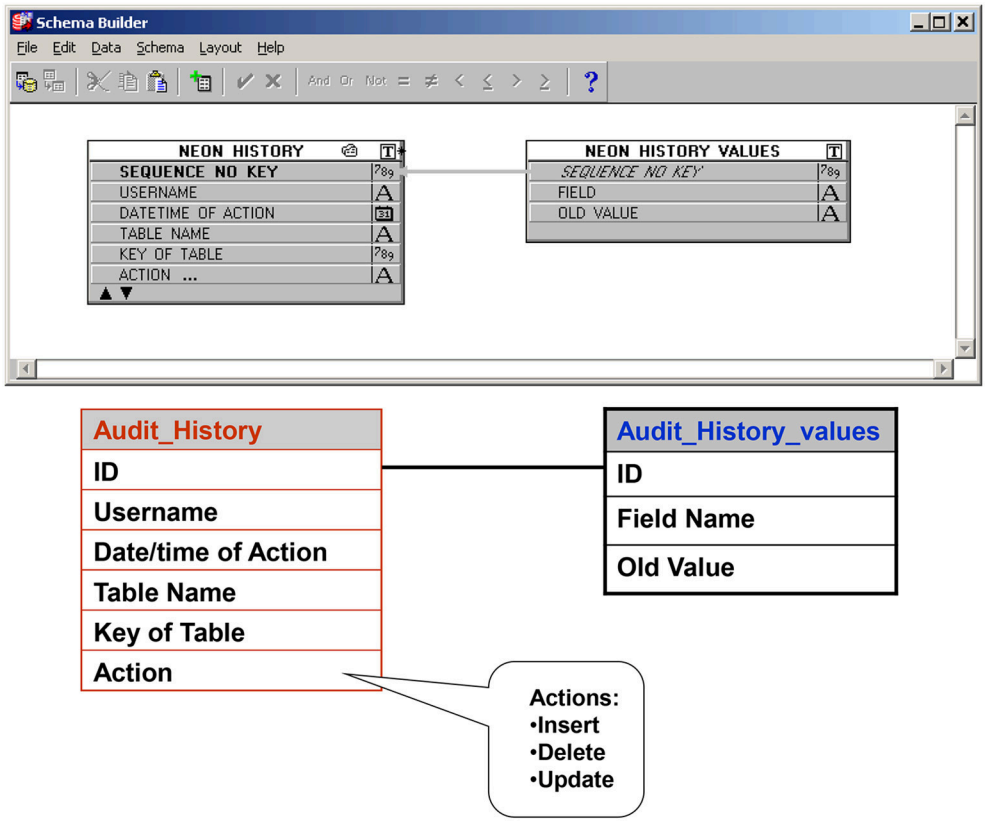


FIGURE 9 | Audit trail table: Ensures that all entries (new or revisions) into the database are documented and traced to the individual who made the entry and the time the entry was made.

to a product that meets the users' needs, has a high level of relevance, acceptance, and utilization and thereby is successful. Participation by the faculty, then, is an element crucial to the longevity of this project.

A key difficulty was the development of a robust data dictionary that clarified the various field definitions, sources, or time frames. This key difficulty was also a key strength of the database, once developed. It continues to be a living breathing document, whereby various aspects are subject to review and adaptation.

Another key difficulty was sustaining the funding. The database is an expensive endeavor, and securing financial support of full-time staff members involved in the day-to-day database activities including data collection, mining, and quality assurance is no small feat. A key strength was the hiring of highly qualified staff members and their retention. Many of the staff members have had a longevity of more than a decade with the department. During times of hardship, and these times are inevitable with a database that spans a long period of time, focus on the core data set and the "bread and butter" was crucial.

In addition to the well-known challenges of developing clinical databases in general (securing the acceptability of end-users, allowing for simple data entry and retrieval methods, and possessing large storage capacity and adequate security safeguards) (18–23), this database posed some unique challenges stemming from its unique aims. These challenges included: (1) Its wide scope (research and administrative purposes, among others); (2) the variety of tumors involved (primary vs. metastatic; brain, spine, skull base, peripheral, and each its own separate entity); and (3) the complexity and multidisciplinary nature of the management approaches, entailing differences in definitions and documentation processes and methodology.

Nevertheless, our group encompassed a wide range of expertise and valuable accumulated experiences. Both of these strengths were essential in overcoming the challenges and securing a successful endeavor. Furthermore, the perceived usefulness and relevance of the database rank high among intended users from various specialties and levels, thereby affording us strong and crucial acceptance and support necessary to overcome future challenges. Although the database represents an efficient and effective approach to handling the data management needs of a sizable multispecialty treatment center, its design and programming methodology can readily be adapted to other healthcare settings.

Single center databases such as the one described in this manuscript are invaluable in terms of the breadth and depth

TABLE 3 | Select case series publications from the neurosurgery oncology database, underscoring the opportunity to investigate the impact of novel surgical techniques and novel variables (e.g., objective measure of extent of resection, perilesional resection) on varied neurosurgical outcomes in large cohorts of patients with nervous system tumors.

References	Focus
Lacroix et al. (2)	Impact of extent of resection on the survival of patients with glioblastoma multiforme
Suki et al. (6)	Risk of leptomeningeal disease after resection or stereotactic radiosurgery for solid tumor metastasis to the posterior fossa
Suki et al. (7)	Risk of leptomeningeal dissemination of cancer after surgery or stereotactic radiosurgery for a single supratentorial solid tumor metastasis
Patel et al. (8)	Factors influencing risk of local recurrence after resection of a single brain metastasis
Marko et al. (3)	Impact of extent of resection on the survival of patients with glioblastoma mutiforme: Personalized survival modeling
Li et al. (4)	Influence of maximum safe resection of glioblastoma on survival
Al-Holou et al. (5)	Effect of perilesional resection of glioblastoma on neurosurgical outcomes
Noll et al. (9)	Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection
Tatsui et al. (10)	Utilization of laser interstitial thermotherapy guided by real-time thermal MRI as an alternative to separation surgery in the management of spinal metastasis.
Chamoun et al. (11)	Surgical management of skull base metastases
Raza et al. (12)	Non-melanoma cutaneous cancers involving the skull base: outcomes of aggressive multimodal management.

of information they provide and the research opportunities they present. They are crucial in providing well-annotated and consistently defined and coded data. They have a critical role to play in advancing knowledge on the topics of nervous system tumors and neurosurgical oncology and should be promoted where feasible and sustainable. That said, these databases can be hard and costly to develop and maintain (an element often underestimated during the planning phases), though the cost varies widely depending on factors such as the general infrastructure in place at the healthcare facility, the medical record system in use, the patient load, the database scope, and the caliber of the data management staff involved, to mention a few. These databases may also be limited by potential referral biases and generalization issues. National databases and registries are another valuable source of information and have allowed for valuable scientific studies. In the US, the Central Brain Tumor Registry of the United States (CBTRUS); the Surveillance, Epidemiology, and End Results (SEER); and the National Cancer Data Base (NCDB) are among the major centralized databases for brain tumor information. Each has its unique attributes, as well as its limitations: The CBTRUS includes primary tumor incidence but lacks patient follow-up data. The SEER database has incidence and follow-up data, but only on malignant brain tumors. The NCDB is the largest non-population-based US database, which identifies all newly diagnosed primary brain tumors, both benign and malignant, and has extensive patient treatment and outcome data, but because its data primarily come from hospitals accredited by the American College of Surgeons (and few unaccredited hospitals), this does not allow for tumor incidence rate estimation. None of these three public databases contain reliable or complete information on infrequently coded surgical details such as piecemeal vs. en bloc resection, dural entry and other similar variables, or outcomes such as objective postoperative tumor volume and extent of resection. In this era of big data and with the technologic advances at hand, combining data from multiple sources, single center databases, as well as national registries and databases, administrative datasets, and others, allows for a more powerful and wide-encompassing analysis of a wide array of data at every level. But an extensive discussion of this is outside the scope of this manuscript.

FUTURE DIRECTIONS

With the advent and widespread use of the EMR, the growing wealth of electronic data encompassing all aspects of humanity, and staggering advances in technology and artificial intelligence making their way at an unprecedented and previously unimaginable pace and scope, we are pressed to pay a close look at where we are and how we should proceed in this new era. For example: (1) Wider utilization of data from various sources, such as patient-reported outcomes, the sequencing and "omics" data which have revolutionized the understanding of nervous system tumors and become essential in any research endeavor, and other data not currently in the database, and (2) linking the database to the institutional biobank will be essential to a better understanding of all relevant aspects at play. (3) Wider adaptation of available technology in an appropriate fashion to replace manual labor and connect various sources of data will decrease cost and increase efficiency. Steps that will add those features to the current ones are currently underway.

AUTHOR CONTRIBUTIONS

The concept of the Neurosurgical Oncology Database was originated by RS and DS. The original manuscript was written by DS, with additions to the manuscript and edits provided by both RS and DW.

FUNDING

This work was supported by Department of Neurosurgery funds, by two database grants from The University of Texas MD Anderson Cancer Center, and by gifts from philanthropic donors, especially the Anne C. Brooks and Anthony D. Bullock III Distinguished Chair in Neurosurgery endowment fund awarded to RS.

REFERENCES

1. Lang FF, Wildrick DM, Demonte F, Sawaya R. Neurosurgical oncology at The University of Texas M. D. Anderson Cancer Center: its genesis and evolution. *Neurosurgery* (2005) 56:841–50. doi: 10.1227/01.NEU.0000156488.39986.A5
2. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg.* (2001) 95:190–8. doi: 10.3171/jns.2001.95.2.0190
3. Marko NF, Weil RJ, Schroeder JL, Lang FF, Suki D, Sawaya RE. Extent of resection of glioblastoma revisited: personalized survival modeling facilitates more accurate survival prediction and supports a maximum-safe-resection approach to surgery. *J Clin Oncol.* (2014) 32:774–82. doi: 10.1200/JCO.2013.51.8886
4. Li YM, Suki D, Hess K, Sawaya R. The influence of maximum safe resection of glioblastoma on survival in 1229 patients: Can we do better than gross-total resection? *J Neurosurg.* (2016) 124:977–88. doi: 10.3171/2015.5.JNS142087
5. Al-Holou W, Hodges TR, Everson R, Freeman J, Zhou S, Suki D, et al. Perilesional resection of glioblastoma is independently associated with improved outcomes. *Neurosurgery* (in press).
6. Suki D, Abouassi H, Patel AJ, Sawaya R, Weinberg JS, Groves MD. Comparative risk of leptomeningeal disease after resection or stereotactic radiosurgery for solid tumor metastasis to the posterior fossa. *J Neurosurg.* (2008) 108:248–57. doi: 10.3171/JNS/2008/108/2/0248
7. Suki D, Hatiboglu MA, Patel AJ, Weinberg JS, Groves MD, Mahajan A, et al. Comparative risk of leptomeningeal dissemination of cancer after surgery or stereotactic radiosurgery for a single supratentorial solid tumor metastasis. *Neurosurgery* (2009) 64:664–74. doi: 10.1227/01.NEU.0000341535.53720.3E
8. Patel AJ, Suki D, Hatiboglu MA, Abouassi H, Shi W, Wildrick DM, et al. Factors influencing the risk of local recurrence after resection of a single brain metastasis. *J Neurosurg.* (2010) 113:181–9. doi: 10.3171/2009.11.JNS09659
9. Noll KR, Sullaway C, Ziu M, Weinberg JS, Wefel JS. Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. *Neuro Oncol.* (2015) 17:580–7. doi: 10.1093/neuonc/nou233
10. Tatsui CE, Stafford RJ, Li J, Sellin JN, Amini B, Rao G, et al. Utilization of laser interstitial thermotherapy guided by real-time thermal MRI as an alternative to separation surgery in the management of spinal metastasis. *J Neurosurg Spine* (2015) 23:400–11. doi: 10.3171/2015.2.SPINE141185
11. Chamoun RB, Suki D, Demonte F. Surgical management of skull base metastases. *Neurosurgery* (2011) 70:802–9. doi: 10.1227/NEU.0b013e318236a700
12. Raza SM, Ramakrishna R, Weber RS, Kupferman ME, Gidley PW, Hanna EY, et al. Nonmelanoma cutaneous cancers involving the skull base: outcomes of aggressive multimodal management. *J Neurosurg.* (2015) 123:781–8. doi: 10.3171/2014.10.JNS141037
13. Fisher LD, Gillespie MJ, Jones M, McBride R. Design of clinical database management systems and associated software to facilitate medical statistical research. *Crit Rev Med Inform.* (1988) 1:323–31.
14. Dolin RH. Outcome analysis: considerations for an electronic health record. *MD Comput.* (1997) 14:50–6.
15. Hasan M, Meara RJ, Bhowmick BK. The quality of diagnostic coding in cerebrovascular disease. *Int J Qual Health Care* (1995) 7:407–10. doi: 10.1093/intqhc/7.4.407
16. Majoor JW, Ibrahim JE, Cicuttini FM, Boyce NW, McNeil JJ. The extraction of quality-of-care clinical indicators from State health department administrative databases. *Med J Aust.* (1999) 170:420–4.
17. Wyatt J. Acquisition and use of clinical data for audit and research. *J Eval Clin Pract.* (1995) 1:15–27. doi: 10.1111/j.1365-2753.1995.tb00004.x
18. Stoodley MA, Foroohar M, Macdonald RL, Weir BK. Multimedia computer database for neurosurgery. *Neurosurgery* (2000) 47:178–86. Discussion 86–8.
19. Kindler H, Densow D, Baranov AE, Fliedner TM, Peter RU. A multimedia database for dermatology. *Stud Health Technol Inform.* (1998) 52(Pt 1):70–4.
20. Testa MA, Simonson DC. The design and structure of clinical research information systems. Implications for data retrieval and statistical analyses. *J Med Syst.* (1985) 9:109–19. doi: 10.1007/BF00996196
21. Perrino AC Jr, Luther MA, Phillips DB, Levin FL. A multimedia perioperative record keeper for clinical research. *J Clin Monit.* (1996) 12:251–9. doi: 10.1007/BF00857647
22. Lowe HJ. Multimedia electronic medical record systems. *Acad Med.* (1999) 74:146–52. doi: 10.1097/00001888-199902000-00014
23. Stoodley MA, Sikorski JM. OASYS: a computerized auditing system for orthopaedic surgery. *Int J Biomed Comput.* (1991) 29:119–31. doi: 10.1016/0020-7101(91)90003-W

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 30 January 2019
doi: 10.3389/fneur.2019.00040

Quality of Life in Brain Cancer: Clinical Validation of the Mexican-Spanish Version of the EORTC QLQ-BN20 Questionnaire

Bernardo Cacho-Díaz[1], *Nydia A. Lorenzana-Mendoza*[1] *and Luis F. Oñate-Ocaña*[2]*

[1] *Unidad de Neurociencias, Instituto Nacional de Cancerología, Mexico City, Mexico,* [2] *Subdirección de Investigación Clínica, Instituto Nacional de Cancerología, Mexico City, Mexico*

Background: Overall survival (OS) of patients with Brain Cancer (BC) is slowly increasing. The disease itself and its treatments deeply impact patient Health-related quality of life (HRQL). Therefore, valid and reliable instruments are needed. In this study, the Mexican-Spanish version of the QLQ-BN20 instrument is psychometrically and clinically validated.

Methods: Patients with brain cancer (BC) (primary or metastatic) evaluated at a tertiary cancer center, were invited to respond to the questionnaire, as well as the core-module QLQ-C30. Tests to demonstrate the instrument's internal consistency, the association of HRQL scales with clinical variables and OS were investigated.

Results: One hundred and nineteen patients were included in this cohort: 77 women and 42 men (mean age, 46.2 years). Patients answered both instruments in < 30 min. Good convergent [all correlation coefficients (CC) > 0.37] and discriminant validity was observed and was associated with significant overlap (CC 0.007–0.68). All four multi-item scales of QLQ-BN20 also demonstrated good reliability (Cronbach $\alpha > 0.7$). Several scales of the QLQ-BN20 were significantly associated with performance status and a modified Recursive Partition Analysis. Of the possible scale correlations, 40 of 161 (24.8%) scales in both instruments, were significantly (directly or inversely) correlated. Visual disorders, Motor dysfunction, Seizures and Weakness of the legs presented association with OS ($p < 0.05$).

Conclusion: The Mexican-Spanish version of the BN20 instrument is valid and reliable and can be used in clinical trials in patients with BC. Some HRQL scales were associated with OS and could therefore be incorporated in future studies of prognostic models.

Keywords: health-related quality of life, brain neoplasms, surveys and questionnaires, validation study, prognostic factors

OPEN ACCESS

Edited by:
Sujit Prabhu,
University of Texas MD Anderson Cancer Center, United States

Reviewed by:
Carsten Friedrich,
University of Rostock, Germany
Yoshua Esquenazi,
University of Texas Health Science Center at Houston, United States

****Correspondence:***
Luis F. Oñate-Ocaña
lfonate@gmail.com

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *28 July 2018*
Accepted: *11 January 2019*
Published: *30 January 2019*

Citation:
Cacho-Díaz B, Lorenzana-Mendoza NA and Oñate-Ocaña LF (2019) Quality of Life in Brain Cancer: Clinical Validation of the Mexican-Spanish Version of the EORTC QLQ-BN20 Questionnaire. Front. Neurol. 10:40. doi: 10.3389/fneur.2019.00040

INTRODUCTION

Brain cancer (BC) constitutes a heterogeneous group of diseases, accounting for 1–2% of all primary cancers in adults (1). These neoplasms (primary or secondary) are characterized by severe and complex symptoms, usually associated with a poor prognosis (1, 2). There is no definite cure for most patients. Therefore, a reasonable primary aim of treatment is to extend survival with effective symptom relief (2, 3).

Efforts with emerging new therapeutic strategies are mainly focused on prolonging survival (4). However, BC is associated to symptoms and complications that negatively impact patients' Health-related quality of life (HRQL). BC may directly provoke disabling symptoms including headache, sensory-motor dysfunction, seizures, mood disorders, personality changes, and cognitive dysfunction (5). Consequently, the clinical benefits of treatment should be evaluated not only according to the classical outcome measures (objective response or survival) but also by ensuring HRQL improvement, and must be weighed against treatment side-effects (5–7).

The clinical consequences of disease can be identified by physical examination and evaluated with neurological and neuropsychological tests. Patients' opinions on their own HRQL differ substantially from the opinions of proxies or health-care personnel. Hence, two instruments have been developed to measure HRQL in the specific case of BC: the FACT-Br, Peds-FACT-BrS, and the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) BN20 (8–11). The MDASI-BT is a symptom inventory designed to measure symptoms and not for HRQL assessment (12).

The QLQ-BN20 measures focus more specifically on function and symptoms, while the FACT-Br assessments cover more psychosocial aspects of the disease. Therefore, the QLQ-BN20 is superior when assessing the treatment outcome and may provide more information in trials that focus on functional endpoints, whereas FACT-Br could be more useful in patients with positive functional capacity but psychosocial concerns, although no instrument is superior to the other (13). Both must be considered as complementary.

The QLQ-BN20 instrument comprises 11 symptom scales that cover the more common complains in patients with BC and it was designed to be used with the core questionnaire QLQ-C30. This core instrument comprises five functional scales, and nine symptom scales plus a global HRQL scale. Both have been translated and validated into several languages and have been extensively used in the medical literature. However, available information on the subject published in Latin-American countries is scarce. The aim of this study was to validate the Mexican-Spanish version of the QLQ-C30 and QLQ-BN20 questionnaires in patients with BC.

MATERIALS AND METHODS

Patients

Patients treated at the Neuro-oncology Unit of the *Instituto Nacional de Cancerología* (INCan) in Mexico City from February 2005 to October 2014, were invited to participate in this study and respond the questionnaires. Inclusion criteria were: Literate individuals of any gender or age, who had a clinical diagnosis of primary or secondary BC. The diagnosis of BC was established by computed tomography scan and/or magnetic resonance imaging. The clinical history was obtained, as well as blood cytology and chemistry, tumor markers, and chest-X ray. The Karnofsky and ECOG status performance scales were assessed. The Institutional Review Board and Ethics committees approved the study protocol (registration codes 014/007/CCI and CEI 865/14). Patients signed the informed consent form in which the purpose of the study and a safety protection policy were detailed and accompanied the questionnaires.

Instruments

The EORTC QLQ-C30 consists of 30 items, which are organized into five functional scales (physical, role, emotional, cognitive, and social functioning); three symptom scales (fatigue, nausea and vomiting, and pain); one global health status scale; and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The QLQ-BN20 includes 20 items, which are organized into four multi-item scales (future uncertainty, visual disorders, motor dysfunction, and communication deficit) and seven single items (headache, seizures, drowsiness, hair loss, itchy skin, weakness of the legs, and bladder control) (11). The validated Mexican-Spanish version of the QLQ-C30 was used (14). The adapted Mexican-Spanish version of the QLQ-BN20 was pilot-tested in 10 patients with BC to identify the adequacy of the translation. All patients responded the questionnaire without assistance, stated that the questions were clear and easy to understand and complete. Both questionnaires were used with permission of the EORTC Quality of Life Group, and they supervised the entire process.

Statistical Analysis

Scale scores were calculated by linear transformation of raw scores into a 0–100 score, with 100 representing best global health, best functional status, or worst symptoms, as described by EORTC (15), and the summary score was also calculated (16). Correlation assessment was obtained with the Spearman Correlation coefficient (CC). Convergent validity was determined calculating the CC between each item and items belonging to their own scale, and the success criteria was CC >0.3. Divergent validity was evaluated calculating the CC between each item and items belonging to other scales, and the success criteria was CC < 0.3. Cronbach's α was used to measure multi-item correlation, and the success criteria was ≥ 0.7. In addition, clinical validity was evaluated by the extent to which scores were able to discriminate among groups of patients who differed in terms of their clinical status. Patients were classified according to treatment intent, the number of metastases (single, multiple or carcinomatosis) and according to Recursive Partitioning Analysis (RPA) (17). Due to the heterogeneity of primary BC and the limited availability of specific prognostic scores for each of the different types of BC, for the purpose of the study, patients with primary BC were classified using the same RPA approach, as if it were metastatic, considering the absence of neoplasm in sites other than the CNS, age (>65 years) and a Karnofsky score >70 (18, 19).

The Kruskal–Wallis test was used to analyze differences between groups. Scale scores were categorized by terciles. The correlation between the different QLQ-C30 and QLQ-BR20 scales was explored to identify differences and clinical overlapping. Overall survival (OS) was considered as the period of time from diagnosis of BC metastases or primary BC to death. The association of HRQL and OS was evaluated using

the Kaplan-Meier method, and differences were tested with the Log rank method. Hazard ratios (HR) were calculated using the Cox model. Sample-size calculation was based on the proposal by Tabachnik and Fidell (20); a minimal ratio of 5 patients per item was required (20 × 5), i.e., a sample size of 100 patients. Any probability value of 0.05 or less was considered significant, and two-tailed statistics were applied in all cases. The SPSS for Mac version 23 software was used for computations (IBM, Inc., Armonk, NY, USA).

RESULTS

Patients

One hundred twenty-seven (127) patients were invited to participate, but eight did not consent. Therefore, 119 patients with BC were included in the study. There were 77 women (64.7%) and 42 men (35.3%), with a mean age of 46.18 years (SD, 15.8; range 17–80). Brain metastases were found in 76 patients (63.9%); among these, the most common primary cancer sites were: 25 breast (32.9%), 18 lung (23.7%), four ovary (5.3%), four non-Hodgkin lymphoma, three Hodgkin's lymphoma (3.9%), three cervix-uteri, three renal, three testicle, two melanoma (2.6%), two endometrial, one acute myeloid leukemia (1.3%), one gastric, one prostate, one metastases to spinal cord from a treated medulloblastoma, one meningeal metastases from a treated medulloblastoma, one rectum, one nasopharynx, one adenoid cystic and one basocellular skin cancer. Primary BC was found in 43 patients (36.1%) and the most frequent diagnoses were: 12 meningioma (27.9%), six astrocytoma (13.9%), five CNS primary germinal neoplasms, four primary CNS lymphoma, four medulloblastoma (9.3%), four high-grade glioma, three pituitary macroadenoma, two oligoastrocytoma, one craniopharyngioma, one ependymoma, one gliosarcoma, one hemangiopericytoma, one oligodendroglioma, one meningeal sarcoma and one

TABLE 1 | Descriptive statistics of EORTC QLQ-C30 and QLQ-BN20 functional and symptom scales in patients with (primary or secondary) brain cancer ($n = 119$).

	Mean (SD)	Median	Floor (%)	Ceiling (%)
QLQ-C30				
Global health/QoL	66.96 (28.1)	66.67	0 (1.6)	100 (18.3)
Functional scales				
Physical	72.67 (27)	80	0 (1.6)	100 (16.7)
Role	73.61 (32.9)	83.33	0 (8.7)	100 (43.7)
Emotional	72.62 (22.5)	75	0 (0.8)	100 (15.9)
Cognitive	75.56 (19.8)	83.33	16.67 (2.4)	100 (94.4)
Social	73.52 (29.7)	83.33	0 (5.6)	100 (37.3)
Symptom scales				
Fatigue	32.24 (23.9)	33.33	0 (11.1)	100 (1.6)
Nausea and vomiting	12.93 (20.9)	0	0 (60.3)	100 (0.8)
Pain	23.11 (24.8)	16.67	0 (34.9)	100 (1.6)
Dyspnea	26.89 (30.5)	0	0 (65.9)	100 (2.4)
Insomnia	26.89 (30.5)	33.33	0 (43.7)	100 (6.3)
Appetite loss	20.73 (29.7)	0	0 (56.3)	100 (5.6)
Constipation	27.45 (30.6)	33.33	0 (43.7)	100 (5.6)
Diarrhea	11.76 (24.8)	0	0 (72.2)	100 (4)
Financial difficulties	47.06 (39.6)	33.33	0 (28.6)	100 (26.2)
Summary score	76.9 (17.04)	81.15	26.11 (0.8)	100 (1.7)
QLQ-BN20				
Symptom scales				
Future uncertainty	28.36 (25.5)	25	0 (17.5)	100 (1.6)
Visual disorders	24.09 (26.1)	22.22	0 (33.3)	100 (2.4)
Motor dysfunction	26.8 (26)	22.22	0 (27)	100 (0.8)
Communication deficit	21.57 (25.2)	11.11	0 (38.9)	100 (0.8)
Headache	25.58 (29.3)	33.33	0 (43.7)	100 (5.6)
Seizures	5.88 (19.7)	0	0 (84.9)	100 (2.4)
Drowsiness	33.05 (31.4)	33.33	0 (32.5)	100 (9.5)
Hair loss	20.45 (30.41)	0	0 (57.9)	100 (6.3)
Itchy skin	18.77 (27.3)	0	0 (57.9)	100 (3.2)
Weakness of legs	28.01 (30.1)	33.33	0 (40.5)	100 (6.3)
Bladder control	16.25 (27.7)	0	0 (64.3)	100 (4.8)

n, number of patients; SD, standard deviation; %, is the percentage of patients with floor or ceiling value.

TABLE 2 | Convergent and discriminant validity of scales of the EORTC QLQ-C30 and QLQ-BN20 instruments in patients with (primary or secondary) brain cancer ($n = 119$).

