Chapter 30

The Role of Artificial Intelligence in Neuro-oncology Imaging

Jennifer Soun, Lu-Aung Yosuke Masudathaya, Arabdha Biswas, and Daniel S. Chow

Abstract

Diagnostic imaging is widely used to assess, characterize, and monitor brain tumors. However, there remain several challenges in each of these categories due to the heterogeneous nature of these tumors. This may include variations in tumor biology that relate to variable degrees of cellular proliferation, invasion, and necrosis that in turn have different imaging manifestations. These variations have created challenges for tumor assessment, including segmentation, surveillance, and molecular characterizations. Although several rule-based approaches have been implemented that relates to tumor size and appearance, these methods inherently distill the rich amount of tumor imaging data into a limited number of variables. Approaches in artificial intelligence, machine learning, and deep learning have been increasingly leveraged to computer vision tasks, including tumor imaging, given their effectiveness for solving image-based challenges. This objective of this chapter is to summarize some of these advances in the field of tumor imaging.

Key words Brain tumors, Radiogenomics, Tumor segmentation, Response Assessment in Neuro-Oncology (RANO), Response Evaluation Criteria in Solid Tumors (RECIST)

1 Introduction

With the recent emergence of artificial intelligence in neuroimaging, there is great interest in harnessing the power of new computational approaches that are inherently quantitative to non-invasively measure and classify features of brain tumors on routine and advanced magnetic resonance imaging (MRIs). Artificial intelligence (AI), including both machine learning (ML) and deep learning (DL), has the potential to automatically detect patterns in images that remain elusive to the eye of a neuroimager and to surpass human-level performance in the prediction of glioma genetics, treatment response, and long-term outcome. Theoretically, these features of AI may enable clinicians to provide greater value to the patient by allowing for expedited and more tailored treatments. This chapter will provide a brief review of primary brain

Olivier Colliot (ed.), *Machine Learning for Brain Disorders*, Neuromethods, vol. 197, https://doi.org/10.1007/978-1-0716-3195-9_30,

tumor epidemiology with emphasis on gliomas, evaluate present challenges in brain tumor imaging, and describe potential applications for AI.

2 Brain Tumor Epidemiology

Primary central nervous system (CNS) tumors are a rare form of cancer, with an incidence rate in adults estimated to be 23.8 per 100,000 persons [1] (*see* Box 1) [2]. However, while these tumors are rare, they constitute a significant fraction of cancer morbidity and mortality. Within the United States, approximately 10 per 100,000 are diagnosed with a primary brain tumor each year, and 6 to 7 per 100,000 are diagnosed with a primary malignant brain tumor [3]. Brain cancer incidence is the highest in Europe (age-standardized incidence rate [ASR]: 5.5 per 100,000 persons) and North America (ASR: 5.3 per 100,000 persons), along with Australia and Western Asia [3, 4]. With regard to tumor types, astrocytomas and gliomas are the second most common malignant brain tumor in adults following metastasis, and gliomas represent approximately 30% of brain tumors and 80% of all primary malignant brain tumors [4]. Gliomas vary in histology from potentially surgically curable grade 1 tumors (e.g., pilocytic astrocytoma) to aggressive grade 4 tumors (e.g., glioblastoma, GBM) with a high risk of recurrence and/or progression [5]. Accurately classifying and characterizing tumors is vital to diagnosing tumors and producing precise prognostication.

Cancer mortality is dependent on subtype and staging, and survival time after diagnosis varies greatly by grade [6, 7]. Gliomas are classified and graded based on histological and molecular markers [6, 7]. GBM is a subtype of glioma which arises from normal glial cells and consists of a group of genetically and phenotypically heterogeneous tumors [7, 8]. GBM is the most common primary CNS tumor in adults, with an incidence of 3.2 per 100,000 adults each year in Europe and America [9]. The incidence increases significantly with age, with a mean age of diagnosis at 64 for primary GBM and a peak incidence of 15.2 cases per 100,000 between the ages of 75 and 84 [9]. GBM occurrence has been associated with several genetic diseases, including tuberous sclerosis, neurofibromatosis type I, and Li-Fraumeni syndrome; however, less than 20% of patients with GBM have a strong family history of cancer, and the only well-established environmental risk factor is exposure to ionizing radiation [10]. GBM has the poorest overall survival among gliomas, with 0.05–4.7% patient survival after 5 years of diagnosis in the United States from 1995 to 2010 (95% CI 4.4–5.0) [4, 11]. Overall, mortality and prognosis vary tremendously depending on grade and subtype, and methods to more accurately predict these factors would help improve treatment and outcomes.