	Item own-scale correlations[a]	Success (%)[b]	Item other-scale correlations[a]	Success (%)[c]	Own-scale multivariate correlations[d]
QLQ-C30					
Global health/QoL	0.787	100	0.06-0.504	51.8	0.888
Functional scales					
Physical	0.416–0.658	100	0.053–0.678	47.2	0.875
Role	0.767	100	0.096–0.678	35.7	0.898
Emotional	0.347–0.569	100	0.053–0.389	69.2	0.787
Cognitive	0.19	0	0.02–0.407	66.1	0.289
Social	0.68	100	0.165–0.63	32.1	0.855
Symptom scales					
Fatigue	0.348–0.561	100	0.061–0.586	27.2	0.703
Nausea and vomiting	0.671	100	0.024–0.546	66.1	0.795
Pain	0.498	100	0.08–0.525	41.1	0.681
Dyspnea	–	–	0.007–0.46	51.7	–
Insomnia	–	–	0.1–0.399	62.1	–
Appetite loss	–	–	0.202–0.504	6.9	–
Constipation	–	–	0.06–0.407	79.3	–
Diarrhea	–	–	0.007–0.373	96.6	–
Financial difficulties	–	–	0.122–0.468	51.7	–
QLQ-BN20					
Symptom scales					
Future uncertainty	0.37–0.593	100	0.027–0.633	32.8	0.777
Visual disorders	0.51–0.657	100	0.046–0.496	25.5	0.801
Motor dysfunction	0.556–0.601	100	0.087–0.633	17.6	0.816
Communication deficit	0.609–0.795	100	0.118–0.548	37.3	0.865
Headache	–	–	0.05–0.412	47.4	–
Seizures	–	–	0.046–0.376	94.7	–
Drowsiness	–	–	0.172–0.498	26.3	–
Itchy skin	–	–	0.027–0.502	84.2	–
Hair loss	–	–	0.046–0.502	89.5	–
Weakness of legs	–	–	0.115–0.683	36.8	–
Bladder control	–	–	0.103–0.449	26.3	–

n, number of patients; [a]Spearman correlation coefficients; [b]success criteria for item own-scale correlations (>0.3); [c]success criteria for item other-scale correlations (<0.3); [d]Cronbach α values. All correlation coefficient values are absolute values.

pinealoblastoma. Among patients with primary BC, one developed breast cancer as a second primary, with brain metastases and meningioma; one patient had a retroauricular mucoepidermoid carcinoma with a metachronous astrocytoma and meningioma; in two patients with primary medulloblastoma, one had meningeal metastases and the other developed spinal cord involvement.

Six patients had a 100% KPS, 39 90%, 41 80%, nine 70% and 27 60% or below KPS. All patients answered both questionnaires in <30 min, and there were 6 missing values (0.1%) in the 50 items of both instruments, including 5,950 possible responses.

Reliability and Internal Validity

Descriptive statistics of the HRQL data are presented in **Table 1**. Most scales of both instruments have a zero floor and a 100 ceiling values, whereby mean scores mainly represent high-functional and low-symptom values. The summary of multi-trait scaling analyses is depicted in **Table 2**; good convergent and discriminant validity is observed for most scales. All multi-item scales presented good own-scale correlations. Divergent validity revealed low correlation for other-scale items but also frequent overlapping. The Cognitive and Pain scales of the QLQ-C30 did not show a Cronbach's α coefficient >0.70, but all four multi-item scales of the QLQ-BN20 did.

Clinical Validity

Many scales of both instruments were significantly associated with clinically relevant factors. **Table 3** describes the association of three categories of ECOG with scale scores of both instruments; nine of Sixteen (including summary score), and four of Eleven scales of the QLQ-C30 and QLQ-BN20, respectively,

TABLE 3 | Mean scale scores of QLQ-C30 and QLQ-BN20 depending on the Eastern Cooperative Oncology Group (ECOG) performance status grading in patients with (primary or secondary) brain cancer ($n = 119$).

	ECOG 0 ($n = 14$)	ECOG 1 ($n = 67$)	ECOG ≥2 ($n = 38$)	*p*
QLQ-C30				
Global health/QoL	75 (27.9)	66.8 (28)	63.6 (28.8)	0.333
Functional scales				
Physical	91.4 (10.3)	81 (17.8)	51.1 (31.4)	**<0.0001**
Role	95.2 (13.7)	81.7 (24.7)	51.3 (38.4)	**<0.0001**
Emotional	76.2 (16.6)	75.7 (22.1)	65.8 (23.9)	0.089
Cognitive	82.1 (13.8)	78.9 (17.7)	67.1 (22.8)	**0.018**
Social	95.2 (12.1)	78.9 (24.5)	57.9 (34.8)	**<0.0001**
Symptom scales				
Fatigue	19.8 (15.8)	29.4 (22.4)	44.7 (24.7)	**0.001**
Nausea and vomiting	5.95 (12.4)	11.5 (19.8)	18 (24.3)	0.223
Pain	17.9 (17.9)	16.4 (20.6)	36.8 (28.5)	**<0.0001**
Dyspnea	2.38 (8.9)	11.9 (20.7)	16.7 (25.4)	0.08
Insomnia	21.4 (24.8)	25.4 (31.3)	31.6 (30.9)	0.43
Appetite loss	9.52 (20.4)	17.4 (26.8)	30.7 (35)	**0.035**
Constipation	26.2 (26.7)	22.4 (28.1)	36.8 (34.5)	0.092
Diarrhea	9.5 (27.5)	7.46 (19.1)	20.2 (30.5)	**0.02**
Financial difficulties	38.1 (34.2)	41.8 (39.5)	59.6 (39.6)	0.065
Summary score	86.7 (10.5)	81.1 (14)	65.9 (18.5)	**<0.0001**
QLQ-BN20				
Symptom scales				
Future uncertainty	16.1 (12.9)	27.9 (25.3)	33.6 (28.2)	0.179
Visual disorders	5.56 (8.4)	22.4 (24.6)	33.9 (28.8)	**0.001**
Motor dysfunction	10.3 (14.1)	22.6 (25.1)	40.4 (25.2)	**<0.0001**
Communication deficit	22.2 (20)	17.4 (23)	28.7 (29.4)	0.105
Headache	14.3 (17.1)	24.5 (28.7)	31.6 (32.8)	0.238
Seizures	0	3.48 (15.5)	12.3 (27.3)	**0.021**
Drowsiness	21.4 (24.8)	30.8 (31.4)	41.2 (32.4)	0.08
Itchy skin	19 (25.2)	18.4 (29.7)	19.3 (24.1)	0.744
Hair loss	21.4 (28.1)	21.4 (33.2)	18.4 (26.5)	0.866
Weakness of legs	7.14 (14.2)	22.9 (29.7)	44.7 (27.2)	**<0.0001**
Bladder control	7.1 (14.2)	15.9 (27.4)	20.2 (31.5)	0.448

n, number of patients; numbers represent means (in parentheses are standard deviation values); p, probability values obtained by Kruskal-Wallis test. Bold values correspond to statistical significant values.

showed significant associations. **Table 4** shows the association of RPA categories (for metastatic and primary BC) with the mean scale scores of both instruments; three of 16 (including summary score), and three of 11 scales of the QLQ-C30 and QLQ-BN20, respectively, did not yield significant associations.

Correlations Between Instruments

Forty-two of 176 (23.8%) possible (16×11) bivariate correlations between QLQ-C30 and QLQ-BN20 scales were significant ($p < 0.05$). As expected, correlation between functional and symptom scales were usually negative. The correlation matrix is shown in the **Table 5**.

Survival

Median follow-up of the cohort was 4.49 years (SD 3.38) (range 0.21–13.8). During this period, 79 patients (66.4%) died from progressive or recurrent disease. Median OS was 3.98 years (95% CI 2.99–4.97). The bivariate association of HRQL and OS were explored; the physical, role, social, fatigue, nausea/vomiting, pain, dyspnea, appetite loss, financial difficulties scales, and the summary score were associated with OS. Of the QLQ-BN20 scales, Visual disorders (HR 1.01 [95%CI 1.002–1.018]), Motor dysfunction (HR 1.011 [95% CI 1.003–1.019]), Seizures (HR 1.013 [95% CI 1.004–1.023]), and Weakness of the legs (HR 1.013 [95% CI 1.007–1.02]) were associated with OS. The Kaplan-Meier OS curves depending on Visual disorders, Motor dysfunction, Seizures and Weakness of the legs scales are depicted in **Figure 1**.

DISCUSSION

In this study, the Mexican-Spanish version of the QLQ-BN20 instrument along with its core instrument QLQ-C30 has been

TABLE 4 | Mean scale scores of QLQ-C30 and QLQ-BN20 depending on the RPA class in patients with (primary or secondary) brain cancer ($n = 119$).

	Class I ($n = 34$)	Class II ($n = 58$)	Class III ($n = 27$)	*p*
QLQ-C30				
Global health/QoL	74.8 (30.1)	64.5 (26.6)	61.4 (27.8)	**0.044**
Functional scales				
Physical	89.3 (13.3)	77.5 (19.6)	41.2 (28.4)	**<0.0001**
Role	89.6 (21)	78.7 (25.7)	42.6 (38.8)	**<0.0001**
Emotional	77.5 (19.8)	75.9 (20.9)	59.6 (24.6)	**0.005**
Cognitive	81.1 (17.3)	79 (16.4)	61.1 (23.1)	**0.001**
Social	88.2 (19.9)	77.3 (24.1)	49.4 (36.2)	**<0.0001**
Symptom scales				
Fatigue	20.6 (23.6)	31.4 (18.3)	52.7 (23.4)	**<0.0001**
Nausea and vomiting	6.9 (21)	13.3 (18.2)	19.8 (24.5)	**0.01**
Pain	13.7 (19)	19.3 (20.4)	43.2 (29.3)	**<0.0001**
Dyspnea	6.9 (13.7)	12.6 (21.5)	18.5 (28.2)	0.19
Insomnia	18.6 (27.5)	28.2 (29.8)	34.6 (33.9)	0.104
Appetite loss	7.8 (18.5)	20.7 (27.8)	37 (37.4)	**0.001**
Constipation	14.7 (22)	26.4 (27.8)	45.7 (37.2)	**0.002**
Diarrhea	9.8 (25.3)	9.2 (17.4)	19.8 (34.9)	0.45
Financial difficulties	33.3 (37.6)	43.7 (38.1)	71.6 (35.5)	**0.001**
Summary score	86.7 (12.1)	79 (13.4)	60.2 (17.7)	**<0.0001**
QLQ-BN20				
Symptom scales				
Future uncertainty	21.6 (23.6)	25.7 (22.9)	42.3 (28.8)	**0.009**
Visual disorders	15.6 (20.1)	21.5 (24.2)	40.3 (30.1)	**0.002**
Motor dysfunction	11.1 (18.8)	26.8 (24.2)	46.5 (24.7)	**<0.0001**
Communication deficit	17 (21.6)	18 (22.3)	35 (31.1)	**0.025**
Headache	15 (21.9)	24.1 (27.8)	42 (34.1)	**0.003**
Seizures	2.9 (12.6)	3.4 (14.9)	14.8 (31.1)	**0.05**
Drowsiness	23.5 (31.3)	32.2 (29.3)	46.9 (32.4)	**0.007**
Itchy skin	16.7 (27.5)	19.5 (27.9)	19.8 (26.6)	0.824
Hair loss	16.7 (28.7)	23 (32)	19.8 (29.6)	0.584
Weakness of legs	9.8 (21)	29.3 (28.7)	48.1 (29.7)	**<0.0001**
Bladder control	10.8 (25.6)	16.1 (24.4)	23.5 (35.6)	0.226

n, number of patients; numbers represent means (in parentheses are standard deviation values); p, probability values obtained by Kruskal-Wallis test. Bold values correspond to statistical significant values.

psychometrically and clinically validated as we found them reliable and valid.

The main traditional outcome measures in oncology research are the frequency of objective responses after therapy, progression-free survival, or OS. However, many brain neoplasms are incurable, and maintenance or improvement of patients' HRQL are, at least, as important as increases in the progression-free survival or OS. On the other hand, a patient-centered approach complementing the decision-making process in Neuro-Oncology is feasible and desirable. Most patients with BC can participate actively in the decisions on their management options if relevant information is presented in a clear and reasonable manner. When informed, most patients are able to identify concepts of HRQL, the capability to maintain functional independence and the influence of treatment on survival as the most relevant factors in determining their decision (21). As physicians, we must be prepared to facilitate this process.

In a 20-year period, only five Randomized clinical trials (RCT) included HRQL evaluations as primary or secondary outcome measurements. However, the quality of reporting HRQL data has not considerably improved (22). In these contexts, the availability of valid instruments to accurately measure HRQL is mandatory. In general terms, the psychometric characteristics of our study were similar to the original report and other validation reports (23, 24).

The original QLQ-BN20 instrument was developed in multilingual and multicultural settings in Europe (including European-Spanish) and has proven to be valid and reliable (11, 25). Our study is the first validation protocol of the instrument in the Mexican-Spanish language, performed in a Cancer Center in Latin America. Similar psychometric findings

TABLE 5 | Correlation matrix of QLQ-C30 and QLQ-BN20 mean scale scores in patients with (primary or secondary) brain cancer ($n = 119$).

QLQ-BN20	FU	VD	MD	CD	HA	SZ	DW	IS	HL	WL	BC
QLQ-C30											
Global health/QoL	−0.474	−0.337	−0.549	−0.365	−0.272	−0.183	−0.46	**−0.074**	**−0.026**	−0.36	−0.214
FUNCTIONAL SCALES											
Physical	−0.516	−0.427	−0.69	−0.315	−0.202	−0.24	−0.394	**−0.054**	**−0.07**	−0.591	−0.192
Role	−0.492	−0.424	−0.704	−0.422	−0.187	−0.271	−0.331	**−0.058**	**−0.025**	−0.599	−0.173
Emotional	−0.51	−0.378	−0.373	−0.405	−0.459	**−0.170**	−0.465	−0.249	**−0.141**	−0.293	−0.285
Cognitive	−0.35	−0.366	−0.503	−0.506	−0.353	−0.183	−0.392	−0.211	**−0.039**	−0.354	−0.293
Social	−0.516	−0.377	−0.504	−0.314	−0.308	−0.191	−0.367	**−0.054**	**−0.094**	−0.486	**−0.169**
SYMPTOM SCALES											
Fatigue	0.619	0.475	0.661	0.388	0.407	0.248	0.532	**0.166**	**0.076**	0.541	0.257
Nausea and vomiting	0.415	0.387	0.427	0.289	0.223	0.211	0.386	**0.122**	0.225	0.386	**0.148**
Pain	0.319	0.368	0.418	0.29	0.536	0.186	0.385	**0.07**	**0.012**	0.383	**0.149**
Dyspnea	0.454	0.431	0.366	0.352	0.292	0.315	0.412	0.232	0.256	0.241	0.178
Insomnia	0.35	0.183	0.381	0.25	0.278	**0.099**	0.349	**0.162**	**0.15**	**0.179**	**0.123**
Appetite loss	0.484	0.355	0.465	0.299	0.219	**0.174**	0.371	**0.033**	**0.121**	0.436	**0.021**
Constipation	0.272	0.195	0.344	0.209	0.335	0.252	0.287	**0.035**	**0.083**	0.227	0.285
Diarrhea	**0.086**	0.182	**0.117**	**0.114**	0.219	**0.004**	**0.115**	**0.029**	**−0.032**	0.199	0.23
Financial difficulties	0.436	0.337	0.477	0.298	0.217	**0.067**	0.255	**0.084**	**0.104**	0.32	0.217
Summary score	−0.589	−0.58	−0.7	−0.517	−0.424	−0.225	−0.575	**−0.164**	**−0.133**	−0.545	−0.337

n, number of patients; numbers represent means (in parentheses are standard deviation values); FU, future uncertainty; VD, visual disorders; MD, motor dysfunction; CD, communication deficit; HA, headache; SZ, seizures; DW, drowsiness; IS, itchy skin; HL, hair loss; WL, weakness of legs; BC, bladder control.
Non-significant correlations are shown in bold numbers ($p > 0.05$).

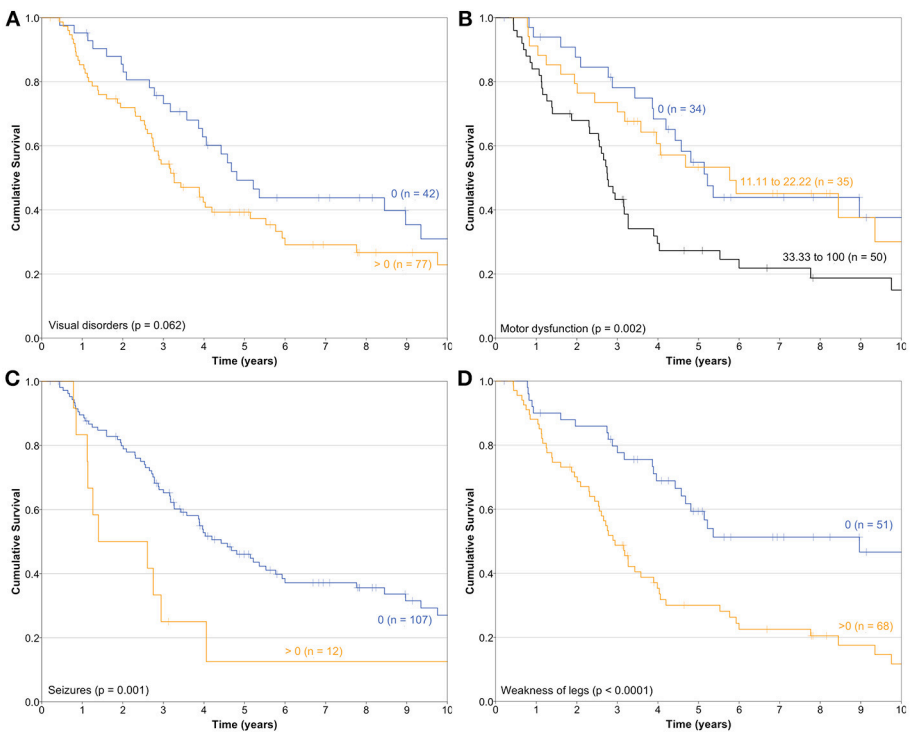


FIGURE 1 | Kaplan-Meier survival curves of the association of health-related quality of life and overall survival constructed depending on **(A)** Visual disorders, **(B)** Motor dysfunction, **(C)** Seizures, and **(D)** Weakness of legs scales of the QLQ-BN20 instrument ($n = 119$).

are described in other validation studies but the association of several HRQL scales and relevant clinical variables has not been previously reported (11, 23–26). In known-group comparisons, the association of the QLQ-BN20 instrument with the ECOG performance status scale, RPA and OS are described.

The main pitfalls of our study are that responsiveness to cancer treatment was not investigated as long as we have performed one HRQL evaluation for each patient, and our relatively small sample size ($n = 119$), when compared with the original report from the EORTC ($n = 891$) (11).

Floor and ceiling values are 0–100 in all scales except in the Cognitive scale of the QLQ-C30 (**Table 1**). In general terms, most patients report high functional and low symptom scales (**Table 1**), reflecting a population with a recent diagnosis and low disease burden. Convergent and divergent validity is adequate for both instruments, as shown in **Table 2**, and as similarly reported in the other four validation studies (11, 23–26). The reliability of the Cognitive scale of the QLQ-C30 is below 0.7 and this finding is similar to the Korean validation study (24), while the other three validation studies did not mention the values of the QLQ-C30 scales (11, 23, 25, 26). Low Cronbach α values in terms of Cognitive scale's reliability are frequent in the literature in patients with diverse types of cancer. Examples of this finding include the original EORTC report of the QLQ-C30 instrument (27), and the original Mexican-Spanish validation study of the QLQ-C30 instrument (14). All multi-item scales of the QLQ-BN20 presented fair Cronbach α values as in the other three validation reports (11, 23–26). Certain QLQ-BN20 mean scale scores revealed important associations with ECOG, RPA and OS (**Tables 3**, **4** and **Figure 1**). No comparison is possible because to our knowledge, these findings have not been previously reported.

Although, there is currently no available cure for advanced BC, survival rates have been increasing over the last few years, so this tool is useful in assessing the development of an effective treatment that improves HRQL (5). The QLQ-BN20 instrument has been cited in 42 publications in PubMed since 2009 and has been used in clinical trials to measure HRQL in BC patients undergoing chemotherapy (Ch) and/or radiotherapy (RT). A recent study compared two treatment outcomes in glioblastoma patients: one received RT alone, while the other group of patients was treated with RT plus adjuvant temozolomide; QLQ-C30 and QLQ-BN20 were used to assess the patients at follow-up and results showed similar HRQL in the two groups with minimal differences in the nausea/vomiting and constipation scales, which were worse in the Ch / RT group than in the RT only group. Nevertheless, the use of adjuvant temozolomide therapy further prolonged patient survival compared to the RT only group (28).

In clinical trials, statistically significant changes in HRQL can be observed by increasing the sample size or in the scenario of multiple comparisons (such as comparison of multiple HRQL scale scores). However, these changes may not be clinically relevant. The meaning of the minimal clinical important difference is pertinent in the design of clinical trials, when proposing an adequate sample size and in the correct interpretation of results. The minimal clinical important difference can be defined as the smallest difference in the mean score which is clinically important (as in between groups or paired comparison designs). In a recent study, a decrease of 6.1 units or 13.8 units was required to represent clinically relevant deterioration of the Seizures or Weakness of legs variables, respectively (29).

In another study of BC patients, 5.2 units change represented the minimal clinically important deterioration in the motor dysfunction scale. Similarly, 9.1 units change represented clinically important improvement in the communication deficit (30).

In general terms, the authors consider that any 10-unit change or difference in the mean score represents a clinically important difference.

Most patients do not report problems with the cognitive functioning scale. This problem may result from their sociocultural background. At the INCan hospital, we mainly treat patients with a low income, illiteracy, a low education level and poor working possibilities.

Distinguishing patients with glioma from those with meningioma was not tested in this study because of the great variability of histopathology diagnoses in the cohort. This is a validation study, so we did not test the impact of different treatments on HRQL. This question and others could be investigated in future research studies, including the usefulness of these instruments in revealing subtle differences associated to novel treatments in randomized clinical trials.

CONCLUSION

In conclusion, the Mexican-Spanish version of the QLQ-BN20 instrument is a valid and reliable test that can be used in clinical studies that include patients with primary or metastatic BC. Some HRQL items were associated with the OS and could be used as prognostic factors or might contribute to assemble prognostic models as aids in treatment trade-offs.

AUTHOR CONTRIBUTIONS

BC-D and LO-O conception and design of the study and analysis and interpretation of data and draft and revise the article. NL-M recruiting patients, acquisition of data, cleaning of the database. All authors have approved the final version to be submitted.

FUNDING

The INCan financially supported this study in its entirety.

ACKNOWLEDGMENTS

Many thanks to Professor Deborah Dion Aleman-Hoey for her kind help and English language editorial review.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* (2018) 68:7–30. doi: 10.3322/caac.21442
2. de Robles P, Fiest KM, Frolkis AD, Pringsheim T, Atta C, St Germaine-Smith C, et al. The worldwide incidence and prevalence of primary brain tumors: a systematic review and meta-analysis. *Neuro Oncol.* (2015) 17:776–83. doi: 10.1093/neuonc/nou283
3. Hayat MA. *Brain Tumors: Tumors of the Central Nervous System*. Vol. 3. New York, NY: Springer (2011).
4. Schiff D, Lee EQ, Nayak L, Norden AD, Reardon DA, Wen PY. Medical management of brain tumors and the sequelae of treatment. *Neuro Oncol.* (2014) 17:488–504. doi: 10.1093/neuonc/nou304.
5. Dirven L, Reijneveld JC, Taphoorn MJ. Health-related quality of life or quantity of life: a difficult trade-off in primary brain tumors? *Semin Oncol.* (2015) 41:541–52. doi: 10.1053/j.seminoncol.2014.06.002
6. Lin NU, Wefel JS, Lee EQ, Schiff D, van den Bent MJ, Soffietti R, et al. Challenges relating to solid tumor brain metastases in clinical trials, part 2: neurocognitive, neurological, and quality-of-life outcomes. A report from the RANO group. *Lancet Oncol.* (2013) 14:e407–16. doi: 10.1016/S1470-2045(13)70308-5
7. Bottomley A, Pe M, Sloan J, Basch E, Bonnetain F, Calvert M, et al. Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) consortium. Analyzing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards. *Lancet Oncol.* (2016) 17:e510–4. doi: 10.1016/S1470-2045(16)30510–1
8. Weitzner MA, Meyers CA, Gelke CK, Byrne KS, Cella DF, Levin VA. The functional assessment of cancer therapy (FACT) scale. Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. *Cancer* (1995) 75:1151–61.
9. Lai JS, Cella D, Tomita T, Bode RK, Newmark M, Goldman S. Developing a health-related quality of life instrument for childhood brain tumor survivors. *Child Nervous Syst.* (2007) 23:47–57. doi: 10.1007/s00381-006-0176-6
10. Osoba D, Aaronson NK, Muller M, Sneeuw K, Hsu MA, Yung WK, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Qual Life Res.* (1996) 5:139–50.
11. Taphoorn MJ, Claassens L, Aaronson NK, Coens C, Mauer M, Osoba D, et al. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. *Eur J Cancer* (2010) 46:1033–40. doi: 10.1016/j.ejca.2010.01.012
12. Armstrong TS, Mendoza T, Gring I, Coco C, Cohen MZ, Eriksen L, et al. Validation of the MD Anderson symptom inventory brain tumor module (MDASI-BT). *J Neurooncol.* (2006) 80:27–35. doi: 10.1007/s11060-006-9135-z
13. Chow R, Lao N, Popovic M, Chow E, Cella D, Beaumont J, et al. Comparison of the EORTC QLQ-BN20 and the FACT-Br quality of life questionnaires for patients with primary brain cancers: a literature review. *Support Care Cancer* (2014) 22:2593–8. doi: 10.1007/s00520-014-2352-7
14. Oñate-Ocana LF, Alcántara-Pilar A, Vilar-Compte D, García-Hubard G, Rojas-Castillo E, Alvarado-Aguilar S, et al. Validation of the Mexican Spanish version of the EORTC C30 and STO22 questionnaires for the evaluation of health-related quality of life in patients with gastric cancer. *Ann Surg Oncol.* (2009) 16:88–95. doi: 10.1245/s10434-008-0175-9
15. Fayers PM, Aaronson NK, Bjordal K, Curran D, Groenvold M. *EORTC QLQ-C30 Scoring Manual*. 3rd Ed. Brussels: EORTC (2001).
16. Giesinger JM, Kieffer JM, Fayers PM, Groenvold M, Petersen MA, Scott NW, et al. EORTC Quality of Life Group. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. *J Clin Epidemiol*. (2016) 69:79–88. doi: 10.1016/j.jclinepi.2015.08.007
17. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys*. (2008) 70:510–4. doi: 10.1016/j.ijrobp.2007.06.074
18. Bell EH, Pugh SL, McElroy JP, Gilbert MR, Mehta M, Klimowicz AC, et al. Molecular-based recursive partitioning analysis model for glioblastoma in the temozolomide era: a correlative analysis based on NRG oncology RTOG 0525. *JAMA Oncol.* (2017) 3:784–92. doi: 10.1001/jamaoncol.2016.6020
19. Abrey LE, Ben-Porat L, Panageas KS, Yahalom J, Berkey B, Curran W, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. *J Clin Oncol.* (2006) 24:5711–5. doi: 10.1200/JCO.2006.08.2941
20. Tabachnik BG, Fidell LS. *Using Multivariate Statistics*. Boston, MA: Pearson (2007).
21. Zeng KL, Raman S, Sahgal A, Soliman H, Tsao M, Wendszicki C, et al. Patient preference for stereotactic radiosurgery plus or minus whole brain radiotherapy for the treatment of brain metastases. *Ann Palliat Med.* (2017) 6:S155–60. doi: 10.21037/apm.2017.06.11
22. Dirven L, Taphoorn MJ, Reijneveld JC, Blazeby J, Jacobs M, Pusic A, et al. The level of patient-reported outcome reporting in randomised controlled trials of brain tumour patients: a systematic review. *Eur J Cancer* (2014) 50:2432–48. doi: 10.1016/j.ejca.2014.06.016
23. Khoshnevisan A, Yekaninejad MS, Ardakani SK, Pakpour AH, Mardani A, Aaronson NK. Translation and validation of the EORTC brain cancer module (EORTC QLQ-BN20) for use in Iran. *Health Qual Life Outcomes* (2012) 10:54. doi: 10.1186/1477-7525-10-54
24. Shin YS, Kim JH. Validation of the Korean version of the European Organization for Research and Treatment of Cancer brain cancer module (EORTC QLQ-BN20) in patients with brain tumors. *Health Qual Life Outcomes* (2013) 11:145. doi: 10.1186/1477-7525-11-145
25. Osoba D, Aaronson NK, Muller M, Sneeuw K, Hsy MA, Yung WK, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Qual Life Res.* (1996) 5:139–50.
26. Zhang K, Tian J, He Z, Sun W, Pekbay B, Lin Y, et al. Validation of the Chinese version of EORTC QLQ-BN20 for patients with brain cancer. *Eur J Cancer Care* (2018) 27:e12832. doi: 10.1111/ecc.12832
27. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. (1993) 85:365–76.
28. Perry JR, Laperriere N, O' Callaghan CJ, Brandes AA, Menten J, Phillips C, et al. Short-course radiation plus temozlomide in elderly patients with glioblastoma. *N Engl J Med.* (2017) 376:1027–37. doi: 10.1056/NEJMoa1611977
29. Wong E, Zhang L, Kerba M, Amalot PF, Danielson B, Tsao M, et al. Minimal clinically important differences in the EORTC QLQ-BN20 in patients with brain metastases. *Support Care Cancer* (2015) 23:2731–7. doi: 10.1007/s00520-015-2637-5
30. Maringwa J, Quinten C, King M, Ringash J, Osoba D, Coens C, et al. Minimal clinically meaningful differences for the EORTC QLQ-C30 and EORTC QLQ-BN20 scales in brain cancer patients. *Ann Oncol.* (2011) 22:2107–12. doi: 10.1093/annonc/mdq726