Box 1 Main Primary Central Nervous System Tumors	
Malignant	
Astrocytomas	20–25%
Oligodendrogliomas	1–2%
Ependymal tumors	<2%
Other	8%
Non-malignant	
Meningiomas	37%
Pituitary	16%
Nerve sheath	8%
Other	7%

GBM remains one of the most lethal malignant solid tumors. The 1-year overall survival of newly diagnosed GBM is 17–30% with a 5-year survival rate of less than 5% [6]. Surgical resection followed by chemotherapy and radiotherapy remains the cornerstone treatment choice for GBM. However, the response to chemotherapy is variable, and nearly all patients suffer from recurrent disease [4]. Additionally, these tumors most frequently arise within the frontal lobe, leading to both cognitive and motor disabilities that result in loss of independence in many patients. Increasingly, molecular markers are being used for glioma classification and characterization. Mutations such as IDH1 can be a strong predictor of favorable prognosis and can assist in distinguishing among glioma subtypes [12]. Characterizing certain genetic features such as IDH1 status can aid in more accurate diagnoses and prognostication.

3 Present Challenges with Brain Tumor Imaging

3.1 Segmentation

While there have been significant advances in neuro-oncology imaging, there remain several challenges in providing accurate measurements of brain tumors. For example, a present limitation is that commonly used techniques to monitor tumor size use unidimensional and bidimensional manual measurements. While this may work for solid tumors that have a more spherical shape, the postsurgical cavity and tumors themselves of neuro-oncology patients tend to be highly irregular in shape, which increases the difficulty in obtaining accurate measurements. This stems from the fact that GBMs themselves and their recurrence commonly

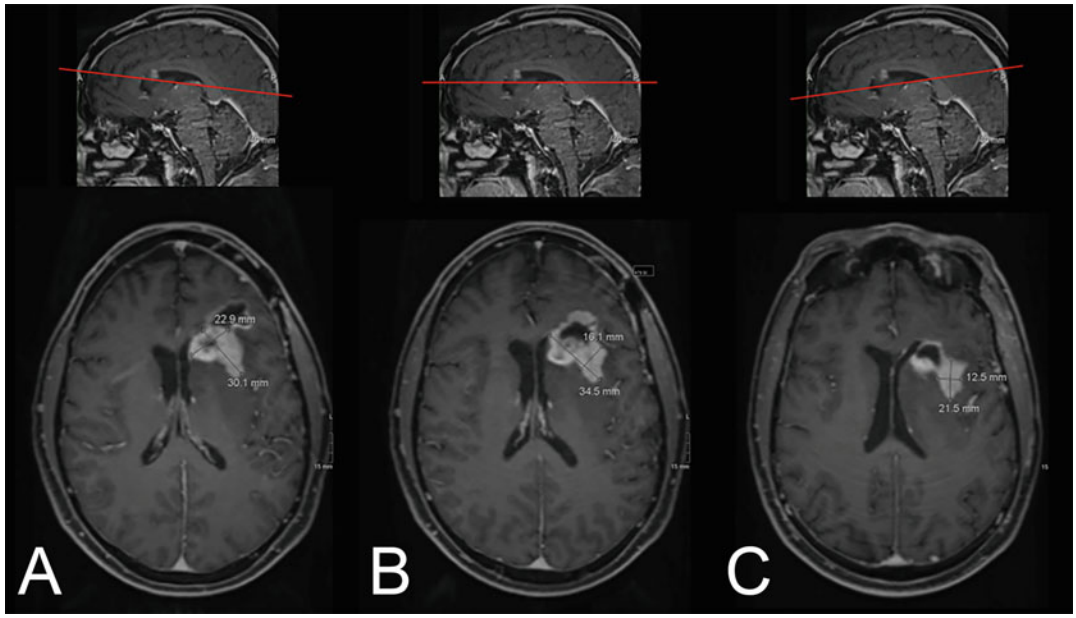

Fig. 1 Head tilt affecting designation. Patient with glioblastoma after resection. Simulation of tilting the patient's head up results in progression of disease (**a**) while in routine positioning demonstrates stable disease (**b**), and tilting downward results in partial response (**c**)

demonstrate eccentric and nodular growth. For patients, such inconsistencies and potential inaccuracies may result in classifying effective treatments as ineffective or vice versa (Fig. 1). Ultimately, this challenge heightens the importance for the need for reliable and reproducible techniques for tumor size measurements.