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

MINI REVIEW
published: 04 February 2019
doi: 10.3389/fonc.2019.00041

Temozolomide Induced Hypermutation in Glioma: Evolutionary Mechanisms and Therapeutic Opportunities

Paul Daniel[1], *Siham Sabri*[2,3], *Ahmad Chaddad*[1,4], *Brian Meehan*[5], *Bertrand Jean-Claude*[3,6], *Janusz Rak*[3,5†] *and Bassam S. Abdulkarim*[1,3*†]

[1] Division of Radiation Oncology, Department of Oncology, McGill University, Montréal, QC, Canada, [2] Department of Pathology, McGill University, Montréal, QC, Canada, [3] Research Institute of the McGill University Health Centre, Montréal, QC, Canada, [4] The Laboratory for Imagery, Vision and Artificial Intelligence, École de Technologie Supérieure, Montréal, QC, Canada, [5] Department of Pediatrics, McGill University, Montréal, QC, Canada, [6] Department of Medicine, McGill University, Montréal, QC, Canada

OPEN ACCESS

Edited by:
Marcos Vinicius Calfat Maldaun, Hospital Sírio-Libanês, Brazil

Reviewed by:
Kamalakannan Palanichamy, The Ohio State University, United States
Sunit Das, St. Michael's Hospital, Canada

***Correspondence:**
Bassam S. Abdulkarim
bassam.abdulkarim@mcgill.ca

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: 26 November 2018
Accepted: 16 January 2019
Published: 04 February 2019

Citation:
Daniel P, Sabri S, Chaddad A, Meehan B, Jean-Claude B, Rak J and Abdulkarim BS (2019) Temozolomide Induced Hypermutation in Glioma: Evolutionary Mechanisms and Therapeutic Opportunities. Front. Oncol. 9:41. doi: 10.3389/fonc.2019.00041

Glioma are the most common type of malignant brain tumor, with glioblastoma (GBM) representing the most common and most lethal type of glioma. Surgical resection followed by radiotherapy and chemotherapy using the alkylating agent Temozolomide (TMZ) remain the mainstay of treatment for glioma. While this multimodal regimen is sufficient to temporarily eliminate the bulk of the tumor mass, recurrence is inevitable and often poses major challenges for clinical management due to treatment resistance and failure to respond to targeted therapies. Improved tumor profiling capacity has enabled characterization of the genomic landscape of gliomas with the overarching goal to identify clinically relevant subtypes and inform treatment decisions. Increased tumor mutational load has been shown to correlate with higher levels of neoantigens and is indicative of the potential to induce a durable response to immunotherapy. Following treatment with TMZ, a subset of glioma has been identified to recur with increased tumor mutational load. These hypermutant recurrent glioma represent a subtype of recurrence with unique molecular vulnerabilities. In this review, we will elaborate on the current knowledge regarding the evolution of hypermutation in gliomas and the potential therapeutic opportunities that arise with TMZ-induced hypermutation in gliomas.

Keywords: glioma, recurrence, MGMT, hypermutation, temozolomide

INTRODUCTION

Glioma refers to a group of malignant brain tumors comprised of oligodendroglioma, anaplastic astrocytoma, and glioblastoma (GBM) (1). Amongst gliomas, GBM is the most commonly diagnosed malignant primary brain tumor making up 54% of all gliomas and 16% of all primary brain tumors (2). GBM is also the most lethal brain tumor with a median survival of only 15 months (2–4). GBM can be further stratified into IDH1 wild-type (90%) and IDH1 mutant (10%). Patients with IDH1 mutations are thought to comprise secondary GBM as they are enriched for ATRX mutations similar to that found in lower-grade glioma and patients survive for a median survival of 31 months which is consistent with lower-grade glioma (5).

The emergence of next-generation sequencing and characterization of the genome, epigenome, and transcriptome of GBMs revealed an increasing level of disease complexity. For example, it is now known that GBM is not a homogenous disease but comprises 3 distinct subtypes; Proneural (PN), Mesenchymal (MES), and Classical (CL) which are able to classify both primary and recurrent disease (6–9). Comparison of these molecular subtypes shows that each subtype is enriched for unique molecular alterations. PN is enriched for aberrations in the gene expression of platelet-derived growth factor receptor alpha (PDGFRA) and *TP53* mutations, whilst MES and CL are enriched for neurofibromatosis type I (NF1), and epidermal growth factor receptor (EGFR) alterations, respectively (8, 9). Similarly, each subtype has also been found to be associated with a specific local immune tumor microenvironment. By comparing immune signatures between each subtype, MES tumors were found to be enriched for macrophages and neutrophil signatures (6). In contrast, PN tumors exhibit suppression of $CD4^+$ T-cell signature while CL tumors were enriched for dendritic cell signatures (6). Studies showing that an individual tumor is comprised of cells from multiple subtypes (i.e., intra-tumoral heterogeneity) have added additional complexity to this picture of heterogeneity (10, 11).

The current treatment regimen for primary GBM implemented since 2005 involves surgical resection followed by concurrent chemoradiation (12). This aggressive upfront trimodal regimen improved 2-years survival from 10% for treatment with radiotherapy (RT) alone to 27% compared to treatment with RT and Temozolomide (TMZ) (12). Despite this improvement, recurrence following treatment remains inevitable, typically occurring within months following completion of treatment at first diagnosis and is ultimately lethal as recurrent disease shows limited response to further chemoradiation. To date, there are currently no known therapies, which provide substantial survival benefit to GBM patients at recurrence, urging investigation into alternative treatment options. Understanding the mechanisms underlying response and emergent resistance to chemotherapy is therefore of utmost importance to inform decisions about the next generation of therapies.

THE CYTOTOXIC EFFECT OF TEMOZOLOMIDE

TMZ, the main chemotherapy utilized for glioma, is an alkylating pro-drug which methylates DNA at the O^6 position of guanine (13). During DNA replication, the maintenance of this methyl-adduct causes a mismatch pairing of guanine with thymine rather than cytosine leading to genomic instability and eventually cell death (13, 14). Two major mechanisms oppose the cytotoxic action of TMZ (**Figure 1A**). O^6 methylguanine-DNA methyltransferase (MGMT), a suicide enzyme able to sequester the methyl-adduct from O^6 guanine through covalent transfer, effectively repairs the alteration prior to replication (15). Consistent with this role for MGMT in driving resistance, *MGMT* promoter methylation, which is an indirect measure of the ability for cells to express the MGMT protein, is one of the strongest predictors of response to TMZ. Comparison of patient cohorts treated with chemoradiation revealed that those with MGMT methylation survive a median on 21.7 months compared to a median survival of just 15.3 months for patients without MGMT methylation (16).

In the absence of MGMT expression, resultant base mismatches invoke the mismatch repair (MMR) pathway. MMR proteins including MSH2, MSH6, MLH1, and PMS2 recognize and bind to the mismatched guanine and cause cells to enter a cycle of DNA repair (13, 17). Mismatches in newly synthesized daughter DNA strands are repaired whilst methyl adducts persist on parental DNA in the absence of MGMT. This leads to a cycle of futile repair followed by mismatching which eventually induces DNA double strand break formation, cell arrest and death (13). MMR capacity is therefore essential to repairing TMZ-induced toxicity. Consistent with this, comparison of MMR protein expression in 80 matched primary and recurrent GBM specimens treated with chemoradiation revealed consistent downregulation of MMR repair genes in recurrent GBM, highlighting the importance of MMR in dictating response to TMZ (18).

RECURRENT GLIOMA AND EMERGENCE OF HYPERMUTATION

The failure of chemoradiation, culminating with the inevitability of recurrence and acquisition of a chemo-resistant phenotype have spurred investigations into novel approaches toward treating recurrent disease. An emerging paradigm for finding effective treatments for recurrent GBM is targeted therapy, where treatment is specifically directed against driver alterations necessary for maintenance of malignant phenotypes. Increased availability and reduced cost of sequencing allowed interrogation of the molecular landscape of disease and identification of clinically relevant "subtypes" spurring further interest in targeted therapies. Notably, subtyping of disease states has been a major advancement in simplifying inter-tumoral heterogeneity whilst facilitating the identification of a targetable subset of patients sharing common molecular features. A recent remarkable finding from several longitudinal observational studies comparing pre- and post-treatment glioma has now established that at least two distinct genomic outcomes exist at recurrence; *hypermutant* and *non-hypermutant* recurrence (7, 19–23). For hypermutant recurrent tumors, the hallmark identifiers include (i) fold increases in subclonal mutations across the whole genome, (ii) enrichment of the C:G>T:A mutational signature indicative of TMZ mutagenesis, and (iii) gain of inactivating mutations in MMR pathway components (7). In comparison, non-hypermutant recurrent tumors do not exhibit any of these features but instead maintain a similar level of tumor mutational burden (TMB) compared to the primary tumor. Greater understanding of the processes which dictate emergence of these subtypes and the underlying molecular mechanisms responsible for maintenance of malignant features will likely be essential for the identification of targeted therapies against each subtype.

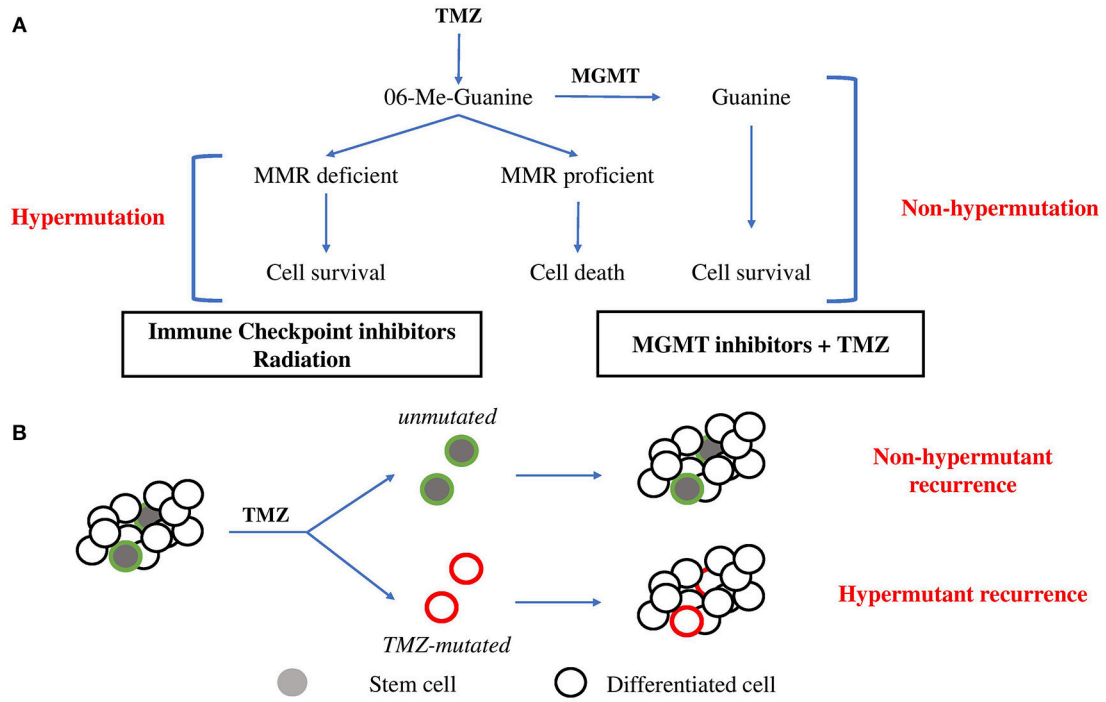


FIGURE 1 | Evolutionary pathways toward hypermutation. **(A)** 06-Me-Guanine are generated through TMZ exposure. In the presence of MGMT, methyl adducts are removed and the cell survives without gain in mutagenesis. In the absence of MGMT, MMR status determines survival. In MMR proficient cells, futile repair leads to double strand breaks and cell death. In cells which lose MMR proficiency, cells gain tolerance to base mismatch and cells acquire genomic hypermutation. Suggested therapies are listed below. **(B)** Stem cell hierarchy of tumor growth may provide an alternate means of resistance to hypermutation. Minor populations of stem cells maintain tumor growth through differentiation. Upon exposure to TMZ, stem cells may be minimally affected by chemotherapy due to greater drug efflux activity and slower proliferation rate and so repopulate tumor mass with non-hypermutant progeny. Alternatively, stem cells which acquire hypermutation will give rise to hypermutant recurrent tumors.

Attempts to understand the processes responsible for emergence of a hypermutant state have thus far been limited to observational studies of glioma, from primary to recurrent states. Although initially observed to be associated with malignant transformation of low-grade to high-grade glioma, TMZ-induced hypermutation has now been observed to occur in grade IV GBM, albeit occurring at a lower frequency compared to low grade (19, 21, 22). Specifically, recent reports from the largest observation study to date found that whilst only ∼10% of GBM display hypermutation at recurrence, a much higher proportion of low grade gliomas emerge as hypermutant following treatment with TMZ (7, 22). This differential capacity for low and high-grade glioma to evolve toward hypermutation raises several questions related to the exact mechanisms which dictate predisposition to undergo mutagenesis.

O-6-METHYLGUANINE-DNA METHYLTRANSFERASE (MGMT)

To date, *MGMT* promoter methylation is the strongest correlative feature which predicts GBM hypermutation at recurrence (7). Unsurprisingly, the importance of MGMT in preventing mismatch pairing during DNA replication due to removal of methyl adducts is likely responsible for this relationship to hypermutation. It is interesting to note however that reports vary regarding the correlation between MGMT protein expression and *MGMT* promoter methylation, making it plausible that methylation status of *MGMT* may play a surrogate role as a biomarker of a state predisposed toward hypermutation (24, 25). One potential alternative is the observation that *MGMT* promoter methylation may be indicative of a global hypermethylated phenotype. Indeed, epigenetic features have now been found to impact the ability for DNA repair to take place, as evidenced by the differential rates of mutagenesis predicated by chromatin accessibility (26). Supporting the impact that epigenetic features can have upon hypermutation, low grade gliomas exhibit a global higher hypermethylated state compared to GBM whilst undergoing hypermutation at a much higher frequency despite exhibiting similar proportions of *MGMT* promoter methylation at first diagnosis (27). Whether hypermethylated subtypes of GBM, defined by IDH1 mutation and a global CpG island methylation phenotype G-CIMP, undergo hypermutation at a higher rate than IDH1 wild-type non-G-CIMP GBM, which are comparatively hypomethylated is not yet known. This would provide critical information regarding the role that epigenetic status plays in dictating the emergence of hypermutation (28).

MISMATCH REPAIR PROTEINS

Along with MGMT methylation, acquired mutations in MMR genes have been strongly correlated with hypermutation (7, 19, 21). As described earlier, MMR represents the main mechanism by which mismatched bases are repaired and downregulation of these genes is a common mechanism by which gliomas acquire resistance to TMZ. Indeed, minimal loss in MMR genes MSH2 and MSH6 have been shown to be sufficient to provide substantial survival benefit to cells (29). It is important to note however that whilst MMR gene downregulation is common to recurrent glioma and may represent a convergent mechanism of acquired chemoresistance, MMR pathway *mutation* seems specifically enriched in hypermutant recurrence(7).

One explanation for why this may occur is the observation that MMR proteins are involved in alternate repair pathways which may contribute to resistance to mutagenesis. For example, non-homologous end joining (NHEJ) and homologous recombination (HR) are alternative DNA repair pathways which may drive repair of double strand breaks (DSB) following TMZ treatment. The MMR protein MSH6 directly binds to KU70, a regulatory subunit of the DNA-dependant protein kinase involved in NHEJ and HR repair (30). Similarly, MSH2 is a critical component of the BRCA1 associated genome surveillance complex that recognizes and initiates response to abnormal DNA structures (31). Consistent with the role of MMR is alternate DNA repair pathways, MSH6 knockout cells display impaired NHEJ typified by accumulation of persistent DSBs (30). Together these findings suggest that the complete loss of function of MMR proteins may be necessary for reduced capacity to repair DNA defects, allowing emergence of hypermutation.

ADDITIONAL INFLUENCES UPON THE EMERGENCE OF HYPERMUTATION

The majority of GBM tumors will recur as non-hypermutant displaying no overt signs of widespread mutagenesis following TMZ treatment (7). This occurs despite MGMT expression being reportedly stable between primary and recurrent disease (32), suggesting additional features are responsible for protecting from the mutagenesis imposed by TMZ. TMZ cytotoxic effects are dependent on the active proliferation of cells and rapid DNA replication to induce mismatches recognized by MMR machinery, which ultimately leads to either repair, death, or hypermutation (33). This implies that slower proliferation or dormancy would be protective against the acquisition of genomic hypermutation from TMZ treatment (**Figure 1B**).

There is accumulating evidence suggesting that solid tumors are driven by a minor population of stem cells (34). These multipotent stem cells give rise to rapidly proliferating progenitor cells, which are the major drivers of immediate tumor growth. Importantly, stem cells are phenotypically distinct from more differentiated progeny, characterized by their multipotent differentiation capacity, slower proliferation and greater drug efflux activity (34, 35). Together these likely contribute to the reportedly enhanced ability for stem cells to survive chemotherapy compared to their more differentiated progeny. Consistent with this, recent evidence has demonstrated that brain tumor stem cells (BTSCs) are responsible for initiating recurrence (36). Following completion of therapy, surviving stem populations exit dormancy and drives repopulation of the tumor mass. Notably, in this hierarchical model of tumor growth, only mutagenesis acquired by these stem cell populations will be represented in the recurrent tumor. Stem cells which emerge from dormancy following treatment result in recurrence with no observable hypermutation, an outcome independent from MGMT expression. It should also be noted that chemotherapy has been proposed to promote acquisition of stem-like features by differentiated cells (37, 38). As such, the traditional hierarchical model of differentiation and growth is likely insufficient to fully describe the disease state. Further investigation of this process of dedifferentiation is needed to understand its impact on the acquisition of hypermutation state at recurrence.

An additional feature which may impact the emergence of hypermutation is the concurrent use of radiation alongside TMZ for glioma. Indeed, radiation has been shown to be able to induce the expression of MGMT (39). Similarly, radiation has the capacity to drive transient growth arrest which as outlined above, may provide temporary resistance to TMZ induced mutagenesis (40). Whilst sufficiently powered datasets are not yet available for recurrent GBM to make definite conclusions regarding this, what is clear is that hypermutant tumors are able to emerge in patients which receive concurrent radiation and TMZ. We predict that generation of animal models exploring the modalities in clonal xenografts and assessment of incidence of hypermutation from using individual and combined treatment modalities will be able to elucidate the exact role of radiation in hypermutation and facilitate additional exploration into alternate means to drive evolution toward specific outcomes.

THERAPEUTIC OPPORTUNITIES IN HYPERMUTANT RECURRENT GBM

Both the diversity of genomic alterations as well as the underlying mechanisms which facilitate acquisition of hypermutation make it likely that the approach toward treating hypermutant tumors may be completely different from that of non-hypermutant recurrence. For example, the mutation of MMR genes is specifically observed in hypermutant but not non-hypermutant recurrent tumours (7, 22). Similarly, an increased neo-antigen load linked to the higher global tumor mutational burden is observed exclusively in hypermutant tumors. Exploitation of these unique features of recurrent GBM may provide the means to personalize patient treatment.

CHECKPOINT INHIBITORS

Immune checkpoint inhibitors (ICI) have shown great promise in the treatment of many diseases. High mutational burden has been identified as the best predictor of response to this treatment option, regardless of disease (41). This has culminated

in the recent approval of the Programmed Death Protein 1 (PD-1) inhibitor pembrolizumab for use in all MMR-deficient or microsatellite instability (MSI)-high tumors. Of note, whilst the link between MMR-deficiency and hypermutation has been observed in several longitudinal studies (7, 20, 22), somewhat counter intuitively MSI is *not* associated with TMZ-mediated hypermutation in GBM (22). Regardless, case reports have suggested the capacity for ICI to be used for GBM in cases with hypermutation. For example, the treatment of GBM patients with germline POLE mutations driving a biallelic mismatch repair deficiency (bMMRd) phenotype characterized by hypermutation of the genome with pembrolizumab was reported to drive radiologically measured tumor regression (42, 43). However, the poor outcomes from the most recent Checkmate 143 trial (NCT02017717) which tested nivolumab and ipilimumab has moderated expectations with no improvement of survival in patients diagnosed with recurrent GBM. Importantly, this trial did not integrate any biomarkers of immunotherapy response such as mutational burden or T-cell inflamed gene expression profiling and as such, retrospective analyses following completion of this trial will likely be able to identify a subset of patients with the potential to respond to immunotherapy.

One feature of glioma which is thought to limit the impact of immunotherapy is the "cold" tumor immune environment of this disease. The blood brain barrier (BBB) comprises a system of pericytes, endothelial cells, astrocytic processes, and basement membrane, which has long been thought to prevent the movement of immune cells to the brain and contribute to the low immunogenicity of glioma. However, leukocyte trafficking across the BBB has been known to play an essential role in the control of several neurodegenerative and infectious diseases (44). Similarly, the paradigm of an intact BBB enforcing an immune privileged environment in GBM is increasingly being challenged as more evidence accumulates demonstrating that the BBB can be severely disrupted during disease in addition to observation of prevalent immune infiltration into the tumour (6, 45). As such, it is likely that the failure of immunotherapy is not limited by the BBB but instead due to intrinsic features of the local immune microenvironment such as immune-suppressive M2 macrophages or T-cell exhaustion which prevent robust immune surveillance and reactivity (46). Targeting these immunomodulatory cells is currently underway and may pave the way toward increasing the efficacy of immunotherapy in GBM.

COMBINING IMMUNOTHERAPY WITH RADIOTHERAPY

A large number of studies have investigated the complex interaction between radiation and the immune system, which has led to the emergence of the radio-immunobiology (47). The most prominent example of this interaction is observation of the "abscopal effect" where irradiation against a primary tumor results in the regression of metastatic clones in disparate areas of the body. This is now understood to be mediated by the immune system: as tumor neo-antigens are released by dying cells, they are taken up by dendritic cells followed by systemic activation of T-cell responses which continue in a feedforward fashion leading to tumor control (48). It should be noted that induced immune response is greatly influenced by dose given per fraction, where increasing dose generates decreasing immune responses. For example, RT has been found to cause upregulation of immunosuppressive factors such as PD-L1 (49). Similarly, immunosuppressive M2 macrophages are more radioresistant than immune-promotive M1 macrophages and targeted radiation has been observed to cause a shift toward a M2 microenvironment in GBM (50). The complex role of radiation has now led to design of companion radio-immunotherapeutics (RIT) which acts to restrict the immunosuppressive effects of radiation. Furthermore, additional parameters such as the total dose of radiation, dose per fraction, and chronological sequencing of radiation and ICI warrant further investigation as to how they can be utilized to sustain immune cell infiltration into the tumor.

RADIATION AND HYPERMUTATION AS A SYNTHETIC LETHAL COMBINATION

In addition to the immunological relevance of hypermutation, the co-occurrence of MMR gene mutation in TMZ-driven hypermutant tumors may offer additional opportunities for exploitation (7, 20, 22). For example, PMS2 knockout cells demonstrate a 4-fold increase in mutations following treatment with radiation compared to their wild-type counterparts (51). Models of population fitness suggest that an increased mutation rate can be beneficial up to a point, beyond which further mutagenesis becomes detrimental due to accumulation of deleterious alterations. Accordingly, mouse models of genomic instability demonstrate a *decreased* tumor growth upon elevation of mutational burden (52). In the context of hypermutation, increasing the number of mutations in hypermutant cells following RT treatment may lead to reduced fitness, making them less aggressive and more amenable toward additional treatments.

CONCLUSION AND FUTURE PERSPECTIVES ON HYPERMUTATION

It is now accepted that hypermutation represents a distinct subtype of recurrent glioma. However, several questions remain unresolved before we can start to understand the impact of hypermutation at recurrence. What is the mechanism behind emergence of hypermutation and is this process targetable? Is hypermutation in GBM associated with better or worse outcome for patients? Does immunotherapy represent a valid therapeutic approach for hypermutant tumors and can this be combined with radiotherapy? We predict that studies seeking to identify the underlying molecular features of hypermutant and non-hypermutant recurrent subtypes will likely pave the way for novel treatment approaches for recurrent GBM.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

ACKNOWLEDGMENTS

This work was performed with support from Varian Medical Systems. Thank you to Henri R. Shibata and the Cedars Cancer Foundation for fellowship support of PD.

REFERENCES

1. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol.* (2016) 131:803–20. doi: 10.1007/s00401-016-1545-1
2. Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. *Neuro Oncol.* (2013) 15 (Suppl. 2):ii1–56. doi: 10.1093/neuonc/not151
3. Koshy M, Villano JL, Dolecek TA, Howard A, Mahmood U, Chmura SJ, et al. Improved survival time trends for glioblastoma using the SEER 17 population-based registries. *J Neurooncol.* (2012) 107:207–12. doi: 10.1007/s11060-011-0738-7
4. Brown TJ, Brennan MC, Li M, Church EW, Brandmeir NJ, Rakszawski KL, et al. Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis. *JAMA Oncol.* (2016) 2:1460–9. doi: 10.1001/jamaoncol.2016.1373
5. Yan H, Parsons W, Jin G, McLendon R, Rasheed BA, Yuan W, et al. *IDH1* and *IDH2* mutations in gliomas. *N Engl J Med.* (2009) 360:765–73. doi: 10.1056/NEJMoa0808710
6. Wang Q, Hu B, Hu X, Kim H, Squatrito M, Scarpace L, et al. Tumor evolution of glioma-intrinsic gene expression subtypes associates with immunological changes in the microenvironment. *Cancer Cell* (2018) 33:152. doi: 10.1016/j.ccell.2017.12.012
7. Wang J, Cazzato E, Ladewig E, Frattini V, Rosenbloom DI, Zairis S, et al. Clonal evolution of glioblastoma under therapy. *Nat Genet.* (2016) 48:768–76. doi: 10.1038/ng.3590
8. Brennan CW, Verhaak RG, McKenna A, Campos B, Noushmehr H, Salama SR, et al. The somatic genomic landscape of glioblastoma. *Cell* (2013) 155:462–77. doi: 10.1016/j.cell.2013.09.034
9. Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell* (2010) 17:98–110. doi: 10.1016/j.ccr.2009.12.020
10. Patel AP, Tirosh I, Trombetta JJ, Shalek AK, Gillespie SM, Wakimoto H, et al. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. *Science* (2014) 344:1396–401. doi: 10.1126/science.1254257
11. Sottoriva A, Spiteri I, Piccirillo SG, Touloumis A, Collins VP, Marioni JC, et al. Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics. *Proc Natl Acad Sci USA.* (2013) 110:4009–14. doi: 10.1073/pnas.1219747110
12. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* (2005) 352:987–96. doi: 10.1056/NEJMoa043330
13. Margison GP, Santibáñez Koref MF, Povey AC. Mechanisms of carcinogenicity/chemotherapy by O6-methylguanine. *Mutagenesis* (2002) 17:483–7. doi: 10.1093/mutage/17.6.483
14. Karran P, Marinus MG. Mismatch correction at O6-methylguanine residues in *E. coli* DNA. *Nature* (1982) 296:868–9. doi: 10.1038/296868a0
15. Pegg AE, Dolan ME, Moschel RC. Structure, function, and inhibition of O6-alkylguanine-DNA alkyltransferase. *Prog Nucleic Acid Res Mol Biol.* (1995) 51:167–223. doi: 10.1016/S0079-6603(08)60879-X
16. Esteller M, Garcia-Foncillas J, Andion E, Goodman SN, Hidalgo OF, Vanaclocha V, et al. Inactivation of the DNA-repair gene *MGMT* and the clinical response of gliomas to alkylating agents. *N Engl J Med.* (2000) 343:1350–4. doi: 10.1056/NEJM200011093431901
17. Kyrtopoulos SA, Anderson LM, Chhabra SK, Souliotis VL, Pletsa V, Valavanis C, et al. DNA adducts and the mechanism of carcinogenesis and cytotoxicity of methylating agents of environmental and clinical significance. *Cancer Detect Prev.* (1997) 21:391–405.
18. Felsberg J, Thon N, Eigenbrod S, Hentschel B, Sabel MC, Westphal M, et al. Promoter methylation and expression of MGMT and the DNA mismatch repair genes MLH1, MSH2, MSH6 and PMS2 in paired primary and recurrent glioblastomas. *Int J Cancer* (2011) 129:659–70. doi: 10.1002/ijc.26083
19. van Thuijl HF, Mazor T, Johnson BE, Fouse SD, Aihara K, Hong C, et al. Evolution of DNA repair defects during malignant progression of low-grade gliomas after temozolomide treatment. *Acta Neuropathol.* (2015) 129:597–607. doi: 10.1007/s00401-015-1403-6
20. Hodges TR, Ott M, Xiu J, Gatalica Z, Swensen J, Zhou S, et al. Mutational burden, immune checkpoint expression, and mismatch repair in glioma: implications for immune checkpoint immunotherapy. *Neuro Oncol.* (2017) 19:1047–57. doi: 10.1093/neuonc/nox026
21. Johnson BE, Mazor T, Hong C, Barnes M, Aihara K, McLean CY, et al. Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. *Science* (2014) 343:189–93. doi: 10.1126/science.1239947
22. Indraccolo S, Lombardi G, Fassan M, Pasqualini L, Giunco S, Marcato R, et al. Genetic, epigenetic and immunologic profiling of MMR-deficient relapsed glioblastoma. *Clin Cancer Res.* (2018). doi: 10.1158/1078-0432.CCR-18-1892. [Epub ahead of print].
23. Hu H, Mu Q, Bao Z, Chen Y, Liu Y, Chen J, et al. Mutational landscape of secondary glioblastoma guides MET-targeted trial in brain tumor. *Cell* (2018) 175:1665–78.e18. doi: 10.1016/j.cell.2018.09.038
24. Uno M, Oba-Shinjo SM, Camargo AA, Moura RP, Aguiar PH, Cabrera HN, et al. Correlation of MGMT promoter methylation status with gene and protein expression levels in glioblastoma. *Clin Sao Paulo Braz.* (2011) 66:1747–55. doi: 10.1590/S1807-59322011001000013
25. Mellai M, Caldera V, Annovazzi L, Chiò A, Lanotte M, Cassoni P, et al. MGMT promoter hypermethylation in a series of 104 glioblastomas. *Cancer Genomics Proteom.* (2009) 6:219–27.
26. Ha K, Kim HG, Lee H. Chromatin marks shape mutation landscape at early stage of cancer progression. *NPJ Genomic Med.* (2017) 2:9. doi: 10.1038/s41525-017-0010-y
27. Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. *Am J Pathol.* (2007) 170:1445–53. doi: 10.2353/ajpath.2007.070011
28. Noushmehr H, Weisenberger DJ, Diefes K, Phillips HS, Pujara K, Berman BP, et al. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. *Cancer Cell* (2010) 17:510–22. doi: 10.1016/j.ccr.2010.03.017
29. McFaline-Figueroa JL, Braun CJ, Stanciu M, Nagel ZD, Mazzucato P, Sangaraju D, et al. Minor changes in expression of the mismatch repair protein MSH2 exert a major impact on glioblastoma response to temozolomide. *Cancer Res.* (2015) 75:3127–38. doi: 10.1158/0008-5472.CAN-14-3616
30. Shahi A, Lee JH, Kang Y, Lee SH, Hyun JW, Chang IY, et al. Mismatch-repair protein MSH6 is associated with Ku70 and regulates DNA double-strand break repair. *Nucleic Acids Res.* (2011) 39:2130–43. doi: 10.1093/nar/gkq1095
31. Wang Y, Cortez D, Yazdi P, Neff N, Elledge SJ, Qin J. BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures. *Genes Dev.* (2000) 14:927–39. doi: 10.1101/gad.14.s8.927
32. Park CK, Kim JE, Kim JY, Song SW, Kim JW, Choi SH, et al. The changes in MGMT promoter methylation status in initial and recurrent glioblastomas. *Transl Oncol.* (2012) 5:393–7. doi: 10.1593/tlo.12253

33. Roos WP, Batista LF, Naumann SC, Wick W, Weller M, Menck CF, et al. Apoptosis in malignant glioma cells triggered by the temozolomide-induced DNA lesion O6-methylguanine. *Oncogene* (2007) 26:186–97. doi: 10.1038/sj.onc.1209785
34. Singh SK, Clarke ID, Terasaki M, Bonn VE, Hawkins C, Squire J, et al. Identification of a cancer stem cell in human brain tumors. *Cancer Res.* (2003) 63:5821–8.
35. Hirschmann-Jax C, Foster AE, Wulf GG, Nuchtern JG, Jax TW, Gobel U, et al. A distinct 'side population' of cells with high drug efflux capacity in human tumor cells. *Proc Natl Acad. Sci USA.* (2004) 101:14228–33. doi: 10.1073/pnas.0400067101
36. Chen J, Li Y, Yu TS, McKay RM, Burns DK, Kernie SG, et al. A restricted cell population propagates glioblastoma growth after chemotherapy. *Nature* (2012) 488:522–6. doi: 10.1038/nature11287
37. Lee G, Auffinger B, Guo D, Hasan T, Deheeger M, Tobias AL, et al. Dedifferentiation of glioma cells to glioma stem-like cells by therapeutic stress-induced HIF signaling in the recurrent GBM model. *Mol Cancer Ther.* (2016) 15:3064–76. doi: 10.1158/1535-7163.MCT-15-0675
38. Garnier D, Meehan B, Kislinger T, Daniel P, Sinha A, Abdulkarim B, et al. Divergent evolution of temozolomide resistance in glioblastoma stem cells is reflected in extracellular vesicles and coupled with radiosensitization. *Neuro Oncol.* (2018) 20:236–48. doi: 10.1093/neuonc/nox142
39. Wilson RE, Hoey B, Margison GP. Ionizing radiation induces O6-alkylguanine-DNA-alkyltransferase mRNA and activity in mouse tissues. *Carcinogenesis* (1993) 14:679–83. doi: 10.1093/carcin/14.4.679
40. Quick QA, Gewirtz DA. An accelerated senescence response to radiation in wild-type p53 glioblastoma multiforme cells. *J Neurosurg.* (2006) 105:111–8. doi: 10.3171/jns.2006.105.1.111
41. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med.* (2017) 377:2500–1. doi: 10.1056/NEJMc1713444
42. Johanns TM, Miller CA, Dorward IG, Tsien C, Chang E, Perry A, et al. Immunogenomics of hypermutated glioblastoma: a patient with germline POLE deficiency treated with checkpoint blockade immunotherapy. *Cancer Discov.* (2016) 6:1230–6. doi: 10.1158/2159-8290.CD-16-0575
43. Bouffet E, Larouche V, Campbell BB, Merico D, de Borja R, Aronson M, et al. Immune checkpoint inhibition for hypermutant glioblastoma multiforme resulting from germline biallelic mismatch repair deficiency. *J Clin Oncol.* (2016) 34:2206–11. doi: 10.1200/JCO.2016.66.6552
44. Takeshita Y, Ransohoff RM. Inflammatory cell trafficking across the blood-brain barrier: chemokine regulation and *in vitro* models. *Immunol Rev.* (2012) 248:228–39. doi: 10.1111/j.1600-065X.2012.01127.x
45. Engler JR, Robinson AE, Smirnov I, Hodgson JG, Berger MS, Gupta N, et al. Increased microglia/macrophage gene expression in a subset of adult and pediatric astrocytomas. *PloS ONE* (2012) 7:e43339. doi: 10.1371/journal.pone.0043339
46. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature* (2015) 523:337–41. doi: 10.1038/nature14432
47. Bockel S, Durand B, Deutsch E. Combining radiation therapy and cancer immune therapies: from preclinical findings to clinical applications. *Cancer Radiother J Soc Francaise Radiother Oncol.* (2018) 22:567–80. doi: 10.1016/j.canrad.2018.07.136
48. Liu Y, Dong Y, Kong L, Shi F, Zhu H, Yu J, et al. Abscopal effect of radiotherapy combined with immune checkpoint inhibitors. *J Hematol Oncol J Hematol Oncol.* (2018) 11:104. doi: 10.1186/s13045-018-0647-8
49. Song X, Shao Y, Jiang T, Ding Y, Xu B, Zheng X, et al. Radiotherapy upregulates programmed death ligand-1 through the pathways downstream of epidermal growth factor receptor in glioma. *EBio Med.* (2018) 28:105–13. doi: 10.1016/j.ebiom.2018.01.027
50. Leblond MM, Pérès EA, Helaine C, Gérault AN, Moulin D, Anfray C, et al. M2 macrophages are more resistant than M1 macrophages following radiation therapy in the context of glioblastoma. *Oncotarget* (2017) 8:72597–612. doi: 10.18632/oncotarget.19994
51. Xu XS, Narayanan L, Dunklee B, Liskay RM, Glazer PM. Hypermutability to ionizing radiation in mismatch repair-deficient, Pms2 knockout mice. *Cancer Res.* (2001) 61:3775–80.
52. McFarland CD, Yaglom JA, Wojtkowiak JW, Scott JG, Morse DL, Sherman MY, et al. The damaging effect of passenger mutations on cancer progression. *Cancer Res.* (2017) 77:4763–72. doi: 10.1158/0008-5472.CAN-15-3283-T

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 15 March 2019
doi: 10.3389/fneur.2019.00212

Health Related Quality of Life in Adult Low and High-Grade Glioma Patients Using the National Institutes of Health Patient Reported Outcomes Measurement Information System (PROMIS) and Neuro-QOL Assessments

*Nicolette Gabel[1], David B. Altshuler[2], Amanda Brezzell[2], Emily M. Briceño[1], Nicholas R. Boileau[1], Zachary Miklja[2], Karen Kluin[3,4], Thomas Ferguson[2], Kaitlin McMurray[2], Lin Wang[2], Sean R. Smith[1], Noelle E. Carlozzi[1] and Shawn L. Hervey-Jumper[2]**

[1] Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, MI, United States, [2] Department of Neurosurgery, University of Michigan, Ann Arbor, MI, United States, [3] Department of Neurology, University of Michigan, Ann Arbor, MI, United States, [4] Department of Speech-Language Pathology, University of Michigan, Ann Arbor, MI, United States

Health related quality of life (HRQOL) measures have become increasingly important in the management of glioma patients in both research and clinical practice settings. Functional impairment is common in low-grade and high-grade glioma patients as the disease has both oncological and neurological manifestations. Natural disease history as well as medical or surgical treatment can negatively influence HRQOL. There are no universal standards for HRQOL assessment in glioma patients. In this study, we examine patient perspectives on functional outcome domains and report the prevalence of impairments rates using the National Institutes of Health (NIH) Patient Reported Outcomes Measurement Information System (PROMIS) and Neuro-QOL item banks as measures of HRQOL. Retrospective analysis of a prospectively collected dataset involving 79 glioma patients reveals that quality of life concerns are the most important consideration behind making decisions about treatment in 80.7% of patients. The prevalence of functional impairment by PROMIS and NEURO-QOL assessment is high, ranging from 28.6% in the physical function domain to 43.9% in the cognitive function domain. Pain and anxiety related to physical decline is higher in LGG patients compared to HGG patients. Aphasia severity also impacts HRQOL. The results of this study suggest that the PROMIS and NEURO-QOL assessments may be important HRQOL metrics for future use in larger clinical research and clinical trial settings.

Keywords: glioma, health-related quality of life, language, neuro-rehabilitation, PROMIS, Neuro-QOL, astrocytoma, glioblastoma

OPEN ACCESS

Edited by:
Luis Souhami, McGill University, Canada

Reviewed by:
Mariko D. DeWire, Cincinnati Children's Hospital Medical Center, United States
David D. Eisenstat, University of Alberta, Canada

***Correspondence:**
Shawn L. Hervey-Jumper
Shawn.Hervey-Jumper@ucsf.edu

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Neurology

Received: *30 September 2018*
Accepted: *19 February 2019*
Published: *15 March 2019*

Citation:
Gabel N, Altshuler DB, Brezzell A, Briceño EM, Boileau NR, Miklja Z, Kluin K, Ferguson T, McMurray K, Wang L, Smith SR, Carlozzi NE and Hervey-Jumper SL (2019) Health Related Quality of Life in Adult Low and High-Grade Glioma Patients Using the National Institutes of Health Patient Reported Outcomes Measurement Information System (PROMIS) and Neuro-QOL Assessments. Front. Neurol. 10:212. doi: 10.3389/fneur.2019.00212

INTRODUCTION

Gliomas are the most frequent primary brain tumor in adults (1). There are currently more than 700,000 people living with a primary central nervous system tumor in the United States. Despite relatively low incidence, gliomas result in a disproportionate share of cancer morbidity and mortality. Brain tumors account for the highest number of years of life lost when compared to non-CNS cancers (2). Despite treatment with maximal safe surgical resection with or without adjuvant chemoradiation, overall survival has remained largely unchanged. Survival is approximately 14 months for glioblastoma and 6 to 15 years for those with WHO II and III glioma (LGG) depending on the genetic profile of the tumor.

Health-related quality of life (HRQOL) metrics have become increasingly important in brain tumor research alongside standard patient outcome measures such as progression-free and overall survival. There are several validated HRQOL assessments used in clinical practice and clinical trials research. Continued efforts to develop and implement HRQOL measurements are needed as research study and clinical endpoints. The relationship between HRQOL and survival in adult glioma is poorly understood. The World Health Organizations' (WHO) International Classification of Functioning Disability and Health (WHO 2010) defines HRQOL based on the following functional domains: physical, social, emotional well-being, and relational (3–5). In the glioma patient population, both disease progression and treatment related effects have been shown to negatively impact HRQOL (6–9).

While HRQOL metrics continue to become incorporated in clinical practice and clinical trials research, there is no consensus regarding assessment measures. The objective of this study was to evaluate patient perspectives on functional domain affecting health related quality of life. We then applied the National Institutes of Health (NIH) Patient Reported Outcomes Measurement Information System (PROMIS) and Quality of Life in Neurological Disorders (Neuro-QOL) instruments as subjective HRQOL patient-reported outcome (PRO) measures in an adult low- and high-grade glioma patient population. Although there are some overlapping domains, PROMIS was developed for use across the general population with multiple chronic health conditions, whereas Neuro-QoL was focused on developing measures that represent HRQOL domains that are specific to neurological disorders (specifically stroke, Parkinson's disease, multiple sclerosis, child and adult epilepsy, amyotrophic lateral sclerosis, and muscular dystrophy). Therefore, the calibration samples and content, while often overlapping, are different for each tool. These tools, PROMIS and Neuro-QoL, may be useful in assessing patient HRQOL and may be an important component of a multidisciplinary treatment approach for glioma patients. Many HRQOL factors may be common to patients with any cancer diagnosis (e.g., pain, emotional distress, sleep disturbance, etc.) and adequately assessed with PROMIS measures; yet, some domains of HRQOL are likely to be uniquely impacted by neurological changes associated with glioma, including cognitive and behavioral functioning in daily life, and may therefore be better captured by Neuro-QOL. To the authors' knowledge this is the first study employing the use of PROMIS and Neuro-QOL prospectively in a cohort of adult low and high-grade gliomas.

METHODS

The study design involved retrospective analysis of a prospectively collected HRQOL single institution data registry. Participants were recruited at the time of an initial clinic visit following the diagnosis of a presumed glioma. Patients remained enrolled in the study after histopathologic confirmation of a new WHO grade I–IV glioma. Exclusion criteria included age <18 and language and/or neurocognitive dysfunction limiting patient ability to complete PROMIS and Neuro-QOL questionnaires. Aphasia was assessed by the Boston Diagnostic Aphasia Examination (BDAE).

All patients were administered the Montreal Cognitive Assessment (MoCA), a screening instrument developed to estimate global cognitive ability in the service of detecting mild cognitive impairment and dementia (10). Several studies have demonstrated its utility in brain tumor populations, wherein it has been shown to have superior sensitivity compared to other screening instruments (11), is correlated with quality of life measures (12), and predicts median overall survival (13).

To examine patient preferences on functional domains and HRQOL, structured interviews were conducted focusing on how patients frame functional and cognitive domains with their disease experiences based on methodology established by Mortensen and Jakobsen (14, 15). Analysis of these semi-structured interviews was used to identify those functional domains considered important to individual glioma patients, which were then developed into a study questionnaire using a Likert scale to identify each domain as extremely important, important, neutral, somewhat important, or not at all important.

Study participants completed PROMIS version 1.0 and Neuro-QOL version 1.1 as HRQOL measures. Examined HRQOL functional domains included Neuro-QOL cognition, PROMIS physical functioning, and PROMIS ability to participate in social roles and activities; impairment domains include PROMIS pain, sleep, fatigue, depression, anxiety, and Neuro-QOL emotional/behavioral dyscontrol. PROMIS Physical Function assesses self-reported (not actual) ability to perform with one's lower extremities (e.g., walking), upper extremities (e.g., dexterity), back, and neck, and to engage in instrumental activities of daily living (16). PROMIS Anxiety assesses anxiety symptoms, including hyperarousal and fear (17, 18). PROMIS Depression measures feelings of worthlessness and sadness among other symptoms of depression. PROMIS Fatigue measures the intensity and impact of fatigue on quality of life (17, 18). PROMIS Sleep disturbances measures perceived quality, adequacy, and satisfaction with sleep as well as difficulties falling asleep and staying asleep (19, 20). PROMIS Ability to participate in social roles and activities measures one's reported ability to participate and be involved in social roles and activities (17, 18). PROMIS Pain interferences assesses the impact of pain on physical, emotional, and recreational activities (17, 18). PROMIS

Pain intensity instrument assesses how much a patient hurts. The pain intensity short form is global (i.e. not site specific) and universal rather than disease specific (16). Neuro-QoL Cognitive function measures perceived executive functioning and memory difficulties (20, 21). Neuro-QOL Emotional and behavioral dyscontrol assesses emotionality and impulsivity (20, 21) Normalized mean t-scores for each domain were standardized to 50. For functional domains, higher scores indicate less distress (score >50 more desirable); for impairment domains, higher scores indicate more distress, higher scores indicate more distress (score <50 more desirable). Analyses were conducted using SAS 9.4 statistical software. Independent *t*-tests were conducted to assess differences between LGG (WHO grades I-II) and HGG (WHO grades III-IV) groups. Prevalence of impairment was assessed in the study population where patients who scored >1 standard deviation beyond the normative mean was considered impaired.

Language assessments were performed by a certified Speech pathologist using the Boston Diagnostic Aphasia Examination Severity rating (BDAE) (22, 23). All assessments were performed in a noise controlled clinical examination room according to standard protocol. BDAE aphasia severity scores reflect the ability to communicate wants, needs, ideas with or without help from listener. BDAE severity scores ranging from 1 to 2 were considered severe aphasia (1 = severe, 2 = moderately-severe). Scores 3–5 were categorized as mild-moderate aphasia (3 = moderate, 4 = mild, 5 = trace) (22). Study inclusion required BDAE aphasia severity score ≥1 (22, 23).

Univariate analyses were conducted to assess differences between HGG and LGG for each of the PROMIS and Neuro-QOL measures. Partial eta-squared (η^2) effect sizes were examined to determine the proportion of variance in HRQOL that was accounted for by tumor-grade (small = 0.01, moderate = 0.09, and large = 0.25) (24). An independent t-test was performed to compare PROMIS and Neuro-QOL scores among patients according to language dysfunction categorized as mild aphasia (BDAE 3-5) vs. severe aphasia (BDAE 1–2).

RESULTS

Seventy-nine patients were eligible for inclusion. Of the 79 patients, 58 had HGG and 21 had LGG. Average patient age was 52 years (SD = 15.6). Global cognitive status was not different between LGG and HGG patient cohorts by the Montreal Cognitive Assessment (MOCA) (mean HGG = 21.8, LGG = 24.8; $P = 0.114$). Additional population characteristics are found in **Table 1**.

Patient Perspectives on Functional Domains of Importance

Study subjects were surveyed about the importance of quality of life concerns vs. survival on medical decision making at the time of diagnosis. Among LGG patients, 81.3% indicated treatment strategies based on quality of life concerns, while 78.6% of HGG patients were concerned primarily with quality of life ($P = 0.69$) (**Table 2**). The functional domains of greatest concern and importance were language, motor, and memory. There were no differences between LGG and HGG patients in these domains; however, HGG patients placed higher importance on creativity/problem-solving and art domains compared to LGG patients ($P = 0.009$).

HRQOL Functional and Impairment Domains Using PROMIS and Neuro-QOL

Prevalence of impairment for the HGG cohort was elevated for PROMIS physical functioning (46.6%), NEURO-QOL cognitive dysfunction (43.9%), PROMIS ability to participate in social roles and activities (28.6%), and PROMIS anxiety (27.6%) (**Figure 1**). Clinical impairment rates for the LGG cohort were elevated for PROMIS pain interferences (38.1%), PROMIS physical functioning (28.6%), PROMIS sleep disturbance (28.6%), and NEURO-QOL cognition (23.8%). There were no significant differences between PROMIS and Neuro-QOL PRO scores between HGG and LGG groups, with the following exceptions: PROMIS pain intensity, in which patients with LGG experienced greater pain-related intensity relative to patients with HGG (*t*-score: HGG 1.76 ± 2, LGG 3.29 ± 3; $P = 0.01$) and greater distress from declining physical function among patients with HGG (*t*-score: HGG 41.83 ± 12.59, LGG 47.74 ± 12.16; $P = 0.05$) (**Table 3**).

Aphasia Severity Impacts HRQOL Functional Domain

In a subgroup of 26 patients with dominant hemisphere gliomas within the perisylvian frontal, parietal, and temporal lobes, 7 had a BDAE aphasia severity score of 1–2 (severe) and 19 had a BDAE score of 3–5 (mild). The mean BDAE severity scores for both HGG and LGG cohorts were 3 ± 1 and 5 ± 0.5, respectively ($P = 0.004$). Aphasia severity had a moderate association with greater distress on PROMIS measures of anxiety ($r = -0.51$; $P = 0.0074$) and NEURO-QOL cognition ($r = 0.55$; $P = 0.0033$) (**Table 4**).

DISCUSSION

HRQOL measurements have become an increasingly important measure in the care of glioma patients. There is a need for reliable patient quality of life assessment measures which are easy to use and clinically relevant for both patients and clinicians. Assessing HRQOL PRO measures in glioma patients can be a challenge because of self-reporting difficulties in this population due to functional and cognitive impairments (25). The PROMIS survey was developed to measure PRO measures for patients with a variety of chronic diseases. PROMIS as a subjective assessment tool for glioma patients has been validated and compared to the more commonly used European Organization for Research and Treatment of Cancer (EORTC-30) and Caregiver Quality of Life Cancer (CQOLC) scales (26). To our knowledge, only one pilot study in a small cohort of 10 patients has described the use of PROMIS as a HRQOL assessment tool in adult high-grade glioma patients (26). Here we are the first to compare

TABLE 1 | Patient demographics and clinical characteristics.