3.2 Surveillance

In addition to tumor segmentation, radiographic assessment has served as an essential tool to monitor patients with brain tumors and has played an important role in clinical trials. Historically, increases and decreases in tumor size using gadolinium contrast-enhanced sequences have served as imaging markers for progression and treatment response, respectively [13, 14]. However, there are limitations of relying solely on contrast enhancement for assessing disease status. Specifically, treatment-related increases in enhancement were observed to mimic progression with increasing frequency following the introduction of standard of care therapy of radiation and temozolomide (TMZ) [15]. This tumor pseudoprogression (psPD) is observed in 20–60% of patients who have undergone radiotherapy with TMZ and defined as increases in edema and contrast enhancement on MRI with or without clinical deterioration that subsequently stabilizes or resolves (Fig. 2) [15–17]. Additionally, the incidence has been reported to be as high as 90% in patients that have increased sensitivity to TMZ, identified with methylation status of the methyltransferase (MGMT) promoter in glioma cells [18].

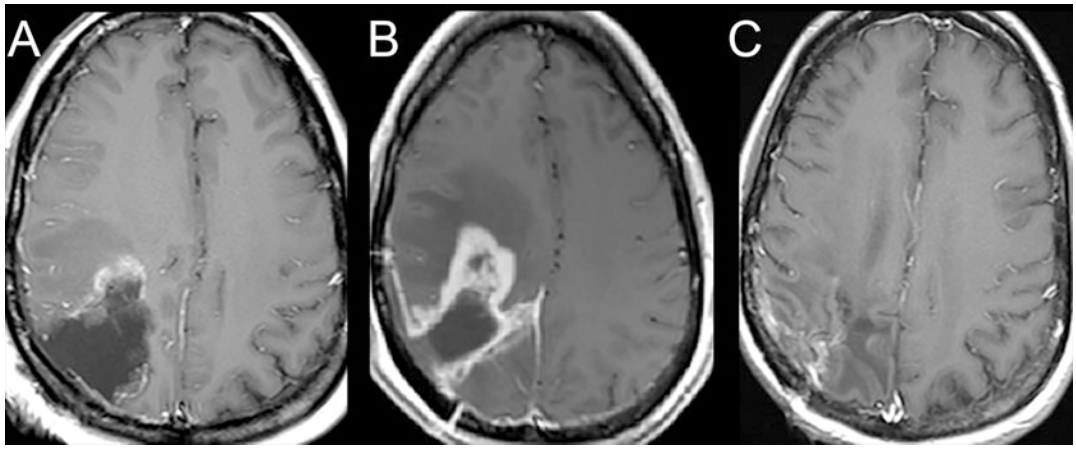

Fig. 2 Pseudoprogression. Example of a 45-year-old female with GBM. Axial post-contrast images immediately after resection show minimal enhancing disease (**a**). Follow-up MRI at 1 month demonstrates new thick enhancement (**b**) that subsequently reduced on images 12 months out (**c**)

Presently, the exact mechanism is still not fully understood, and the only accepted standard to distinguish true progression of disease (PD) from treatment-related psPD is invasive tissue sampling or short interval imaging or clinical follow-up, which may delay and compromise management changes in an aggressive tumor [16, 17]. In 2010, the Response Assessment in Neuro-Oncology (RANO) working group set criteria to address some of these challenges, including psPD [19]. However, evaluation of psPD remains limited with conventional imaging techniques. Challenges in monitoring GBM patients due to psPD are also observed in other newer treatments, including immunotherapies [20, 21]. The immune-related response criteria working group (iRANO) has made guidelines to address challenges of radiographic worsening in order to avoid classifying effective treatments as ineffective in instances of psPD; however, the group acknowledges that future research and solutions incorporating advanced imaging are necessary to improve assessment in these patients [21, 22].

3.3 Molecular Classification

3.3.1 Impact of Glioma Inter-tumoral Heterogeneity

Glioma inter-tumoral genetic heterogeneity has been shown to impact both prognosis and response to therapy. For example, isocitrate dehydrogenase (IDH)-mutant GBMs demonstrate significantly improved survivorship compared to IDH-wild GBMs (31 months vs. 15 months) [12, 23]. Recognition of the importance of genetic information has led the World Health Organization (WHO) to place considerable emphasis on the integration of molecular markers for its classification schemes in its 2021 update, including IDH status [24]. Regarding treatment response, it is becoming increasingly evident that GBMs' differing genetic attributes also result in mixed responses [25]. One of the early

mutations discovered was O6-methylguanine-DNA methyltransferase (MGMT) promoter silencing, which reduces tumor cells' ability to repair DNA damage from alkylating agents such as temozolomide (TMZ). Hegi et al. [26] subsequently observed that MGMT promoter methylation silencing was observed in 45% of GBM patients, who demonstrated a survival benefit when treated with a combination of TMZ and radiotherapy versus radiotherapy alone (21.7 months versus 15.3 months). It is critical that future GBM monitoring integrates imaging and genetic data in order to provide accurate prognostic information and guide personalized therapies.