Variable	High-grade glioma ($n = 58$)	Low-grade glioma ($n = 21$)	All ($N = 79$)	p-value
Mean age, years (SD)	55.2 (15.0)	42.7 (13.6)	51.9 (15.6)	**0.01**
Mean body mass index (SD)	28.5 (5.8)	30.3 (5)	29.0 (5.6)	0.25
Gender (%)				0.06
Female	24 (41.4)	5 (23.8)	29 (36.7)	
Male	34 (58.6)	16 (76.2)	50 (63.3)	
Education (%)				0.56
Completed college	48 (82.8)	15 (71.4)	63 (79.7)	
Did not complete college	10 (17.2)	6 (28.6)	16 (20.3)	
Employment at time of diagnosis (%)				0.31
Employed	27 (46.6)	12 (57.1)	40 (50.6)	
Unemployed	31 (53.4)	9 (42.9)	39 (49.4)	
Handedness (%)				0.35
Right-handed	51 (87.9)	21 (100.0)	72 (91.1)	
Left-handed	6 (10.3)	0 (0.0)	6 (7.6)	
Both	1 (1.7)	0 (0.0)	1 (1.3)	
Smoking status (%)				0.34
Smoker	4 (6.9)	3 (14.3)	7 (8.9)	
Non-smoker	54 (93.1)	18 (85.7)	72 (91.1)	
Major presenting symptom (%)				0.60
Cognitive dysfunction	14 (24.1)	4 (19.0)	18 (22.8)	
Headaches	4 (6.9)	2 (9.5)	6 (7.6)	
Incidental	3 (5.2)	4 (19.0)	7 (8.9)	
Aphasia	10 (17.2)	2 (9.5)	12 (15.2)	
Weakness	8 (13.8)	2 (9.5)	10 (12.7)	
Seizure	19 (32.8)	7 (33.3)	26 (32.9)	
Tumor location (%)				0.22
Frontal	19 (32.8)	5 (23.8)	28 (35.4)	
Parietal	14 (24.1)	2 (9.5)	16 (20.3)	
Temporal	13 (22.4)	4 (19.0)	17 (21.5)	
Occipital	2 (3.4)	1 (4.8)	3 (3.8)	
Insular	6 (10.3)	4 (19.0)	10 (12.7)	
Other (thalamus, brainstem, cerebellum)	4 (6.9)	5 (23.8)	9 (11.4)	
Tumor side (%)				0.37
Left	29 (50.0)	9 (42.9)	38 (48.1)	
Midline	5 (8.6)	2 (9.5)	7 (8.9)	
Right	24 (41.4)	10 (47.6)	34 (43.0)	

Bold values mean significant p value (<0.05).

HRQOL using PROMIS and Neuro-QOL between adult LGG and HGG patients.

Perhaps unsurprisingly, 79.3% of all patients reported that they value quality of life over survival at the point of diagnosis. After cross sectional analysis of PROMIS and NEURO-QOL data, we found that LGG patients experienced more pain intensity and greater distress from declining physical function when compared with HGG patients. The biologic and psychological correlates to explain these differences are unclear; however, this information carries significance when caring for patients and determining clinical trial efficacy. Cognitive dysfunction is more commonly found in HGG patients; therefore distress measures in PRO domain such as pain intensity might be reported at different rates in LGG and HGG patients. We also found a high rate of impairment in the PROMIS functional domains assessed in our study population, again indicating that patient functional wellness should be carefully considered in an individualized treatment approach. Future studies may compare these prevalences to other cancer patient populations. Our results also demonstrate that aphasia severity is associated with increased anxiety and cognitive distress. We find a higher prevalence of severe aphasia in HGG patients relative to LGG, which may be due to selection bias due to small sample size or differences in intrinsic tumor biology.

TABLE 2 | Functional domain of importance and quality of life concerns influencing medical decision-making in adult patients with low- or high-grade glioma.

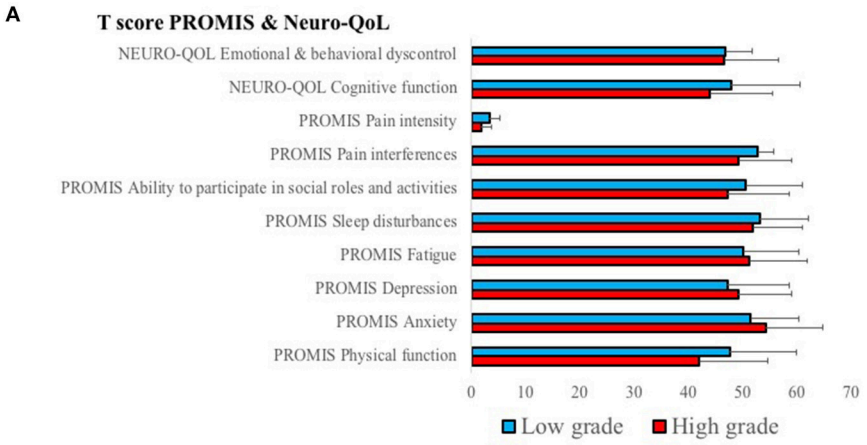
	High-grade glioma						Low-grade glioma						All						
	n	Mean	SD	SE	95% CI Lower	95% CI Upper	*n*	Mean	SD	SE	95% CI Lower	95% CI Upper	*n*	Mean	SD	SE	95% CI Lower	95% CI Upper	*p*-value
FUNCTIONAL DOMAIN																			
Mathematical abilities	58	**3.2**	1.35	0.21	2.78	3.62	21	2.75	1.34	0.34	2.04	3.47	79	**3.08**	1.35	0.18	2.72	3.43	0.258
Language	58	**4.43**	0.86	0.13	4.16	4.70	21	4.56	0.73	0.18	4.18	4.95	79	**4.47**	0.82	0.11	4.25	4.68	0.583
Motor abilities	58	**4.38**	1.06	0.16	4.05	4.71	21	4.25	1.00	0.25	3.72	4.78	79	**4.35**	1.04	0.14	4.07	4.62	0.671
Attention and distractibility	58	**4.12**	0.97	0.15	3.82	4.42	21	4.06	0.85	0.21	3.61	4.52	79	**4.10**	0.93	0.12	3.86	4.35	0.838
Memory	58	**4.24**	1.03	0.16	3.92	4.56	21	4.06	0.85	0.21	3.61	4.52	79	**4.19**	0.95	0.13	3.93	4.45	0.547
Coordination of movement	58	**4.14**	0.90	0.14	3.86	4.42	21	4.00	1.03	0.26	3.45	4.55	79	**4.10**	0.93	0.12	3.86	4.35	0.606
Music	58	**3.29**	1.27	0.20	2.89	3.68	21	2.75	1.34	0.34	2.04	3.47	79	**3.14**	1.30	0.17	2.80	3.48	0.164
Art	58	**2.91**	1.34	0.21	2.49	3.32	21	1.94	0.77	0.19	1.53	2.35	79	**2.64**	1.28	0.17	2.30	2.98	**0.009**
Creativity and problem-solving	58	**4.10**	0.88	0.14	3.82	4.37	21	3.31	1.45	0.36	2.54	4.08	79	**3.88**	1.11	0.15	3.59	4.17	**0.015**

Bold values mean significant p value (<0.05).

Glioma patients suffer from a wide range of possible neurological and functional limitations which influences quality of life and survival. Aphasia and cognitive disorders are more prevalent in patients with WHO III and IV tumors. Cognitive dysfunction, as determined by global cognitive task performance, occurs in 35.9% of HGG patients and 23.7% of patients experience aphasia throughout their disease trajectory (27). It is therefore of little surprise that our Neuro-QoL analysis determined that 43.9% of HGG patients experience distress from impairment of cognitive function (**Figure 1**). Similar results are seen for distress from physical function in HGG patients. Despite the absence of identifiable oncological differences between our LGG and HGG cohorts, pain intensity scores were higher in LGG patients (**Figure 1**). This could be caused at least in part by the increased rate of cognitive dysfunction resulting in under reporting of pain in HGG patients. These differences bring to light important considerations when interpreting PRO in the adult glioma population. Looking beyond survival, when designing clinical trials, is critical given the extensive burden of symptoms experienced by glioma patients. Furthermore, it cannot be assumed that LGG and HGG patients experience the same symptoms and distress profile.

Patient reported outcome (PRO) measures are used in clinical practice as a mechanism to understand the natural history of disease or as a health measure of clinical change. There are few publications focused on thresholds constituting meaningful clinical change. Clinical judgment must be applied for the interpretation of clinically meaningful PRO. Defining the magnitude of change that is clinically important is necessary and there's a growing body of evidence for this important area of study. There are several terms for clinically relevant HRQOL change, including, minimally important difference (MID). "True" differences do not exist in HRQOL assessments and the magnitude of a score is an estimate which must be interpreted with clinical judgment (28). There is no empirical literature on which to base MID estimate; therefore, many use a half standard deviation (5 points on a T score metric). However clinical significance has been illustrated at a lower threshold (28, 29). MID for the adult glioma population are currently unavailable and a topic of future study. For example, patients with advanced stage cancer illustrate fatigue PROMIS MID of 3.0–5.0, pain interference MID of 4.0–6.0, and physical function MID of 4.0–6.0 (29). It is important to note that MID estimates vary based on cross sectional and longitudinal analysis. Furthermore, these assessments of clinical significance are averages across subjects; therefore, individual patients may require more or less to be clinically meaningful. The objective of this study was to evaluate adult glioma patient perspectives on functional domain affecting health related quality of life and apply cross sectional analysis of the PROMIS and Neuro-QOL instruments as subjective PRO measures in an adult low and high-grade glioma patient population. MID estimates were beyond the scope of this initial study which was focused on characterization of disease. Moving forward we hope to define MID and clinical relevance in the adult glioma population.

Other study limitations include the single institution small sample size which prohibited stratification of patients by



B **Impairment Rates**

	High grade (%)	Low grade (%)
PROMIS Physical function	46.6	28.6
PROMIS Anxiety	27.6	19
PROMIS Depression	15.5	19
PROMIS Fatigue	19.3	19
PROMIS Sleep disturbances	19.3	28.6
PROMIS Ability to participate in social roles and activities	28.6	14.3
PROMIS Pain interferences	12.3	38.1
NEURO-QOL Cognitive function	43.9	23.8
NEURO-QOL Emotional & behavioral dyscontrol	5.3	14.3

FIGURE 1 | (A) PROMIS and Neuro-QoL domains were measured for low- and high-grade glioma patients. **(B)** Impairment rates were determined based on patients who scored >1 standard deviation beyond the normative mean.

TABLE 3 | Comparison of HRQOL scores for low- and high-grade glioma groups.

Variable	High-grade glioma ($n = 58$)		Low-grade glioma ($n = 21$)		η^2	*F*-value	*P*-value
	Mean	SD	Mean	SD			
Physical function	41.8	12.6	47.7	12.2	0.05	3.75	**0.05**
Anxiety	54.3	10.4	51.5	8.8	0.01	1.21	0.28
Depression	49.1	10.0	47.2	11.4	0.01	0.55	0.46
Fatigue	51.3	10.6	50.2	10.2	0.00	0.17	0.68
Sleep disturbances	52.01	9.2	53.2	9.0	0.00	0.23	0.64
Ability to participate in social roles and activities	47.2	11.4	50.7	10.4	0.02	1.44	0.23
Pain interferences	49.3	9.8	52.8	10.4	0.02	1.83	0.18
Pain intensity	1.8	2.0	3.3	3.0	0.08	6.72	**0.01**
Cognitive function	44.0	11.6	47.9	9.3	0.02	1.86	0.18
Emotional and behavioral dyscontrol	46.7	9.9	46.9	12.8	0.00	0.01	0.94

SD, standard deviation. Bold values mean significant p value (<0.05).

additional potential confounders including tumor location, volume, or burden of disease at the time of assessment. Given our small sample size, within the LGG cohort we do not see the expected distribution across male and female patients. This difference does not reach statistical difference; however, it's not in line with expected results for the general population (30). Gender differences may contribute to variations in health outcomes. These differences in PRO have been reported primarily with pain and pain related disorders; however, it is certainly possible that gender differences impact this dataset focused on adult glioma patients (31). Furthermore, pain intensity interpretation is limited given that PROMIS is specifically focused on global pain making the distinction between headaches and neuropathy impossible. It is well known that both patient perspectives and HRQOL PRO measures vary with time (32). For this reason, our current analysis focused solely on HRQOL at the time of initial

TABLE 4 | Pearson correlation coefficients comparing the impact of aphasia on health-related quality of life functional and impairment domains.

	Aphasia
Physical function	0.09
Anxiety	**−0.51**
Depression	−0.31
Fatigue	−0.20
Sleep disturbances	−0.09
Ability to participate in social roles and activities	0.00
Pain interferences	−0.03
Pain intensity	−0.08
Cognition	**0.55**
Emotional and behavioral dyscontrol	−0.27

Bold values mean significant p value (<0.05).

diagnosis with the goal of longitudinal analysis throughout the course of disease to better understand how responses change with time. This and other limitations will be mitigated by increasing the sample size in future studies. Additionally, while subjective patient PRO measures are valuable, it should be noted that they are excellent HRQOL measures of distress but not dysfunction (25). Objective measures of function should also be incorporated into patient assessment.

CONCLUSIONS

HRQOL measurements have become increasingly important in glioma research and clinical practice. There has been limited and slow progress in developing effective treatments for glioma patients. The natural history of the disease in addition to treatment related side-effects can also negatively impact patient function and HRQOL. Treatment of glioma patients should focus on both prolonging life in addition to maintaining quality of life. The PROMIS and NEURO-QOL are two measures, which are valuable for quantifying patient reported HRQOL. The current study will hopefully lead to the use of these tools in more robust clinical research and practice settings.

ETHICS STATEMENT

This study was performed in accordance with the University of Michigan institutional ethics committee (IRB- HUM00092238). The protocol was approved by the UM-IRB and all subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

NG: manuscript preparation, data analysis, data interpretation; DA, NB, EB, LW: manuscript preparation, data analysis; AB, ZM: data acquisition, data analysis; KK: data acquisition, manuscript preparation; TF, KM: data acquisition; SS, NC: concept, study design, manuscript preparation; SH-J: concept, study design, data acquisition, data analysis, manuscript preparation, manuscript editing.

FUNDING

Senior author (SH-J)—Alfred A. Taubman Foundation and Mark Trauner Brain Research Fund.

REFERENCES

1. Hervey-Jumper SL, Li J, Lau D, Molinaro AM, Perry DW, Meng L, et al. Awake craniotomy to maximize glioma resection: methods and technical nuances over a 27-year period. *J Neurosurg.* (2015) 123:325–39. doi: 10.3171/2014.10.JNS141520
2. Rouse C, Gittleman H, Ostrom QT, Kruchko C, Barnholtz-Sloan JS. Years of potential life lost for brain and CNS tumors relative to other cancers in adults in the United States, 2010. *Neuro Oncol.* (2016) 18:70–7. doi: 10.1093/neuonc/nov249
3. Perez L, Huang J, Jansky L, Nowinski C, Victorson D, Peterman A, et al. Using focus groups to inform the neuro-QOL measurement tool: exploring patient-centered, health-related quality of life concepts across neurological conditions. *J Neurosci Nurs.* (2007) 39:342–53. doi: 10.1097/01376517-200712000-00005
4. Cella DF. Methods and problems in measuring quality of life. *Support Care Cancer.* (1995) 3:11–22. doi: 10.1007/BF00343916
5. Cella DF, Bonomi AE. Measuring quality of life: 1995 update. *Oncology (Williston Park).* (1995) 9:47–60.
6. Halkett GKB, Lobb EA, Rogers MM, Shaw T, Long AP, Wheeler HR, et al. Predictors of distress and poorer quality of life in high grade Glioma patients. *Patient Educ Couns.* (2015) 98:525–32. doi: 10.1016/j.pec.2015.01.002
7. Giovagnoli AR. Quality of life in patients with stable disease after surgery, radiotherapy, and chemotherapy for malignant brain tumour. *J Neurol Neurosurg Psychiatry.* (1999) 67:358–63. doi: 10.1136/jnnp.67.3.358
8. Scheibel RS, Meyers CA, Levin VA. Cognitive dysfunction following surgery for intracerebral glioma: influence of histopathology, lesion location, and treatment. *J Neurooncol.* (1996) 30:61–9. doi: 10.1007/BF00177444
9. Weitzner MA, Meyers CA. Cognitive functioning and quality of life in malignant glioma patients: a review of the literature. *Psychooncology.* (1997) 6:169–77. doi: 10.1002/(SICI)1099-1611(199709)6:3<169::AID-PON269>3.0.CO;2-#
10. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x
11. Olson RA, Chhanabhai T, McKenzie M. Feasibility study of the Montreal Cognitive Assessment (MoCA) in patients with brain metastases. *Support Care Cancer.* (2008) 16:1273–8. doi: 10.1007/s00520-008-0431-3
12. Olson RA, Iverson GL, Carolan H, Parkinson M, Brooks BL, McKenzie M. Prospective comparison of two cognitive screening tests: diagnostic accuracy and correlation with community integration and quality of life. *J Neurooncol.* (2011) 105:337–44. doi: 10.1007/s11060-011-0595-4
13. Olson R, Tyldesley S, Carolan H, Parkinson M, Chhanabhai T, McKenzie M. Prospective comparison of the prognostic utility of the mini mental state examination and the montreal cognitive assessment in patients with brain metastases. *Support Care Cancer.* (2011) 19:1849–55. doi: 10.1007/s00520-010-1028-1
14. Mortensen GL, Jakobsen JK. Patient perspectives on quality of life after penile cancer. *Dan Med J.* (2013) 60:A4655.
15. Singer PA, Martin DK, Kelner M. Quality end-of-life care: patients' perspectives. *JAMA.* (1999) 281:163–8. doi: 10.1001/jama.281.2.163
16. Cook KF, Jensen SE, Schalet BD, Beaumont JL, Amtmann D, Czajkowski S, et al. PROMIS measures of pain, fatigue, negative affect, physical function, and social function demonstrated clinical validity across

a range of chronic conditions. *J Clin Epidemiol.* (2016) 73:89–102. doi: 10.1016/j.jclinepi.2015.08.038
17. Bode RK, Hahn EA, DeVellis R, Cella D, Patient-Reported Outcomes Measurement Information System social domain working group. Measuring participation: the patient-reported outcomes measurement information system experience. *Arch Phys Med Rehabil.* (2010) 91:S60–5. doi: 10.1016/j.apmr.2009.10.035
18. Cella D, Yount S, Rothrock N, Gershon R, Cook K, Reeve B, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. *Med Care.* (2007) 45:S3–11. doi: 10.1097/01.mlr.0000258615.42478.55
19. Quach CW, Langer MM, Chen RC, Thissen D, Usinger DS, Emerson MA, et al. Reliability and validity of PROMIS measures administered by telephone interview in a longitudinal localized prostate cancer study. *Qual Life Res.* (2016) 25:2811–23. doi: 10.1007/s11136-016-1325-3
20. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol.* (2010) 63:1179–94. doi: 10.1016/j.jclinepi.2010.04.011
21. Salsman JM, Victorson D, Choi SW, Peterman AH, Heinemann AW, Nowinski C, et al. Development and validation of the positive affect and well-being scale for the neurology quality of life (Neuro-QOL) measurement system. *Qual Life Res.* (2013) 22:2569–80. doi: 10.1007/s11136-013-0382-0
22. Chang EF, Raygor KP, Berger MS. Contemporary model of language organization: an overview for neurosurgeons. *J Neurosurg.* (2015) 122:250–61. doi: 10.3171/2014.10.JNS132647
23. Wilson SM, Lam D, Babiak MC, Perry DW, Shih T, Hess CP, et al. Transient aphasias after left hemisphere resective surgery. *J Neurosurg.* (2015) 123:581–93. doi: 10.3171/2015.4.JNS141962
24. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: L. Erlbaum Associates (1988).
25. Hickmann AK, Hechtner M, Nadji-Ohl M, Janko M, Reuter AK, Kohlmann K, et al. Evaluating patients for psychosocial distress and supportive care needs based on health-related quality of life in primary brain tumors: a prospective multicenter analysis of patients with gliomas in an outpatient setting. *J Neurooncol.* (2017) 131:135–51. doi: 10.1007/s11060-016-2280-0
26. Romero MM, Flood LS, Gasiewicz NK, Rovin R, Conklin S. Validation of the national institutes of health patient-reported outcomes measurement information system survey as a quality-of-life instrument for patients with malignant brain tumors and their caregivers. *Nurs Clin North Am.* (2015) 50:679–90. doi: 10.1016/j.cnur.2015.07.009
27. IJzerman-Korevaar M, Snijders TJ, de Graeff A, Teunissen SCCM, de Vos FYF. Prevalence of symptoms in glioma patients throughout the disease trajectory: a systematic review. *J Neurooncol.* (2018) 140:485–96. doi: 10.1007/s11060-018-03015-9
28. Kozlowski AJ, Cella D, Nitsch KP, Heinemann AW. Evaluating individual change with the quality of life in neurological disorders (neuro-QoL) short forms. *Arch Phys Med Rehabil.* (2016) 97:650–4.e8. doi: 10.1016/j.apmr.2015.12.010
29. Yost KJ, Eton DT, Garcia SF, Cella D. Minimally important differences were estimated for six patient-reported outcomes measurement information system-cancer scales in advanced-stage cancer patients. *J Clin Epidemiol.* (2011) 64:507–16. doi: 10.1016/j.jclinepi.2010.11.018
30. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. *Neuro Oncol.* (2018) 20:iv1–86. doi: 10.1093/neuonc/noy131
31. Chow S, Ding K, Wan BA, Brundage M, Meyer RM, Nabid A, et al. Gender differences in pain and patient reported outcomes: a secondary analysis of the NCIC CTG SC. 23 randomized trial. *Ann Palliat Med.* (2017) 6:S185–94. doi: 10.21037/apm.2017.08.12
32. Sagberg LM, Solheim O, Jakola AS. Quality of survival the 1st year with glioblastoma: a longitudinal study of patient-reported quality of life. *J Neurosurg.* (2016) 124:989–97. doi: 10.3171/2015.4.JNS15194

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

ORIGINAL RESEARCH
published: 23 April 2019
doi: 10.3389/fonc.2019.00299

Impacts of Surgery on Symptom Burden and Quality of Life in Pituitary Tumor Patients in the Subacute Post-operative Period

*Mark R. Waddle[1], Mollie D. Oudenhoven[2], Casey V. Farin[3], Allison M. Deal[4], Riane Hoffman[5], Hojin Yang[4], Jennifer Peterson[1], Terri S. Armstrong[6], Matthew G. Ewend[5] and Jing Wu[6]**

[1] Department of Radiation Oncology Mayo Clinic, Jacksonville, FL, United States, [2] Department of Pediatrics, University of Colorado, Denver, CO, United States, [3] Department of Neurology, Duke University, Durham, NC, United States, [4] Lineberger Comprehensive Cancer Center Biostatistics Core Facility, UNC, Chapel Hill, NC, United States, [5] Department of Neurosurgery, University of North Carolina, Chapel Hill, NC, United States, [6] Neuro-Oncology Branch, National Cancer Institute/National Institutes of Health, Bethesda, MD, United States

OPEN ACCESS

Edited by:
Sujit Prabhu,
University of Texas MD Anderson Cancer Center, United States

Reviewed by:
David D. Eisenstat,
University of Alberta, Canada
David M. Peereboom,
Cleveland Clinic Lerner College of Medicine, United States

***Correspondence:**
Jing Wu
jing.wu3@nih.gov

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: 30 August 2018
Accepted: 01 April 2019
Published: 23 April 2019

Citation:
Waddle MR, Oudenhoven MD, Farin CV, Deal AM, Hoffman R, Yang H, Peterson J, Armstrong TS, Ewend MG and Wu J (2019) Impacts of Surgery on Symptom Burden and Quality of Life in Pituitary Tumor Patients in the Subacute Post-operative Period. Front. Oncol. 9:299. doi: 10.3389/fonc.2019.00299

Background: Pituitary tumors are rare but are associated with significant symptoms that impact patients' quality of life (QOL). Surgery remains one of the most effective treatment options for long term disease control and symptom benefit, but symptom, and quality of life recovery in the subacute period has not been previously reported. This study aimed to better understand the impact of surgery on patients' symptom burden and QOL in the subacute post-surgical period.

Methods: Twenty-three adult patients with pituitary tumors undergoing surgical resection at University of North Carolina Cancer Hospital were enrolled in this study. M.D. Anderson Symptom Inventory Brain Tumor Module, European Organization for Research and Treatment of Cancer QLQ-C30 and QLQ-BN20 questionnaires were collected pre- and 1-month post- surgical resection and differences were analyzed for individual and groups of symptoms and QOL using Wilcoxon signed-rank tests.

Results: Twenty adult patients had both pre-operation and post-operation follow-up visits; 60% had functional pituitary adenomas. Seven symptoms including fatigue, memory, vision, numbness, speaking, appearance, and weakness were significantly improved at the 1-month post-operation visit while one symptom, sleep, worsened. Global Health Status/QOL measurements was improved minimally from 63 (SD 25) at pre-operation to 67 (SD 22) at 1-month post-operation without statistical significance.

Conclusions: This study demonstrated a rapid improvement of many symptoms in the subacute post-operative period in pituitary tumor patients. Disturbed sleep was identified as the only symptom to worsen post-operatively, encouraging potential prospective interventions to improve sleep, and subsequently improve the QOL in pituitary tumor patients following surgical intervention.

Keywords: pituitary, adenoma, surgery, QOL, subacute, post-operative

INTRODUCTION

Pituitary tumors are relatively rare primary central nervous system (CNS) tumors in adults (1) but make up 10% of all neurosurgical interventions in the United States (2). They are often an incidental finding in autopsies and brain imaging studies (3). Although these tumors are usually benign, pituitary tumors have a significant impact on a patient's health and have been shown to cause cognitive dysfunction (4, 5), visual deficits (6–8), headaches (7), and an overall decline in quality of life (QOL) at the time of diagnosis (3, 8, 9). Multiple studies have demonstrated the adverse clinical effects of these tumors at presentation, yet there are little data to describe how these symptoms, and thus QOL, are impacted with treatment. Surgery, the primary definitive treatment for these tumors, carries risk of damage to surrounding structures such as the internal carotid artery and optic nerve, CSF leak, and/or hormone abnormalities (10). Van der Klaauw's group showed that patients with all subtypes of pituitary tumors experienced decreased QOL as far as 10–15 years after treatment when compared with healthy controls, but the added impact of surgery on these outcomes was not described (11, 12). Other studies have shown improved sino-nasal functioning in the long term, but have mixed results in the subacute period (13). Further, there is currently limited evidence for the impact of surgery on many other important quality of life metrics which may impact a patient's ability to function (13–15).

The burden of patient symptoms and QOL is an essential consideration and has been increasingly recognized in literature as a primary end point for both benign and malignant tumors (16–18). The World Health Organization defines QOL as "an individual's perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" (7). The importance of the symptom and QOL endpoint in oncology care has resulted in a multitude of validated scales and surveys which are routinely used in research and in practice. The goal of this study is to characterize the common symptoms, side effects, and overall QOL of patients with pituitary tumors before and after surgical intervention in the subacute period with the use of validated QOL instruments. Additionally, we hope this study will help identify potential biologic underpinnings and guide early intervention, symptom screening following intervention, and to aid in general clinical management to further improve QOL in patients with pituitary tumors who undergo surgical resection.

MATERIALS AND METHODS

Patient Population

This is a prospective study using validated questionnaires of symptom burden and QOL. The study was undertaken in accordance of Good Clinical Practice guidelines and the Declaration of Helsinki. All eligible patients were provided with IRB-approved consent forms and all participating patients provided written informed consent. Approvals for the study protocol and consent forms were obtained from the Institutional Review Board (IRB) at the University of North Carolina at Chapel Hill (UNC).

Eligible patients were 18 years old or above, English speaking, with adequate mental capacity to fill out questionnaire, and no other malignancy that required active anti-neoplastic treatment in the past 3 years. All patients had histological diagnosis of pituitary tumor at UNC from June 2011 to March 2014.

Study Design

With UNC IRB approval, all eligible patients were provided with informed consent forms. Patients were given the questionnaires including M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT), European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-BN20, at their pre-operative clinic visit within 7 days prior to surgery. Longitudinal follow up was completed with the same pre-operative surveys given post-operatively at 1 month after surgery, which was defined as the "Sub-acute post-surgical period." Patients without histological diagnosis of pituitary tumors were considered non-evaluable after the pathology reports were reviewed.

Outcome Assessment

Three extensively validated symptom inventory questionnaires were selected to assess patient's symptom burden and QOL: the MDASI-BT, EORTC QLQ-C30, and EORTC QLQ-BN20. Baseline and one-month post-operative symptom burden and QOL scores were recorded for each questionnaire. Changes relative to baseline were calculated for each patient and those values were averaged and reported for symptom scores and QOL.

MDASI-BT

MDASI-BT consists of 28 questions which can be completed in an average time of 5–10 min. It is composed of questions rated on an 11-point scale (0–10) to indicate the presence and severity of each symptom in the last 24 h, with 0 being "not present" and 10 being "as bad as you can imagine." A total of 28 questions include 22 symptom questions (13 core symptoms, 9 brain-tumor-specific symptoms) (19, 20) and six interference with life questions, which are further divided into activity and mood-related items. The 22 symptom specific questions on MDASI-BT also measure six underlying constructs: (1) an affective factor comprised of distress, fatigue, sleep, sadness, and irritability, (2) a cognitive factor comprised of difficulty understanding, remembering, speaking and concentrating, (3) focal neurological deficits factor, including seizure, numbness, pain, and weakness, (4) treatment-related symptoms such as dry mouth, drowsiness, and appetite, (5) generalized disease status symptoms, including change in vision, change in appearance, change in bowel patterns, and shortness of breath, and (6) GI related factors, including nausea and vomiting (20). Symptoms on the MDASI-BT are those common in the brain tumor population as well as those associated with cancer therapies. The MDASI-BT has evidence of content and construct validity, discriminant validity by performance status and disease progression, and internal consistency (20).

TABLE 1 | Patient Characteristics for Studied Subjects.

Characteristic	Category	Total (percentage)
Age	<65 years	18 (90)
Mean: 51	>65 years	2 (10)
GENDER		
	Male	10 (50)
	Female	10 (50)
RACE		
	White	14 (70)
	Black	6 (30)
BASELINE KPS		
	80	12 (60)
	90	8 (40)
	100	0 (0)
Cellular classification of pituitary tumor	Non-functional adenoma	8 (40)
	Prolactinoma	6 (30)
	GH secreting pituitary adenoma	4 (20)
	Pituitary tumor secreting >1 hormone	2 (10)

KPS, Karnofsky Performance Status; GH, Growth Hormone.

EORTC QLQ-C30 and QLQ-BN20

EORTC QLQ-C30 (Version 3.0) is composed of 30 questions organized into a global health status/QOL scale that include 5 functional scales (physical, role, emotional, cognitive, and social), 3 symptom scales (fatigue, nausea and vomiting, and pain), and a number of single items assessing additional difficulties (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

EORTC QLQ-Brain Cancer Module (EORTC QLQ-BN20) is a supplement to the EORTC QLQ-C30 specifically designed for brain tumor patients and consists of 20 questions scored as four multi-item scales (future uncertainty, visual disorder, motor dysfunction, and communication deficit) and seven single-item symptom scales (headaches, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control).

The responses to both questionnaires were scored as outlined in the QLQ-C30 scoring manual to a score from 0–100 where a higher score represents a high/healthy level of functioning and a high quality of life, but a high level of symptomatology/problems, depending on the question (21, 22).

Statistical Analysis

Descriptive statistics are provided for patient characteristics and questionnaire results. Wilcoxon signed-rank tests are used to evaluate if changes in symptom burden and QOL were significantly different compared to baseline for both the symptom burden and QOL, and unadjusted *p*-values are reported. All analysis was done using SAS software v9.3 (Cary, NC).

RESULTS

Patient Characteristics

A total of 23 patients diagnosed with a pituitary tumor at UNC hospital from June 2011 to March 2014 completed pre-operative questionnaires. Of these, one subject withdrew, one did not have surgery, and one subject was lost to follow up. The remaining 20 subjects underwent first time surgery for a pituitary tumor and completed the 1 month follow up questionnaire in the subacute surgical period.

Age of all evaluable patients ranged from 24 to 77 years with a median age of 49 years and 50% were male. The baseline Karnofsky Performance Score (KPS) ranged from 80 to 90. Functional adenomas were most common representing 60% of all studied patients including 30% prolactinomas and 20% GH secreting adenomas (**Table 1**).

TABLE 2A | MDASI symptom severity score and standard deviation for each symptom at pre-operation and 1 month post-operation.

How severe is your _____ at its worst (0-10)	Pre-op (*SD*)	One month Post-op (*SD*)
Fatigue	**5.0 ± 2.7**	3.4 ± 2.4 ▼
Pain	3.9 ± 3.5	3.0 ± 3.4
Impaired memory	3.7 ± 2.8	2.3 ± 2.1 ▼
Drowsiness	3.6 ± 3.4	3.4 ± 3.0
Vision	3.4 ± 2.9	1.0 ± 1.0 ▼
Disturbed sleep	3.1 ± 2.9	**4.8 ± 3.2** ▲
Numbness/tingling	3.1 ± 2.9	1.7 ± 2.9 ▼
Feeling distressed	2.9 ± 3.3	3.0 ± 3.4
Irritability	2.7 ± 3.2	2.3 ± 3.1
Lack of appetite	2.3 ± 3.0	1.4 ± 2.5
Difficulty concentrating	2.2 ± 2.7	1.2 ± 1.3
Nausea	2.1 ± 3.0	0.6 ± 1.4
Shortness of breath	2.0 ± 2.4	1.1 ± 1.9
Dry mouth	1.9 ± 3.0	2.3 ± 2.7
Difficulty speaking	1.8 ± 2.4	0.8 ± 1.2 ▼
Appearance	1.8 ± 2.0	0.4 ± 1.0 ▼
Sadness	1.6 ± 2.5	1.6 ± 2.6
Change in bowel pattern	1.5 ± 2.5	1.6 ± 2.0
Weakness on one side	1.4 ± 2.3	0.4 ± 1.0 ▼
Difficulty understanding	0.8 ± 1.3	0.7 ± 1.2
Vomiting	0.8 ± 1.7	0.1 ± 0.2
Seizures	0.2 ± 0.5	0.4 ± 1.2
HOW HAVE YOUR SYMPTOMS INTERFERED WITH: (0–10)		
Work	**3.4 ± 3.8**	**2.5 ± 2.9**
General activity	3.2 ± 3.4	1.8 ± 2.6 ▼
Enjoyment of life	2.8 ± 3.2	1.6 ± 2.7 ▼
Mood	2.7 ± 3.0	2.2 ± 2.9
Walking	2.4 ± 3.3	1.0 ± 1.9 ▼
Relations	1.9 ± 2.7	1.6 ± 2.7

Symptoms with a statistically significant change ($p < 0.05$) relative to pre-operative values are marked with an arrow, indicating the direction of change. (▼ indicates less symptoms, ▲ indicates more symptoms). The most severe symptoms for each time point are marked with bold text.

Symptom Burden Questionnaire Results

MDASI-BT symptom severity scores are shown in **Table 2A**. Pre-operative MDASI-BT questionnaire results showed the most severe symptom was fatigue, with mean

TABLE 2B | MDASI symptom severity main category and subcategory scores, and standard deviation for each symptom group at pre-operation and 1 month post-operation.

How severe is your _____ at its worst (0–10)	Pre-op ± *SD*	One month Post-op ± *SD*
MDASI MAIN GROUPINGS (0–10)		
Interference with Life	**3.0 ± 3.3**	1.7 ± 2.1 ▼
22 Symptoms (Core + Brain Tumor Specific)	2.4 ± 1.8	**1.7 ± 1.4**
MDASI SUBCATEGORY GROUPINGS (0–10)		
Affective factors	**3.0 ± 2.2**	**3.0 ± 2.5**
Treatment related	2.6 ± 2.4	2.3 ± 2.1
Cognitive	2.2 ± 2.0	1.3 ± 1.0 ▼
Neurologic	2.2 ± 1.7	1.5 ± 1.7 ▼
Generalized disease	2.2 ± 1.7	1.0 ± 1.0 ▼
Gastrointestinal	1.4 ± 2.1	0.3 ± 0.7 ▼

Symptoms with a statistically significant change ($p < 0.05$) relative to pre-operative values are marked with an arrow indicating the direction of change. (▼indicates less symptoms, ▲indicates more symptoms). The most severe symptoms for each time point are marked with bold text.

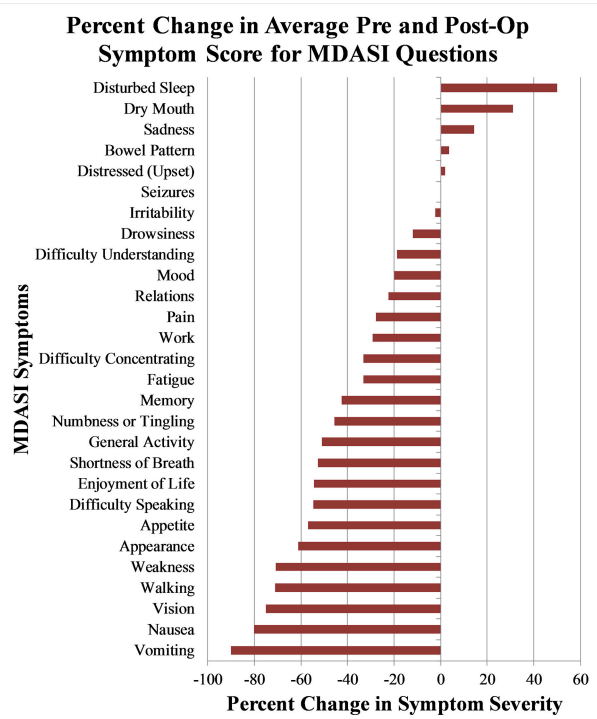


FIGURE 1 | Percentage change of mean MDASI-BT symptom severity score between pre-operative questionnaire and 1 month post-operative questionnaires.

(standard deviation) severity scores of 5.0 (SD 2.7). Seizure was the least severe symptom with mean scores of 0.2 (SD 0.5).

At 1-month post-operation, only one symptom, disturbed sleep, significantly worsened with a mean symptom severity score of 4.8 (*SD* 3.2, $p = 0.03$), a 55% increase from the baseline value of 3.5. Seizures also worsened by 166% from 0.15 (*SD* 0.5) to 0.4 (*SD* 1.2), and dry mouth slightly worsened from 1.9 (*SD* 3.0) to 2.3 (*SD* 2.7), both of which were small absolute changes and statistically non-significant. For the same time point, significant improvements were found in fatigue, impaired memory, vision, numbness/tingling, difficulty speaking, appearance, and weakness. The symptom that improved the most was vision, with a symptom severity score of 1.0 (*SD* 1.0), an improvement of 71% from the baseline. The percentage change of symptom severity score from baseline for all measured items can be seen in **Figure 1**.

The mean symptom severity scores for all symptoms pre-operation and 1-month post-operation were 2.3 (*SD* 1.2) and 1.7 (*SD* 1.2), respectively. In the interference with life category, three areas significantly improved from pre-operation to 1-month post-operation: general activity, enjoyment of life, and walking ($p < 0.05$).

Aggregate scores and their changes were calculated for the two MDASI-BT main categories and six MDASI-BT sub-categories, shown in **Table 2B**. Interference with life was significantly improved at 1-month post-operation, with a 43% improvement from the baseline. When the 22 symptom specific questions were analyzed in subgroups measuring six underlying constructs, four subgroups, including cognitive, neurologic, generalized disease, and gastrointestinal related factors were significantly improved by 41, 32, 55, and 79% from baseline, respectively, at 1-month post-operation follow-up ($p < 0.05$). Affective related factors did not show significant improvement at 1-month follow-up. The percent changes from baseline for the six subgroups are shown in **Figure 2**.

Quality of Life Results

EORTC QLQ-C30 and QLQ-BN20 questionnaire results are shown in **Table 3**. Pre-operatively, the most severe symptoms were headaches, drowsiness, fatigue, pain, and insomnia. Headaches were most severe with a symptom severity score of 53 (*SD* 35). The least severe was seizures with a symptom score of 0.

By 1-month post-operation, the symptom that improved the most was visual disorders, which improved by 67%, while insomnia worsened the most, by 33%. Headaches remained the most severe symptom at 47 (*SD* 40). Statistically significant improvements were shown in cognitive functioning ($p < 0.01$) and visual disorders ($p < 0.01$) from pre-operation to 1-month post- operation.

Global status of health/QOL was stable from pre-operative baseline to 1-month post-operation with scores of 63 (*SD* 25) and 67 (*SD* 22), respectively, an improvement of 5%.

DISCUSSION

This study is consistent with prior studies and demonstrates that the majority of patients are symptomatic prior to intervention (11, 12). However, we successfully showed a novel finding that

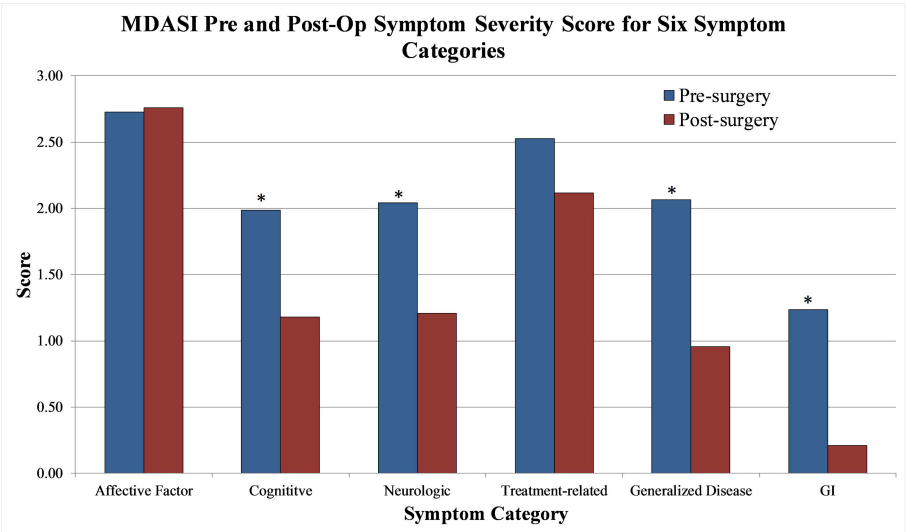


FIGURE 2 | MDASI-BT symptom severity score pre-operative and 1 month post-op for six symptom categories.

in this group of otherwise healthy individuals, many symptoms improve rapidly with surgical intervention, as outlined in the result section above.

The initial improvement in vision was expected. Vision loss is a well-known symptom of pituitary tumors due to compression of the overlying optic chiasm and nerves which improves rapidly following surgical decompression and removal of the tumor (6). However, many other symptoms including fatigue, memory, appearance, difficulty speaking, numbness, and appetite showed improvement in the subacute post-operative period in this study, which is a finding with little to no prior data for comparison in this patient population.

Two interference items, walking and enjoyment of life also improved. In fact, the interference with life category and four of six subcategories for symptom burden in MDASI-BT (cognitive, neurologic, generalized disease, and gastrointestinal) showed statistically significant improvement at 1-month post-operation, as shown in **Table 2B**, demonstrating a multitude of improvements in symptom burden and quality of life. These findings may be useful in counseling patients' suffering from these symptoms or clinicians looking to weigh the risk/benefit ratio of surgery for a given patient.

Patients' functioning improved as well. Self-reported measures of cognitive functioning improved significantly from pre-operation to 1-month post-operation, while role functioning, emotional functioning, physical functioning and social functioning remained the same.

Our findings are unique. A prior study by Glicksman et al. showed that at 3 months post-operatively there was a significant improvement of sino-nasal symptoms per the Sinonasal Outcome Test (SNOT-22), which demonstrated improvements in Rhinologic, Extranasal, Ear/facial, Psychological, and Sleep domains, that continued to improve over a 2 year period (23). However, this study failed to report on either acute or subacute changes in QOL. Another study by McCoul et al. (13) reported generalized symptom burden at 3 weeks and showed transient overall worsening of symptoms at this time point, driven largely by site specific factors such as intranasal edema, crusting, and hyposmia, but reported minimal to no improvement in other quality of life endpoints until 6–12 weeks post-operatively (13). However, these studies were both limited by the quality of life metrics they reported on and did not test for symptoms which showed dramatic improvements in our study, such as memory, appearance, difficulty speaking, numbness, appetite, cognitive function, walking, and enjoyment of life. Therefore, our findings are encouraging that, despite a possible worsening of surgery related symptoms in the subacute surgical period after sino-nasal resection shown in prior studies, many symptoms that can have a dramatic impact on a patient's QOL did improve rapidly. Additionally, we found that the MDASI-BT in this patient population was an excellent test to accurately define quality of life changes which are pertinent and important. The MDASI-BT has evidence of content and construct validity, discriminant validity by performance status and disease progression, and internal consistency. For this reason, we encourage its use for patients undergoing treatment of pituitary adenomas. However, more extensive research and experiences of evaluating pituitary patients with current QOL questionnaires may lead to a pituitary specific QOL instrument, which could better serve this patient population.

One symptom, disturbed sleep, did show worsening in the subacute period 1-month post-operation and was the most severe symptom following surgery in our studied patients. Disturbed sleep increased from a low range severity before surgery to nearly high range severity after surgery, an increase of 55%. Similarly, insomnia increased in severity by 33% in the EORTC-C30 questionnaire testing, but without statistical significance. Impairments in sleep have been previously described in patients with cancer, and may correlate with decreased total and free

TABLE 3 | EORTC QLQ-C30 and BN20 scaled scores and standard deviation for each symptom at pre-operation and 1 month post-operation.

QLQ-C30 during the past week, have you had trouble with: (0–100)	**Pre-op ± *SD***	**One month Post-op ± *SD***
Fatigue	**31 ± 24**	35 ± 30
Pain	**31 ± 27**	34 ± 36
Insomnia	30 ± 32	**40 ± 34**
Financial difficulties	28 ± 35	25 ± 36
Constipation	19 ± 30	18 ± 26
Dyspnea	17 ± 23	18 ± 28
Nausea and vomiting	13 ± 19	5 ± 15
Appetite loss	13 ± 17	12 ± 27
Diarrhea	8 ± 15	7 ± 17
FUNCTIONAL SCALES (0–100)		
Cognitive functioning	71 ± 29	79 ± 22▲
Role functioning	75 ± 29	73 ± 31
Emotional functioning	78 ± 24	77 ± 27
Physical functioning	82 ± 19	80 ± 25
Social functioning	83 ± 27	81 ± 32
Global health status/QoL (0–100)	**63 ± 25**	**67 ± 22**
BN-20 during the past week, have you had trouble with: (0–100)		
Headaches	**53 ± 35**	**47 ± 40**
Drowsiness	37 ± 29	25 ± 24▼
Visual disorder	24 ± 27	8 ± 13▼
Itchy skin	23 ± 34	12 ± 20
Future uncertainty	21 ± 27	12 ± 17
Weakness of legs	20 ± 33	13 ± 23
Motor dysfunction	16 ± 23	16 ± 22
Communication deficit	16 ± 23	12 ± 20
Hair loss	12 ± 27	9 ± 24
Bladder control	10 ± 24	5 ± 16
Seizures	0 ± 0	2 ± 8

Symptoms with a statistically significant change ($p < 0.05$) relative to pre-operative values are marked with an arrow indicating the direction of change. (▼indicates less symptoms, ▲indicates improved functioning) The most severe symptoms and the lowest level of functioning for each time point are marked with bold text.

cortisol levels, due to a disrupted hypothalamus-pituitary-adrenal (HPA) axis (24). Our patients had similar sleep impairments, and our findings suggest that pituitary surgery for pituitary tumors may temporarily further disrupt the HPA axis, possibly worsening an already impaired sleep-wake cycle. Alternatively, the patient's daily routine may be temporarily altered leading to poor sleep hygiene, and the patients may be on treatment such as steroids which are known to have side effects such as disturbed sleep. Regardless of the underlying cause, disturbed sleep is likely a symptom that could benefit from routine screening possibly with sleep studies, avoidance of steroids if possible, and/or prophylactic treatment post-operatively, and prior studies are encouraging in that this symptom significantly improves by 6 months to 12 months post-operatively (23).

Another troubling symptom on the secondary questionnaire testing was headaches, which was the most severe symptom reported in both pre-operative and post-operative surveys. This symptom marginally improved from baseline with an improvement of 11% at 1-month post-operation, although not statistically significant. While this is a symptom well known to clinicians treating pituitary tumors, the severity and lack of change with treatment indicate that, on average, patients are experiencing significant distress from this symptom. Continued attention should be given to symptomatic relief of headaches even after resection, as surgical treatment is not expected to dramatically improve this problem, at least in this studied population.

This study has several limitations. The primary limitations, and ones common to studies of pituitary tumors, was that the sample size obtained was not large and thus only powered to detect large differences, and that limited follow-up data is available to assess for further longitudinal effects. Although the study took place at a large academic hospital with a robust pituitary program, the number of patients undergoing first time pituitary surgery was not as large as predicted, and there were several gaps in patient accrual. Additionally, several patients were excluded for not speaking English, as described in the inclusion criteria. As a result, there were 20 patients followed to 1-month post-operation. While a size of 20 subjects was adequate to find statistical significance in very large changes, it is likely that many more subtle changes were not identified. As an example, sleep disturbance was found to have a statistically significant worsening after surgery on the MDASI-BT, whereas insomnia was worse, but not statistically significant on EORTC QLQ-C30. This is likely a matter of sample size resulting in two validated questionnaires yielding similar results, yet only one reaching statistical significance. Future studies could be improved by collaboration with multiple other institutions to increase accrual and by having questionnaires and consent forms available in multiple languages.

Finally, we were unable to conduct a sub-group analysis between pituitary tumor types, hormone status, or patient demographics. Studies have shown symptoms vary between pituitary tumor groups and hormone status. For example, appearance score has been found to be the worst in patients with acromegaly, and patients with Cushing disease secondary to pituitary adenomas have the most impaired QOL (7, 12). Sub-group analysis would allow physicians to identify certain patient groups with more severe symptoms to better target symptom control or prevention.

Despite the above limitations, we believe that this study has important clinical implications. This study successfully prospectively characterizes specific symptoms which have previously not been investigated in pituitary adenomas. A strength of this study is that, to our knowledge, it is the first prospective study examining symptom burden in a number of measures following pituitary tumor surgery. Additionally, the use of comprehensive and very well validated questionnaires, MDASI-BT, EORTC-C30, and EORTC-BN20, allowed a complete assessment of symptoms in this disease group. We successfully identified sleep disturbance and headaches as symptoms that can be targeted clinically either with improved monitoring, pre-emptive treatment, and/or prospective future study. The study results also identified several other symptoms which significantly improved after the surgery. Future

interventional studies may include multi-centered collaboration with well-established research infrastructure for the investigation of symptom burden and health related quality of life. We hope these data will aid clinicians both in pre-operative and post-operative patient counseling, provide clinicians with improved awareness of troublesome symptoms associated with surgery, and continue the progress being made in the quality of life of brain tumor patients.

ETHICS STATEMENT

The study was undertaken in accordance of Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided their written informed consent. Approvals for the study protocol and consent forms were obtained from the Institutional Review Board (IRB) at the University of North Carolina at Chapel Hill (UNC). Eligible patients were of or above 18 years old.