3.3.2 Challenges of Personalized Therapy

Discoveries in genetic profiling have spurred the development of new targeted therapies [27] with over 140 clinical trials presently evaluating personalized or targeted therapies for GBMs alone. These therapies are tailored to exploit genetically driven therapeutic targets. However, an apparent roadblock to these individualized approaches is the growing evidence of GBM intra-tumoral heterogeneity. Patel et al. demonstrated that GBMs consist of a mixture of cells with variable gene expression profiles using single-cell RNA sequencing [28]. Likewise, Sottoriva et al. observed genome-wide variability using surgical multisampling approach from 11 GBM patients [29]. Thus, each brain tumor may reflect multiple unique tumor habitats with corresponding differences in response and resistance to therapy, challenging the identification, development, and implementation of individualized care.

3.3.3 MRI Biomarkers of Tumor Biology and Genetic Heterogeneity

Both spatial and temporal variations in genetic expression result in alterations in tumor biology, including changes in apoptosis, cellular proliferation, cellular invasion, and angiogenesis [30]. In turn, these biologic changes manifest in the heterogeneous imaging features of brain tumors, resulting in varying degrees of enhancement and edema. For example, imaging changes on contrast-enhanced MRI result from the breakdown of the blood-brain barrier and can demonstrate areas of necrosis as a marker for apoptosis. Additionally, MRI sequences based on physiology such as apparent diffusion coefficient (ADC) and perfusion imaging have been shown to relate to tumoral cellularity and angiogenesis, respectively. Furthermore, promising efforts have shown that tumors with lower cerebral blood volume (CBV) on perfusion are more likely to be IDH mutants and have longer overall survival (OS) [31, 32]. Other reports have used enhancement patterns and ADC to predict IDH status with some success [33, 34]. Currently, efforts to provide molecular classification for brain tumors based on these MRI features have had mixed results. For example, classification of IDH and MGMT mutant status has had some success; however, methods for 1p19q and EGFR have demonstrated less reproducibility [35–37]. Different mutations may have similar MRI

features, and a "single" tumor can have multiple different mutations internally. Several approaches have emerged to provide standardized visual interpretation of gliomas for tissue classification. For example, the Visually AcceSAble Rembrandt Images (VASARI) feature set is a rule-based lexicon to improve the reproducibility of interpretation [38]. However, these methods rely on human visual interpretation, which is inherently subjective and prone to inter-rater variability. Ultimately, steps are needed to provide reliable and reproducible methods to accurately classify molecular subtypes a priori.

4 Potential Applications for Machine Learning

4.1 Segmentation

Radiographic assessment serves an important role for clinical follow-up and research trials in oncology. Currently, the RANO criteria rely on 2D measurements of the enhancing disease as well as subjective assessment of the FLAIR non-enhancing tumor, which is then used to guide treatment strategies. However, the postsurgical cavity tends to be highly irregular in shape, which may increase the difficulty in obtaining accurate and reproducible measurements. Additionally, linear measurements obtained for cystic and necrotic tumors are often overestimated [39]. Intuitively, 3D segmentation provides a more accurate method for assessing tumor size compared to linear 2D approaches and techniques [40–42]. For example, Dempsey et al. [43] observed that 3D segmentation allows for better survival prediction compared with traditional diameter-based analysis.

Deep learning, an emerging branch of artificial intelligence, has been shown to rapidly outperform other machine learning approaches' imaging benchmarks for various computer vision tasks [44, 45], including imaging 3D segmentation tasks. For example, Zhang et al. [46] observed that a CNN approach performed significantly better than other techniques, including random forest, support vector machine (SVM, a traditional linear machine learning technique), coupled level sets, and majority voting for brain segmentation.

Since 2012, the Multimodal *Bra*in *T*umor Image *S*egmentation (BraTS) challenge has demonstrated the efficacy of deep learning approaches for tumor segmentation [47]. This unique dataset provides developers access to GBM images, which now includes over 2000 patients from 37 institutions. As result, multiple groups have developed fully automated brain tumor segmentation tools which rely on various AI techniques to identify lesion margins and provide a more accurate estimate for disease burden (Fig. 3) [48–51]. In 2020, Isensee et al. [52] took first place with Sørensen-Dice coefficient scores of 88.95, 85.06, and 82.03 for whole tumor, tumor core, and enhancing tumor, respectively. Most recently in 2021,