AUTHOR CONTRIBUTIONS

JW, TA, ME, CF, MO, JP, and MW contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. AD and HY contributed to the statistical analysis. RH contributed to design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

REFERENCES

1. Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. *Neuro Oncol.* (2013) 15 (Suppl. 2):1–56. doi: 10.1093/neuonc/not151
2. Johnson MD, Woodburn CJ, Vance ML. Quality of life in patients with a pituitary adenoma. *Pituitary.* (2003) 6:81–7. doi: 10.1023/B:PITU.0000004798.27230.ed
3. Lleva RR, Inzucchi SE. Diagnosis and management of pituitary adenomas. *Curr Opin Oncol.* (2011) 23:53–60. doi: 10.1097/CCO.0b013e328341000f
4. Fairfield WP. Neurocognitive dysfunction in patients with pituitary adenomas, neuroendocrine. *Bull Newslett Bullet.* (1998) 4:Winter. Available online at: https://pituitary.mgh.harvard.edu/NCBV5I1.htm
5. Guinan EM, Lowy C, Stanhope N, Lewis PD, Kopelman MD. Cognitive effects of pituitary tumours and their treatments: two case studies and an investigation of 90 patients. *J Neurol Neurosurg Psychiatry.* (1998) 65:870–6. doi: 10.1136/jnnp.65.6.870
6. Okamoto Y, Okamoto F, Yamada S, Honda M, Hiraoka T, Oshika T. Vision-related quality of life after transsphenoidal surgery for pituitary adenoma. *Invest Ophthalmol Vis Sci.* (2010) 51:3405–10. doi: 10.1167/iovs.09-3763
7. Pereira-Neto A, Borba AM, Mello PA, Naves LA, Araújo AS Jr, Casulari LA. Mean intrasellar pressure, visual field, headache intensity and quality of life of patients with pituitary adenoma. *Arq Neuropsiquiatr.* (2010) 68:350–4. doi: 10.1590/S0004-282X2010000300004
8. Karabatsou K, O'Kelly C, Ganna A, Dehdashti AR, Gentili F. Outcomes and quality of life assessment in patients undergoing endoscopic surgery for pituitary adenomas. *Br J Neurosurg.* (2008) 22:630–5. doi: 10.1080/02688690802220379
9. Budrukkar A, Jalali R, Dutta D, Sarin R, Devlekar R, Parab S, et al. Prospective assessment of quality of life in adult patients with primary brain tumors in routine neurooncology practice. *J Neurooncol.* (2009) 95:413–9. doi: 10.1007/s11060-009-9939-8
10. Ciric I, Ragin A, Baumgartner C, Pierce D. Complications of transsphenoidal surgery: results of a national survey, review of the literature, and personal experience. *Neurosurgery.* (1997) 40:225–36; discussion 236–7. doi: 10.1097/00006123-199702000-00001
11. Santos A, Resmini E, Martínez MA, Martí C, Ybarra J, Webb SM. Quality of life in patients with pituitary tumors. *Curr Opin Endocrinol Diabetes Obes.* (2009) 16:299–303. doi: 10.1097/MED.0b013e32832cdec9
12. van der Klaauw AA, Kars M, Biermasz NR, Roelfsema F, Dekkers OM, Corssmit EP, et al. Disease-specific impairments in quality of life during long-term follow-up of patients with different pituitary adenomas. *Clin Endocrinol.* (2008) 69:775–84. doi: 10.1111/j.1365-2265.2008.03288.x
13. McCoul ED, Bedrosian JC, Akselrod O, Anand VK, Schwartz TH. Preservation of multidimensional quality of life after endoscopic pituitary adenoma resection. *J Neurosurg.* (2015) 123:813–20. doi: 10.3171/2014.11.JNS14559
14. McCoul ED, Anand VK, Schwartz TH. Improvements in site-specific quality of life 6 months after endoscopic anterior skull base surgery: a prospective study. *J Neurosurg.* (2012) 117:498–506. doi: 10.3171/2012.6.JNS111066
15. Little AS, Kelly DF, Milligan J, Griffiths C, Prevedello DM, Carrau RL, et al. Comparison of sinonasal quality of life and health status in patients undergoing microscopic and endoscopic transsphenoidal surgery for pituitary lesions: a prospective cohort study. *J Neurosurg.* (2015) 123:799–807. doi: 10.3171/2014.10.JNS14921
16. Mahner S, Burges A. Quality of life as a primary endpoint in ovarian cancer trials. *Lancet Oncol.* (2014) 15:363–4. doi: 10.1016/S1470-2045(14)70084-1
17. Armstrong TS, Vera-Bolanos E, Gning I, Acquaye A, Gilbert MR, Cleeland C, et al. The impact of symptom interference using the MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) on prediction of recurrence in primary brain tumor patients. *Cancer.* (2011) 117:3222–8. doi: 10.1002/cncr.25892
18. Armstrong TS. Measuring clinical benefit: use of patient-reported outcomes (PRO) in primary brain tumor clinical trials. *Curr Oncol Rep.* (2013) 15:27–32. doi: 10.1007/s11912-012-0276-2
19. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer.* (2000) 89:1634–46.
20. Armstrong TS, Mendoza T, Gning I, Gring I, Coco C, Cohen MZ, et al. Validation of the M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT). *J Neurooncol.* (2006) 80:27–35. doi: 10.1007/s11060-006-9135-z
21. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The european organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* (1993) 85:365–76. doi: 10.1093/jnci/85.5.365
22. Fayers ANPM, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. *The EORTC QLQ-C30 Scoring Manual (3rd Edn).* European Organisation for Research and Treatment of Cancer (2001).
23. Glicksman JT, Parasher AK, Brooks SG, Workman AD, Lambert JL, Bergman JE, et al. Sinonasal quality of life after endoscopic resection of malignant sinonasal and skull base tumors. *Laryngoscope.* (2018) 128:789–93. doi: 10.1002/lary.26833
24. Wu HS, Davis JE, Natavio T. Fatigue and disrupted sleep-wake patterns in patients with cancer: a shared mechanism. *Clin J Oncol Nurs.* (2012) 16:E56–68. doi: 10.1188/12.CJON.E56-E68

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

MINI REVIEW
published: 21 May 2019
doi: 10.3389/fonc.2019.00374

Radiomics in Glioblastoma: Current Status and Challenges Facing Clinical Implementation

*Ahmad Chaddad[1], Michael Jonathan Kucharczyk[1], Paul Daniel[1], Siham Sabri[2,3], Bertrand J. Jean-Claude[3,4], Tamim Niazi[1] and Bassam Abdulkarim[1,3]**

[1] Division of Radiation Oncology, Department of Oncology, McGill University, Montreal, QC, Canada, [2] Department of Pathology, McGill University, Montreal, QC, Canada, [3] Research Institute of the McGill University Health Centre, Glen Site, Montreal, QC, Canada, [4] Department of Medicine, McGill University, Montreal, QC, Canada

Radiomics analysis has had remarkable progress along with advances in medical imaging, most notability in central nervous system malignancies. Radiomics refers to the extraction of a large number of quantitative features that describe the intensity, texture and geometrical characteristics attributed to the tumor radiographic data. These features have been used to build predictive models for diagnosis, prognosis, and therapeutic response. Such models are being combined with clinical, biological, genetics and proteomic features to enhance reproducibility. Broadly, the four steps necessary for radiomic analysis are: (1) image acquisition, (2) segmentation or labeling, (3) feature extraction, and (4) statistical analysis. Major methodological challenges remain prior to clinical implementation. Essential steps include: adoption of an optimized standard imaging process, establishing a common criterion for performing segmentation, fully automated extraction of radiomic features without redundancy, and robust statistical modeling validated in the prospective setting. This review walks through these steps in detail, as it pertains to high grade gliomas. The impact on precision medicine will be discussed, as well as the challenges facing clinical implementation of radiomic in the current management of glioblastoma.

Keywords: brain, cancer, diagnosis, glioma, MRI, radiomics, glioblastoma

OPEN ACCESS

Edited by:
Marcos Vinicius Calfat Maldaun, Hospital Sírio-Libanês, Brazil

Reviewed by:
Sunit Das, St. Michael's Hospital, Canada
Riccardo Soffietti, University of Turin, Italy

***Correspondence:**
Bassam Abdulkarim
bassam.abdulkarim@mcgill.ca

Specialty section:
This article was submitted to Neuro-Oncology and Neurosurgical Oncology, a section of the journal Frontiers in Oncology

Received: *26 November 2018*
Accepted: *23 April 2019*
Published: *21 May 2019*

Citation:
Chaddad A, Kucharczyk MJ, Daniel P, Sabri S, Jean-Claude BJ, Niazi T and Abdulkarim B (2019) Radiomics in Glioblastoma: Current Status and Challenges Facing Clinical Implementation. Front. Oncol. 9:374. doi: 10.3389/fonc.2019.00374

INTRODUCTION

Glioblastoma (GBM) is the most common astrocytic primary brain malignancy, with an annual incidence of 2–3 cases per 100,000 adults in North America and Europe (1, 2). The standard of care for newly diagnosed GBM combines maximum safe resection followed by chemo-radiation and adjuvant courses of temozolomide (TMZ) (3). The median overall survival is poor at 14.6 months and 5-year survival rates are under 10% following standard of care treatment. If patients tolerate the chemoradiotherapy without progression, they may be considered for tumor-treatment fields. Even in this setting, the survival is still limited at a median of 20.9 months (4). Given these poor outcomes, there is hope that up-and-coming therapies will show benefit in the randomized setting (5, 6). It will be essential to ascertain which patients can benefit from these therapies, highlighting the need for efficacious tools to offer personalized medicine.

Magnetic resonance imaging (MRI) is the preferred imaging modality for both the diagnosis and monitoring of central nervous system (CNS) malignancies (7). It provides a massive amount of information to clinicians. Unfortunately, clinicians are typically restricted to qualitative descriptors or subjective quantitative assessments to articulate changes in imaging. The resulting clinical evaluations have a significant potential for bias.

Clinicians immensely value non-invasive approaches that can direct patients to the correct therapeutic approach in an objective fashion. This begins at diagnosis, where various molecular factors differentiate the diagnosis between low-grade glioma, high-grade glioma, or GBM (8). Such factors may also be predict the efficacy of a systemic agent (9, 10). This information requires tissue, introducing patient morbidity, an additional procedure, and a variety of expensive molecular assessments.

Radiomics has demonstrated remarkable progress in demonstrating that it may be a tool that can derive this information. Radiomics is a field of biomedical imaging using advanced non-invasive assessments of complex imaging characteristics within the MRI images that are too complex for a human to appreciate (11–14). These characteristics are known as *features*. Imaging features have been associated with a CNS tumor's histological features (14), progression (15) grade (16), or even overall survival (17–21). Radiomics analysis thus hosts a major role in producing novel non-invasive biomarkers acquired from a test—MRI—that is already routinely acquired from patients as part of the standard of care.

RADIOMICS METHODOLOGY

A standard pipeline of radiomic analysis has been described by several studies in the past (**Figure 1**) as mentioned previously by several studies (12, 13, 19, 21–23). This review discusses recent studies in the development of MRI-based radiomics analysis in relationship to this pipeline. For CNS malignancies, the literature discusses the most significant cause of diagnostic and management dilemmas—low and high-grade glioma. To facilitate an understanding of the process, there are sections on the: (1) preprocessing and image acquisition for developing a radiomic model; (2) segmentation/labeling of the cancer; (3) identification of relevant features types that may relate to the molecular properties of the tumor (14, 24) and (4) statistical modeling to describe a radiomic profile's relationship with a clinical outcomes. Given the number of variables at each step, collaboration is essential. Radiologists and oncologists must ensure that the appropriate regions are being assessed and the right questions are being asked. Molecular scientists must communicate the relevant genetic and proteomic characteristics that will influence a patient's clinical course. Engineering teams must determine what information can be reliably extracted from the images and then adapt the machine learning to fashion a reliable model. Consultation with statisticians will allow for a methodological approach allows for a potentially statistically significant solution.

Image Acquisition

MRI radiomics has repeatedly shown the ability to differentiate low and high-grade glioma, which have different management strategies (https://www.nccn.org/) and a remarkably different prognosis (25–28). One reason this data can be more rapidly generated is that there is a wealth of clinical information available—glioma patients have regular MRIs throughout their lives. However, reproducibility is a significant issue at different stages of the radiomics pipeline. The issues begin at image acquisition. Different academic groups acquire their MRI images to different settings at the first step of the pipeline. This is one reason that radiomic analysis collaboration has been limited between research groups. Standardization offers a rational solution to overcome this barrier.

Standardization

Potential variations in images are often secondary to the MRI scanner model, including image resolution (i.e., pixel size and slice spacing), image contrast, slice thickness, patient position, and further variations introduced by different reconstruction algorithms. When generating or applying a radiomics model, standardization must occur so the data can be assumed that it was extracted from similar settings. To accomplish this, volume datasets are usually re-sampled to a common voxel resolution of 1 mm^3 and an image size of 256^3 (or 512^3) voxels.

A common further step is normalizing the intensities within each volume image to the [0,1] or [0,255] range. Less commonly adopted normalization approaches have included gaussian and Z-score normalization. For example in Ellingson et al. (29), Gaussian normalization was the best normalization technique for image intensity correction. The need for standardization would be reduced if radiomic analysis could be performed with data acquired at a single geographical site. However, a single site would only provide a limited dataset. Thus, several studies have augmented their datasets through the use of multiple sites and an imputation technique to facilitate standardization (30).

The lack of standardization is a recognized problem. The *Quantitative Imaging Biomarker Alliance* offers an expert consensus after reviewing the available data. This group offers insightful guidelines for standardization that should be heavily considered in present and future studies. Such guidelines will be dynamic. Radiomic features may change from site to site or have new ways to be extracted or MRI image acquisition may change. Standardization in either of these contexts will a challenge in the future. Ongoing communication between institutions and robust reporting of new methodological approaches will be essential to groups studying radiomics.

Segmentation of Brain Tumors

Accurate labeling of brain tumors in the images is required for radiomic analysis. It first involves defining the tumor volume, known as the *region of interest* (ROI), so it can then have its radiomic features extracted. The act of employing clinical, pathological and imaging features to mark out the ROI on the two-dimensional MRI images is called either the *segmentation* or *labeling* process. Segmentation is performed by clinicians—typically a radiologist or oncologist. The process

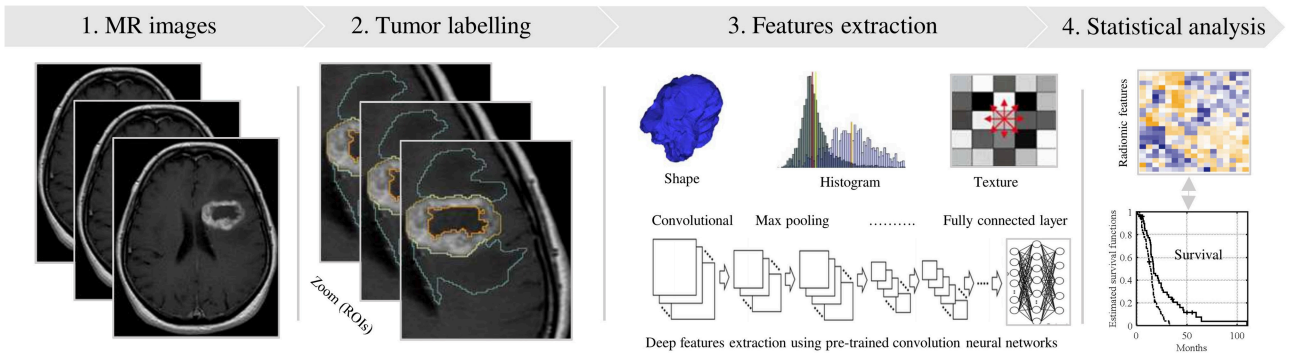


FIGURE 1 | Standard pipeline of the radiomics analysis. (1) MR Image acquisition with a standardization. (2) Tumor labeling viewing in 3D (e.g., red, yellow and cyan contours). (3) Radiomic features extraction using shape, texture and convolution neural network techniques. (4) Statistical analyses, based significance test and classifier models, to identify relevant features for predicting the clinical outcome.

is subject to inter-rater variability, as the ROI definition will inevitably differ between clinicians. An approach to overcome this variation is different clinicians each generating their own ROI. The geographical regions common between the different ROIs is considered the true tumor mask. This tumor mask is then matched with the corresponding brain images to then extract the imaging features (i.e., radiomic features).

Since MRI generates several image sequences, the registration step involves matching the mask to the relevant MR series (ex. T1 weighted, T1-post contrast, T2 weighted, FLAIR), a well-described process (20, 31). Many tools used to delineate the ROI, such as the publicly accessible 3D Slicer (32), require slice by slice labeling on each series to ensure accuracy and precision (21). For efficiency and to minimize both inter- and intra-user variability, several studies have explored segmentation to all relevant MRI sequences without registration across the sequences (33). Registration distortions between MRI series may limit this approach (34). Distortion could cause incorrect localization of the ROI, directing the radiomic analyses to the incorrect MRI-defined anatomy. More investigation is required to allow for the trans-sequence application of user-generated segmentation data.

To overcome user variability in registration, (semi-)automated segmentation has been explored in various studies (35–38). Strong signals for a successful model, a promising Dice Similarity Coefficient (DSC) of 80%, have been reported with fully automated segmentation based on an adaptive algorithm with multi-level of thresholding (38). When deep learning radiomics (DLR) was applied to multiple tumor regions, the ability to label the tumor subregions achieved a DSC of 90% (35). DLR has become a success story for machine learning integral to limiting user variability. The use of DLR's convolutional neural networks (CNNs) to the various steps of the radiomics pipeline is elegantly described elsewhere (39). As to fully automated segmentation, further validation is required. Success here could enable the rapid integration of radiomics into personalized medicine.

Radiomic Features Extraction

Extracting radiomic features is the first step in analyzing the segmented image. The features themselves are measures of the heterogeneity within the ROI (40). The degree to which these different features are present is a radiomics feature cluster, perhaps better conceptualized as an ROI's radiomic signature. There are different types of features, the most common and presently relevant are outlined in the **Table 1**.

Feature-Analyses

Once the features have been extracted, statistical modeling can highlight relationships between the extent a given feature is present and a clinical characteristic. There are various methodologies to analyze this, including minimizing the number of features likely to contribute to the statistical analysis. Feature selection methods (60) or reducing dimensionality in another fashion can accomplish this minimization. This has included sorting features by their minimum redundancy maximum relevance, mutual information, principal component analysis feature rank or the importance of features in other classifier models (31, 61–65). Once the features that are potentially relevant for analysis are determined, they are typically subject to assessments of their significance (e.g., Wilcoxon test, Kruskal-Wallis, log-rank, etc.) and correlation (e.g., Spearman rank, Pearson). These forms of *univariate analysis* determine if a feature is a significant predictor for the selected clinical outcome, with significance typically being defined as either a $p < 0.01$ or 0.05. The p-values should be corrected by the Bonferroni or Holm-Bonferroni procedure to limit the influence of random chance, including the false discovery rate (21, 60, 66).

Multivariate Analysis and Model Building

Multivariate analysis fills an essential role in separating seemingly relevant features on univariate analysis from those that are likely *independent* predictors for the clinical outcome being assessed for. This is a critical step, limiting non-contributory features from influencing our eventual final statistical model (67). Once these features are selected from multi-variate analysis, the radiomics team must determine how many of their finite number of clinical

TABLE 1 | Features extraction techniques used in radiomic analysis.

Histogram features: These are first-order statistics computed from image's histogram of voxel/pixel intensities. Histogram features (e.g., average, standard deviation, skewness, kurtosis, energy and entropy) encode the voxel intensities and the shape of the data's distribution (41, 42). In non-CNS malignancies, these features have been associated with histological features, subtype and grade (43, 44).
Texture features: Texture features use second order statistics to characterize the spatial relationship between voxel intensities, describing the local spatial arrangement of intensities in the image. The features encode several matrices that represent the special intensity distribution in several ways. Not included in the list below are also texture features based on several conventional techniques that have been predictive of clinical outcomes, such as: as scale-invariant feature transform (SIFT), histogram of oriented gradients (HOG), fractal texture analysis (FTA) and local binary patterns (LBP) (45–47). Elsewise, the most common texture features are: *Gray-level co-occurrence matrix* (GLCM)—the most commonly used texture feature. Considering only voxels within a specific range of gray values, it produces a matrix of the spatial relationships of pairs of voxels (48). *Joint intensity matrix* (JIM)—evaluates the spatial relationships of pairs of voxels within given intensity ranges across different MRI different sequences. This is in contrast to GLCM, which is restricted to a single MRI sequence (21). *Neighborhood gray-tone difference matrix* (NGTDM)—a description of the differences in signal intensity, or gray-tone, between each voxel and its neighboring voxels (49). It has been used in several topics of images analysis and classifications (45). *Neighboring gray-level dependence matrix* (NGLDM)—Similar to NGTDM, is computed from the gray tone relationship between every element in the image and all of its neighbors at a certain distance (50, 51). *Gray-level run length matrix* (GLRLM)—A matrix of all the voxels within the same gray level value (52).
Multiscale texture features: These features have been derived from filters, such as the Laplacian or Gaussian filter (53), that serve as a generic differential operator. Multiscale texture features provide an excellent description of local image variations, such as edges or blobs. The ROI's image is filtered in a multiscale way—from fine to coarse texture—that can be quantified by parameters like entropy (31, 54). The wavelet decomposition of an image generates multiscale texture images based on multiband frequencies, a radiographic characteristic called a *detail*. Each of these bands has a scale of the texture inside the image. A quantifier function then evaluates the texture of the images, using the resultant value as an input for a classifier model (42, 55).
Deep features: These features are derived from deep neural networks, the process of which is well-described in a recent review (56). To accomplish this, a pre-trained network must be established prior to texture extraction. As a case study from the literature, (1) ImageNET was pretrained to identify textures, (2) the CNN analyzed a fully connected layer of ImageNet, deriving 4,096 texture features, then (3) these features were used an input for a classifier model, which could also incorporate a CNN (as described in this review's Radiomics Analysis step) (39). However, CNNs require numerous examples to develop a reliable model. In general, studies implementing CNNs require more patients than the number of features being analyzed. Achieving this sample size can be a challenge, so alternative methods of model generation are needed for many studies. One such example reported the conditional entropy from a texture of the CNN's feature map. This was a reliable alternative when implemented into a random forest classifier, instead of another different standard CNN model (57).
Shape features: Shape features describe the 3D (or 2D) geometrical composition of the ROI considered the size (e.g., volume), form (e.g., sphericity, solidity, major length axis) and tumor location. As with traditional radiological assessment, shape is a characteristic that does relate to tumor characteristics with radiomics as well (19, 58, 59).

cases will be used to produce/train their model and how many need to be reserved to validate the model.

Increasing the size of the training cohort will increase the model's accuracy. Thus, typically 70–80% of the dataset is used for the training stage. Alternatively, if an external dataset is available, then all the datasets can train the model. This is the preferred scenario, allowing for a demonstration of external validity. If the datasets are limited in size, k-folds cross-validation can mitigate some of the statistical concerns (31, 68, 69).

Machine learning changes the available options. If unsupervised, the program can utilize different methods (e.g., k-means, nearest neighbors) to partition the features into different groups, then compare the relationships of the different features within their group—*not* the clinical data. After this is completed, the ability of the different groups to predict the clinical outcome is assessed, even though the clinical data did not contribution to the model's development (70). In comparison, supervised machine learning techniques (e.g., support vector machine, Bayes model, neural network nearest neighbors, random forests) will place varying numbers of the pre-determined relevant features into groups. Then their relative contribution to the model's ability to predict for the clinical outcome is altered until the most reliable combination of weightings is determined. Random forest classifier is a simple model that automatically selects the relevant features. Furthermore, random forest has shown the great ability to predict for survival (71) and endure an imputation technique to account for censored patients (31). Alternatively, the least absolute shrinkage and selection operator (LASSO) Cox regression model has also been reported reliably predict for survival in glioma (72, 73).

A third option is semi-supervised machine learning, wherein *some* complete clinical data is provided to the program generating the model, but other data is complete. For example, the program would have a range of radiomic features that it knows correspond to high grade glioma and a range of radiomic features that belong to an unknown clinical entity. Thus, all the dataset is used for a training step. The validation step is then a question if the program can correctly identify the unlabeled data. This process has been used to suggest brain tumor histology and prognosis (74).

PROGRESS OF RADIOMICS IN GBM

Radiomics has provided key insight into critical features of GBM, as advanced radiomic analysis seek to establish reliable associations between key clinical features and those features derived from images. For example, radiomics has been used to predict for clinical, proteomic (e.g., Ki-67 expression), genomic (e.g., IDH1 status) and transcriptomic characteristics (75–77). This evolution of the radiomics field

has been titled multi-omics or radiogenomics, dependent on the source (21, 78–80). This will be part of the future of radiomics, as these details are pertinent to physicians due to their influence on treatment and prognosis (8). In addition, recent advancements have been made in defining radiomic subtypes. By utilizing T1 and FLAIR sequencing, researchers were able to define three distinct imaging subtypes—rim enhancing, irregular and solid. Each subtype represents a distinct phenotype enriched in unique molecular alterations such as MGMT methylation and EGFRvIII mutations (37). Continued advancements in defining tumor heterogeneity using imaging features may offer a complimentary means with which to characterize GBM and provide personalized treatments for patients.

Radiomics analysis has the capacity to answer critical questions facing clinicians such as the discrimination between pseudoprogression and progressive disease in GBM patients. For example, combining the *diffusion tensor imaging* and *dynamic susceptibility contrast* MRI features can improve accuracy treatment response and may aid in individualized treatment of patients with GBM (81). Recently, a deep radiomics model used the MR images with clinical features demonstrate the capacity to predict the PsP from progression for patients with GBM (82). While, another study showed that the radiomics analysis is not able to distinguish between true-progression and PsP (83). However, many of these steps exist in an early developmental stage. Combining all such information into an artificial intelligence model would be a promising direction to advance personalized medicine.

INTRATUMOURAL HETEROGENEITY AND RADIOGENOMICS

Perhaps the greatest utility of radiomics in the management of gliomas lies in the application of radiogenomics. Radiogenomics implements radiomics analysis to predict specific genetic characteristics. Classically, gliomas have been managed based on their grade—a histopathological characterization made by specialized physicians (neuropathologists) to articulate the likely behavior of the malignancy. Over the past two decades, molecular assessment of the tumor's genome, protein expression, and epigenetic state have become more common as the relevance of these features to outcome and/or therapeutic response is being increasingly understood (84). Given the relative abundance of high quality MRI data which accumulates over time during standard of care for glioma patients (85–87) radiomics offers a potentially efficient and non-invasive method of tumoral evaluation (37, 88, 89). Indeed, recent efforts have generated radiomic signatures to predict the majority of information sought by classical histopathological and modern molecular assessments including: isocitrate dehydrogenase mutations (79, 90–92), 1p/19q codeletion loss of heterozygosity (24, 92, 93), O^6-methylguanine-DNA methyltransferase promoter methylation (45, 94) and ATRX mutations (95). This has culminated in recent findings demonstrating a conserved radiomic signature can predict CD8+ T-cell infiltration and response to immunotherapy (96).

However, intratumoral heterogeneity significantly confounds both molecular and histopathological assessments as the entirety of a tumor cannot be assessed by neuropathologists. Disparate clonal populations may be minimally represented in histopathological sampling introducing sampling errors and limiting relevance for informing treatments (97–101). Radiomics offers an opportunity to overcome this limitation as analysis is performed upon the complete tumor enabling spatial mapping of distinct genetic features. In addition, radiomics offers the means to provide quantitative values (e.g., % of tumor mutated) rather than binary designations (e.g., mutant or not) to describe molecular features which may have important implications for predicting response to therapies. Utilizing co-clinical models, researchers are starting to establish radiomic signatures which are closely associated with specific molecular features in an attempt to describe intratumoral heterogeneity (102). Further development of pre-clinical models and correlation with clinical datasets will be essential to drive this field forward toward improving the utility of radiomics for diagnosis in GBM.

FUTURE RADIOMICS

Radiomics needs massive amounts of biomedical data, so-called "Big data (103)," to validate it's deep-learning approaches and expanding applications. The development of strong public datasets has empowered these approaches, with such initiatives including The Cancer Genome Atlas (TCGA) (85), The Cancer Imaging Archive (86), and The Quantitative Imaging Network (87). However, there is still the barrier of segmentation—such as acquiring clinician input to identify the relevant ROIs. While the clinician will still be sought as the gold standard, deep-learning strategies have the potential to define ROIs without the bias of human segmentation (104). To accomplish this, even larger datasets will be required—further emphasizing the need for reliable Big Data. These strategies have begun in part, but developing validated models to all the clinically relevant questions will simply require more data (105, 106).

The potential applications for radiomics is expanding, with logistical and technical challenges needing to be overcome prior to true clinical deployment. We view these as: (1) expanding what is included in and the access to Big Data, (2) establishing common criteria from image acquisition to feature definitions, (3) agreement on the clinical questions that radiomics must address, and (4) developing a clinically implementable and prospectively validated statistical model to answer those questions.

CONCLUSIONS

This review explained how the vast amount of radiological data not used by the clinicians managing CNS malignancies can be used to generate radiological signatures that can predict the

characteristics of these brain tumours. In a step-by-step process we outlined how this data can be used to predict for numerous pertinent biological outcomes. With constant progress in deep-learning processes and expanding public access to Big Data, radiomics has the potential to non-invasively address numerous clinical questions or support clinical decision making. There are numerous future directions for radiomics, but a continued focus on ensuring there is public access to large databases of clinical and radiological correlated data will be instrumental to seeing those directions leading to a desirable destination.

AUTHOR CONTRIBUTIONS

AC conception and design. AC, PD, and MK drafting the manuscript and review of the literature. MK, PD, BJ-C, TN, SS, and BA critical revision of the manuscript.

ACKNOWLEDGMENTS

Research supported by grant from Varian Medical System.

REFERENCES

1. Koca T, Basaran H, Sezen D, Karaca S, Ors Y, Arslan D, Aydin A. Comparison of linear accelerator and helical tomotherapy plans for glioblastoma multiforme patients. *Asian Pac J Cancer Prev*. (2014) 15:7811–6. doi: 10.7314/APJCP.2014.15.18.7811
2. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011–2015. *Neuro Oncol.* (2018) 20:iv1–86. doi: 10.1093/neuonc/noy131
3. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJB, Janzer RC, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. (2009) 10:459–66. doi: 10.1016/S1470-2045(09)70025-7
4. Stupp R, Taillibert S, Kanner A, Read W, Steinberg D, Lhermitte B, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA*. (2017) 318:2306–16. doi: 10.1001/jama.2017.18718
5. Kong X-T, Nguyen NT, Choi YJ, Zhang G, Nguyen HN, Filka E, et al. Phase 2 Study of bortezomib combined with temozolomide and regional radiation therapy for upfront treatment of patients with newly diagnosed glioblastoma multiforme: safety and efficacy assessment. *Int J Radiation Oncol Biol Phys.* (2018) 100:1195–203. doi: 10.1016/j.ijrobp.2018.01.001
6. Desjardins A, Gromeier M, Herndon JE, Beaubier N, Bolognesi DP, Friedman AH, et al. Recurrent glioblastoma treated with recombinant poliovirus. *N Engl J Med*. (2018) 379:150–61. doi: 10.1056/NEJMoa1716435
7. Cao Y, Tseng C-L, Balter JM, Teng F, Parmar HA, Sahgal A. MR-guided radiation therapy: transformative technology and its role in the central nervous system. *Neuro Oncol.* (2017) 19:ii16–29. doi: 10.1093/neuonc/nox006
8. Louis DN, Perry A, Reifenberger G, Deimling A von, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. (2016) 131:803–20. doi: 10.1007/s00401-016-1545-1
9. Kaley T, Touat M, Subbiah V, Hollebecque A, Rodon J, Lockhart AC, et al. BRAF Inhibition in BRAFV600-mutant gliomas: results from the VE-BASKET study. *JCO*. (2018) JCO.2018.78.9990. doi: 10.1200/JCO.2018.78.9990
10. Alexander BM, Trippa L, Gaffey SC, Arrillaga I, Lee EQ, Tanguturi SK, et al. Individualized screening trial of innovative glioblastoma therapy (INSIGhT). *Am Soc Clin Oncol.* (2017). doi: 10.1200/JCO.2017.35.15_suppl.TPS2079
11. Aerts HJWL. The potential of radiomic-based phenotyping in precision medicine: a review. *JAMA Oncol.* (2016) 2:1636. doi: 10.1001/jamaoncol.2016.2631
12. Aerts HJ, Velazquez ER, Leijenaar RT, Parmar C, Grossmann P, Cavalho S, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. *Nat Commun.* (2014) 5:5644. doi: 10.1038/ncomms5644
13. Chaddad A, Daniel P, Niazi T. Radiomics evaluation of histological heterogeneity using multiscale textures derived from 3D wavelet transformation of multispectral images. *Front Oncol*. (2018) 8:96. doi: 10.3389/fonc.2018.00096
14. Chaddad A, Desrosiers C, Toews M. GBM heterogeneity characterization by radiomic analysis of phenotype anatomical planes. In: Martin AS, Elsa DA, editors. *Medical Imaging 2016 Image Processing*. Orlando, FL: International Society for Optics and Photonics. p. 978424.
15. Abrol S, Kotrotsou A, Hassan A, Elshafeey N, Hassan I, Idris T, et al. Radiomic analysis of pseudo-progression compared to true progression in glioblastoma patients: a large-scale multi-institutional study. *Am Soc Clin Oncol.* (2017). doi: 10.1200/JCO.2017.35.15_suppl.2015
16. Zacharaki EI, Wang S, Chawla S, Soo Yoo D, Wolf R, Melhem ER, et al. Classification of brain tumor type and grade using MRI texture and shape in a machine learning scheme. *Magn Reson Med*. (2009) 62:1609–18. doi: 10.1002/mrm.22147
17. Grabowski MM, Recinos PF, Nowacki AS, Schroeder JL, Angelov L, Barnett GH, et al. Residual tumor volume versus extent of resection: predictors of survival after surgery for glioblastoma. *J Neurosurg*. (2014) 121:1115–23. doi: 10.3171/2014.7.JNS132449
18. Cui Y, Ren S, Tha KK, Wu J, Shirato H, Li R. Volume of high-risk intratumoral subregions at multi-parametric MR imaging predicts overall survival and complements molecular analysis of glioblastoma. *Eur Radiol*. (2017) 27:3583–92. doi: 10.1007/s00330-017-4751-x
19. Chaddad A, Desrosiers C, Hassan L, Tanougast C. A quantitative study of shape descriptors from glioblastoma multiforme phenotypes for predicting survival outcome. *Br J Radiol.* (2016) 89: 20160575. doi: 10.1259/bjr.20160575
20. Chaddad A, Tanougast C. Extracted magnetic resonance texture features discriminate between phenotypes and are associated with overall survival in glioblastoma multiforme patients. *Med Biol Eng Comput*. (2016) 54:1707–18. doi: 10.1007/s11517-016-1461-5
21. Chaddad A, Daniel P, Desrosiers C, Toews M, Abdulkarim B. Novel radiomic features based on joint intensity matrices for predicting glioblastoma patient survival time. *IEEE J Biomed Health Informat.* (2019) 23:795–804. doi: 10.1109/JBHI.2018.2825027
22. Kumar V, Gu Y, Basu S, Berglund A, Eschrich SA, Schabath MB, et al. Radiomics: the process and the challenges. *Magn Reson Imaging*. (2012) 30:1234–48. doi: 10.1016/j.mri.2012.06.010
23. Lambin P, Leijenaar RTH, Deist TM, Peerlings J, de Jong EEC, van Timmeren J, et al. Radiomics: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol*. (2017) 14:749–62. doi: 10.1038/nrclinonc.2017.141
24. Lu C-F, Hsu F-T, Hsieh KL-C, Kao Y-CJ, Cheng S-J, Hsu JB-K, et al. Machine learning-based radiomics for molecular subtyping of gliomas. *Clin Cancer Res.* (2018). 24:4429–36. doi: 10.1158/1078-0432.CCR-17-3445
25. Qin J, Liu Z, Zhang H, Shen C, Wang X, Tan Y, et al. Grading of gliomas by using radiomic features on multiple magnetic resonance imaging (MRI) sequences. *Med Sci Monit*. (2017) 23:2168–78. doi: 10.12659/MSM.901270
26. Zhang X, Yan L-F, Hu Y-C, Li G, Yang Y, Han Y, et al. Optimizing a machine learning based glioma grading system using multi-parametric MRI histogram and texture features. *Oncotarget*. (2017) 8:47816–30. doi: 10.18632/oncotarget.18001
27. Chang K, Bai HX, Zhou H, Su C, Bi WL, Agbodza E, et al. Residual convolutional neural network for the determination of IDH status in low-and

high-grade gliomas from MR imaging. *Clin Cancer Res.* (2018) 24:1073–81. doi: 10.1158/1078-0432.CCR-17-2236
28. Cho H, Park H. Classification of low-grade and high-grade glioma using multi-modal image radiomics features. In: *Engineering in Medicine and Biology Society (EMBC), 2017 39th Annual International Conference of the IEEE* (Jeju Island: IEEE), 3081–4.
29. Ellingson BM, Zaw T, Cloughesy TF, Naeini KM, Lalezari S, Mong S, et al. Comparison between intensity normalization techniques for dynamic susceptibility contrast (DSC)-MRI estimates of cerebral blood volume (CBV) in human gliomas. *J Magn Reson Imag.* (2012) 35:1472–7. doi: 10.1002/jmri.23600
30. Newman DA. Longitudinal modeling with randomly and systematically missing data: a simulation of *ad hoc*, maximum likelihood, and multiple imputation techniques, Longitudinal Modeling with Randomly and Systematically Missing Data: a simulation of *ad hoc*, maximum likelihood, and multiple imputation techniques. *Organ Res Methods*. (2003) 6:328–362. doi: 10.1177/1094428103254673
31. Chaddad A, Sabri S, Niazi T, Abdulkarim B. Prediction of survival with multi-scale radiomic analysis in glioblastoma patients. *Med Biol Eng Comput*. (2018) 1–14. doi: 10.1007/s11517-018-1858-4
32. *3D Slicer*. Available online at: http://www.slicer.org/ (accessed October 20, 2014).
33. Zhou H, Vallières M, Bai HX, Su C, Tang H, Oldridge D, et al. MRI features predict survival and molecular markers in diffuse lower-grade gliomas. *Neuro-oncology*. (2017) 19:862–70. doi: 10.1093/neuonc/now256
34. Lin JS, Fuentes DT, Chandler A, Prabhu SS, Weinberg JS, Baladandayuthapani V, et al. Performance assessment for brain MR imaging registration methods. *AJNR Am J Neuroradiol*. (2017) 38:973–80. doi: 10.3174/ajnr.A5122
35. Kamnitsas K, Ledig C, Newcombe VFJ, Simpson JP, Kane AD, Menon DK, et al. Efficient multi-scale 3D CNN with fully connected CRF for accurate brain lesion segmentation. *Med Image Anal.* (2017) 36:61–78. doi: 10.1016/j.media.2016.10.004
36. Bakas S, Zeng K, Sotiras A, Rathore S, Akbari H, Gaonkar B, et al. GLISTRboost: combining multimodal MRI segmentation, registration, and biophysical tumor growth modeling with gradient boosting machines for glioma segmentation. In: *Brainlesion: Glioma, Multiple Sclerosis, Stroke and Traumatic Brain Injuries Lecture Notes in Computer Science.* (Cham: Springer), 144–155.
37. Rathore S, Akbari H, Rozycki M, Abdullah KG, Nasrallah MP, Binder ZA, et al. Radiomic MRI signature reveals three distinct subtypes of glioblastoma with different clinical and molecular characteristics, offering prognostic value beyond IDH1. *Sci Rep.* (2018) 8:5087. doi: 10.1038/s41598-018-22739-2
38. Chaddad A, Tanougast C. Quantitative evaluation of robust skull stripping and tumor detection applied to axial MR images. *Brain Inform.* (2016) 3:53–61. doi: 10.1007/s40708-016-0033-7
39. Krizhevsky A, Sutskever I, Hinton GE. Imagenet classification with deep convolutional neural networks. In: Pereira F, Burges CJC, Bottou L, Weinberger KQ, editors. *Advances in Neural Information Processing Systems* (Lake Tahoe, NV: Curran Associates Inc.), 1097–1105.
40. McGarry SD, Hurrell SL, Kaczmarowski AL, Cochran EJ, Connelly J, Rand SD, et al. Magnetic resonance imaging-based radiomic profiles predict patient prognosis in newly diagnosed glioblastoma before therapy. *Tomography*. (2016) 2:223. doi: 10.18383/j.tom.2016.00250
41. Chaddad A, Tanougast C. High-throughput quantification of phenotype heterogeneity using statistical features. *Adv Bioinform.* (2015) 2015:e728164. doi: 10.1155/2015/728164
42. Aerts HJWL, Velazquez ER, Leijenaar RTH, Parmar C, Grossmann P, Carvalho S, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. *Nat Commun.* (2014) 5:4006. doi: 10.1038/ncomms5006
43. Downey K, Riches SF, Morgan VA, Giles SL, Attygalle AD, Ind TE, et al. Relationship between imaging biomarkers of stage I cervical cancer and poor-prognosis histologic features: quantitative histogram analysis of diffusion-weighted MR images. *AJR Am J Roentgenol.* (2013) 200:314–20. doi: 10.2214/AJR.12.9545
44. Rosenkrantz AB. Histogram-based apparent diffusion coefficient analysis: an emerging tool for cervical cancer characterization? *AJR Am J Roentgenol.* (2013) 200:311–3. doi: 10.2214/AJR.12.9926
45. Li Z-C, Bai H, Sun Q, Li Q, Liu L, Zou Y, et al. Multiregional radiomics features from multiparametric MRI for prediction of MGMT methylation status in glioblastoma multiforme: a multicentre study. *Eur Radiol.* (2018) 28:3640–50. doi: 10.1007/s00330-017-5302-1
46. Chen Y, Li Z, Wu G, Yu J, Wang Y, Lv X, et al. Primary central nervous system lymphoma and glioblastoma differentiation based on conventional magnetic resonance imaging by high-throughput SIFT features. *Int J Neurosci.* (2018) 128:608–18. doi: 10.1080/00207454.2017.1408613
47. Yang D, Rao G, Martinez J, Veeraraghavan A, Rao A. Evaluation of tumor-derived MRI-texture features for discrimination of molecular subtypes and prediction of 12-month survival status in glioblastoma. *Med Phys.* (2015) 42:6725–35. doi: 10.1118/1.4934373
48. Haralick RM, Shanmugam K, Dinstein I. Textural features for image classification. *IEEE Trans Syst Man Cyber.* (1973) SMC-3:610–21. doi: 10.1109/TSMC.1973.4309314
49. Amadasun M, King R. Textural features corresponding to textural properties. *IEEE Trans Syst Man Cyber.* (1989) 19:1264–74. doi: 10.1109/21.44046
50. Sun C, Wee WG. Neighboring gray level dependence matrix for texture classification. *Comp Vision Graphics Image Process.* (1983) 23:341–52. doi: 10.1016/0734-189X(83)90032-4
51. Berry JR, Goutsias J. A comparative study of matrix measures for maximum likelihood texture classification. *IEEE Trans Syst Man Cyber.* (1991) 21:252–61. doi: 10.1109/21.101156
52. Chu A, Sehgal CM, Greenleaf JF. Use of gray value distribution of run lengths for texture analysis. *Pattern Recogn Lett.* (1990) 11:415–9. doi: 10.1016/0167-8655(90)90112-F
53. Gonzalez RC, Woods RE, Eddins SL. *Digital Image Processing Using MATLAB*. Pearson Education India (2004).
54. Skogen K, Schulz A, Helseth E, Ganeshan B, Dormagen JB, Server A. Texture analysis on diffusion tensor imaging: discriminating glioblastoma from single brain metastasis. *Acta Radiol.* (2018) 60:356–66. doi: 10.1177/0284185118780889
55. Chaddad A, Bouridane A, Hassan L, Tanougast C. Wavelet based radiomics for brain tumour phenotypes discrimination. In *Proceedings—CIE 45: 2015 International Conference on Computers and Industrial Engineering* (Metz: NY Curran Associates Inc.), 1167–74. Available online at: http://nrl.northumbria.ac.uk/26740/ (accessed October 24, 2017).
56. Litjens G, Kooi T, Bejnordi BE, Setio AAA, Ciompi F, Ghafoorian M, van der Laak JAWM, van Ginneken B, Sánchez CI. A survey on deep learning in medical image analysis. *Medical Image Analysis.* (2017) 42:60–88. doi: 10.1016/j.media.2017.07.005
57. Chaddad A, Desrosiers C, Niazi T. Deep radiomic analysis of MRI related to Alzheimer's disease. *IEEE Access.* (2018) 6:58213–21. doi: 10.1109/ACCESS.2018.2871977.
58. Chaddad A, Desrosiers C, Toews M. Phenotypic characterization of glioblastoma identified through shape descriptors. In: *Proceedings Volume 9785, Medical Imaging 2016: Computer-Aided Diagnosis*. San Diego, CA: International Society for Optics and Photonics (2016).
59. Czarnek N, Clark K, Peters KB, Mazurowski MA. Algorithmic three-dimensional analysis of tumor shape in MRI improves prognosis of survival in glioblastoma: a multi-institutional study. *J Neurooncol.* (2017) 132:55–62. doi: 10.1007/s11060-016-2359-7
60. Yu L, Liu H. Feature selection for high-dimensional data: a fast correlation-based filter solution. In: T. Fawcett, and N. Mishra (Eds.), *Proceedings, Twentieth International Conference on Machine Learning.* Vol. 2 (2003), pp. 856–863.
61. Xing EP, Jordan MI, Karp RM. Feature selection for high-dimensional genomic microarray data. In: *ICML* (Citeseer), 601–608.
62. Nguyen HT, Franke K, Petrovic S. Towards a generic feature-selection measure for intrusion detection. In: *Pattern Recognition (ICPR), 2010 20th International Conference on* (Istanbul: IEEE), 1529–1532.

63. Ramírez-Gallego S, Lastra I, Martínez-Rego D, Bolón-Canedo V, Benítez JM, Herrera F, et al. Fast-mRMR: fast minimum redundancy maximum relevance algorithm for high-dimensional big data. *Int J Intelligent Syst.* 32:134–52. doi: 10.1002/int.21833
64. Chaddad A. Automated feature extraction in brain tumor by magnetic resonance imaging using gaussian mixture models. *Int J Biomed Imag.* (2015) 11:868031. doi: 10.1155/2015/868031
65. Song F, Guo Z, Mei D. Feature selection using principal component analysis. In: *Engineering Design and Manufacturing Informatization 2010 International Conference on System Science* (Yichang).p. 27–30.
66. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat.* (1979) 6:65–70.
67. Witten IH, Frank E. *Data Mining: Practical Machine Learning Tools and Techniques, Second Edition*. San Francisco, CA: Morgan Kaufmann (2005).
68. Arlot S, Celisse A. A survey of cross-validation procedures for model selection. *Statist Surv*. (2010) 4:40–79. doi: 10.1214/09-SS054
69. Krstajic D, Buturovic LJ, Leahy DE, Thomas S. Cross-validation pitfalls when selecting and assessing regression and classification models. *J Cheminform.* (2014) 6:10. doi: 10.1186/1758-2946-6-10
70. Guan X, Vengoechea J, Zheng S, Sloan AE, Chen Y, Brat DJ, et al. Molecular subtypes of glioblastoma are relevant to lower grade glioma. *PLoS ONE.* (2014) 9:e91216. doi: 10.1371/journal.pone.0091216
71. Parmar C, Grossmann P, Bussink J, Lambin P, Aerts HJWL. Machine learning methods for quantitative radiomic biomarkers. *Sci Rep*. (2015) 5:13087. doi: 10.1038/srep13087
72. Lao J, Chen Y, Li Z-C, Li Q, Zhang J, Liu J, et al. A deep learning-based radiomics model for prediction of survival in glioblastoma multiforme. *Sci Rep.* (2017) 7:10353. doi: 10.1038/s41598-017-10649-8
73. Kim H, Bredel M. Feature selection and survival modeling in The Cancer Genome Atlas. *Int J Nanomed.* (2013) 8:57–62. doi: 10.2147/IJN.S40733
74. Cruz-Barbosa R, Vellido A. Semi-supervised analysis of human brain tumours from partially labeled MRS information, using manifold learning models. *Int J Neural Syst*. (2011) 21:17–29. doi: 10.1142/S0129065711002626
75. Kong D-S, Kim J, Ryu G, You H-J, Sung JK, Han YH, et al. Quantitative radiomic profiling of glioblastoma represents transcriptomic expression. *Oncotarget*. (2018) 9:6336–45. doi: 10.18632/oncotarget.23975
76. Kickingereder P, Burth S, Wick A, Götz M, Eidel O, Schlemmer H-P, et al. Radiomic profiling of glioblastoma: identifying an imaging predictor of patient survival with improved performance over established clinical and radiologic risk models. *Radiology*. (2016) 280:880–9. doi: 10.1148/radiol.2016160845
77. Zhang B, Tian J, Dong D, Gu D, Dong Y, Zhang L, et al. Radiomics features of multiparametric MRI as novel prognostic factors in advanced nasopharyngeal carcinoma. *Clin Cancer Res*. (2017) 23:4259–69. doi: 10.1158/1078-0432.CCR-16-2910
78. Beig N, Patel J, Prasanna P, Partovi S, Varadhan V, Madabhushi A, et al. Radiogenomic analysis of hypoxia pathway reveals computerized MRI descriptors predictive of overall survival in Glioblastoma. In: *SPIE Medical Imaging* (International Society for Optics and Photonics), p. 101341U
79. Mazurowski MA, Clark K, Czarnek NM, Shamsesfandabadi P, Peters KB, et al. Radiogenomics of lower-grade glioma: algorithmically-assessed tumor shape is associated with tumor genomic subtypes and patient outcomes in a multi-institutional study with The Cancer Genome Atlas data. *J Neuro-Oncol.* (2017) 133:27–35. doi: 10.1007/s11060-017-2420-1
80. Kickingereder P, Bonekamp D, Nowosielski M, Kratz A, Sill M, Burth S, et al. Radiogenomics of glioblastoma: machine learning–based classification of molecular characteristics by using multiparametric and multiregional MR imaging features. *Radiology*. (2016) 281:907–18. doi: 10.1148/radiol.2016161382
81. Wang S, Martinez-Lage M, Sakai Y, Chawla S, Kim SG, Alonso-Basanta M, et al. Differentiating tumor progression from pseudoprogression in patients with glioblastomas using diffusion tensor imaging and dynamic susceptibility contrast MRI. *Am J Neuroradiol.* (2016) 37:28–36. doi: 10.3174/ajnr.A4474
82. Jang B-S, Jeon SH, Kim IH, Kim IA. Prediction of Pseudoprogression versus progression using machine learning algorithm in glioblastoma. *Sci Rep.* (2018) 8:12516. doi: 10.1038/s41598-018-31007-2
83. Rowe LS, Butman JA, Mackey M, Shih JH, Cooley-Zgela T, Ning H, et al. Differentiating pseudoprogression from true progression: analysis of radiographic, biologic, and clinical clues in GBM. *J Neurooncol*. (2018) 139:145–52. doi: 10.1007/s11060-018-2855-z
84. van den Bent MJ, Dubbink HJ, Marie Y, Brandes AA, Taphoorn MJB, Wesseling P, et al. IDH1 and IDH2 mutations are prognostic but not predictive for outcome in anaplastic oligodendroglial tumors: a report of the European Organization for Research and Treatment of Cancer Brain Tumor Group. *Clin Cancer Res*. (2010) 16:1597–604. doi: 10.1158/1078-0432.CCR-09-2902
85. Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature*. (2008) 455:1061–8. doi: 10.1038/nature07385
86. Prior FW, Clark K, Commean P, Freymann J, Jaffe C, Kirby J, et al. TCIA: an information resource to enable open science. *Conf Proc IEEE Eng Med Biol Soc*. (2013) 2013:1282–5. doi: 10.1109/EMBC.2013.6609742
87. Kalpathy-Cramer J, Freymann JB, Kirby JS, Kinahan PE, Prior FW. Quantitative imaging network: data sharing and competitive algorithmvalidation leveraging the cancer imaging archive. *Transl Oncol*. (2014) 7:147–52. doi: 10.1593/tlo.13862
88. Liu Y, Xu X, Yin L, Zhang X, Li L, Lu H. Relationship between glioblastoma heterogeneity and survival time: an MR imaging texture analysis. *Am J Neuroradiol.* (2017) 38:1695–701. doi: 10.3174/ajnr.A5279
89. Chow D, Chang P, Weinberg BD, Bota DA, Grinband J, Filippi CG. Imaging genetic heterogeneity in glioblastoma and other glial tumors: review of current methods and future directions. *Am J Roentgenol.* (2017) 210:30–38. doi: 10.2214/AJR.17.18754
90. Liang S, Zhang R, Liang D, Song T, Ai T, Xia C, et al. Multimodal 3D DenseNet for IDH genotype prediction in gliomas. *Genes.* (2018) 9:9080382. doi: 10.3390/genes9080382
91. Eichinger P, Alberts E, Delbridge C, Trebeschi S, Valentinitsch A, Bette S, et al. Diffusion tensor image features predict IDH genotype in newly diagnosed WHO grade II/III gliomas. *Sci Rep*. (2017) 7:13396. doi: 10.1038/s41598-017-13679-4
92. Delfanti RL, Piccioni DE, Handwerker J, Bahrami N, Krishnan A, Karunamuni R, et al. Imaging correlates for the 2016 update on WHO classification of grade II/III gliomas: implications for IDH, 1p/19q and ATRX status. *J Neurooncol*. (2017) 135:601–9. doi: 10.1007/s11060-017-2613-7
93. Han Y, Xie Z, Zang Y, Zhang S, Gu D, Zhou M, et al. Non-invasive genotype prediction of chromosome 1p/19q co-deletion by development and validation of an MRI-based radiomics signature in lower-grade gliomas. *J Neurooncol*. (2018) 140:297–306. doi: 10.1007/s11060-018-2953-y
94. Wei J, Yang G, Hao X, Gu D, Tan Y, Wang X, et al. A multi-sequence and habitat-based MRI radiomics signature for preoperative prediction of MGMT promoter methylation in astrocytomas with prognostic implication. *Eur Radiol*. (2019) 29:877–88. doi: 10.1007/s00330-018-5575-z
95. Hong EK, Choi SH, Shin DJ, Jo SW, Yoo R-E, Kang KM, et al. Radiogenomics correlation between MR imaging features and major genetic profiles in glioblastoma. *Eur Radiol*. (2018) 28:4350–61. doi: 10.1007/s00330-018-5400-8
96. Sun R, Limkin EJ, Vakalopoulou M, Dercle L, Champiat S, Han SR, et al. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. *Lancet Oncol*. (2018) 19:1180–91. doi: 10.1016/S1470-2045(18)30413-3
97. Scherer HJ. Cerebral astrocytomas and their derivatives. *Am J Cancer*. (1940) 40:159–198.
98. Kros JM, van Run PR, Alers JC, Avezaat CJ, Luider TM, van Dekken H. Spatial variability of genomic aberrations in a large glioblastoma resection specimen. *Acta Neuropathol*. (2001) 102:103–9. https://www.ncbi.nlm.nih.gov/pubmed/11547944
99. Woodworth GF, McGirt MJ, Samdani A, Garonzik I, Olivi A, Weingart JD. Frameless image-guided stereotactic brain biopsy procedure: diagnostic yield, surgical morbidity, and comparison with the frame-based technique. *J Neurosurg*. (2006) 104:233–7. doi: 10.3171/jns.2006.104.2.233
100. Steinmetz MP, Barnett GH, Kim BS, Chidel MA, Suh JH. Metastatic seeding of the stereotactic biopsy tract in glioblastoma multiforme: case

report and review of the literature. *J Neurooncol*. (2001) 55:167–71. doi: 10.1023/A:1013873431159
101. Perrin RG, Bernstein M. Iatrogenic seeding of anaplastic astrocytoma following stereotactic biopsy. *J Neurooncol*. (1998) 36:243–6. doi: 10.1023/A:1005823805767
102. Zinn PO, Singh SK, Kotrotsou A, Hassan I, Thomas G, Luedi MM, et al. A coclinical radiogenomic validation study: conserved magnetic resonance radiomic appearance of periostin-expressing glioblastoma in patients and xenograft models. *Clin Cancer Res*. (2018) 24:6288–99. doi: 10.1158/1078-0432.CCR-17-3420
103. McNutt TR, Benedict SH, Low DA, Moore K, Shpitser I, Jiang W, et al. Using big data analytics to advance precision radiation oncology. *Int J Radiation Oncol Biol Phys*. (2018) 101:285–91. doi: 10.1016/j.ijrobp.2018.02.028
104. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature*. (2015) 521:436–44. doi: 10.1038/nature14539
105. Djuric U, Zadeh G, Aldape K, Diamandis P. Precision histology: how deep learning is poised to revitalize histomorphology for personalized cancer care. *Precision Oncol*. (2017) 1:22. doi: 10.1038/s41698-017-0022-1
106. Hosny A, Parmar C, Quackenbush J, Schwartz LH, Aerts HJWL. Artificial intelligence in radiology. *Nat Rev Cancer*. (2018) 18:500–10. doi: 10.1038/s41568-018-0016-5

Conflict of Interest Statement: Author PD's fellowship was partly funded by a grant from Varian Medical System. The funder had no role in study design, data collection and analysis, or preparation of the manuscript.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership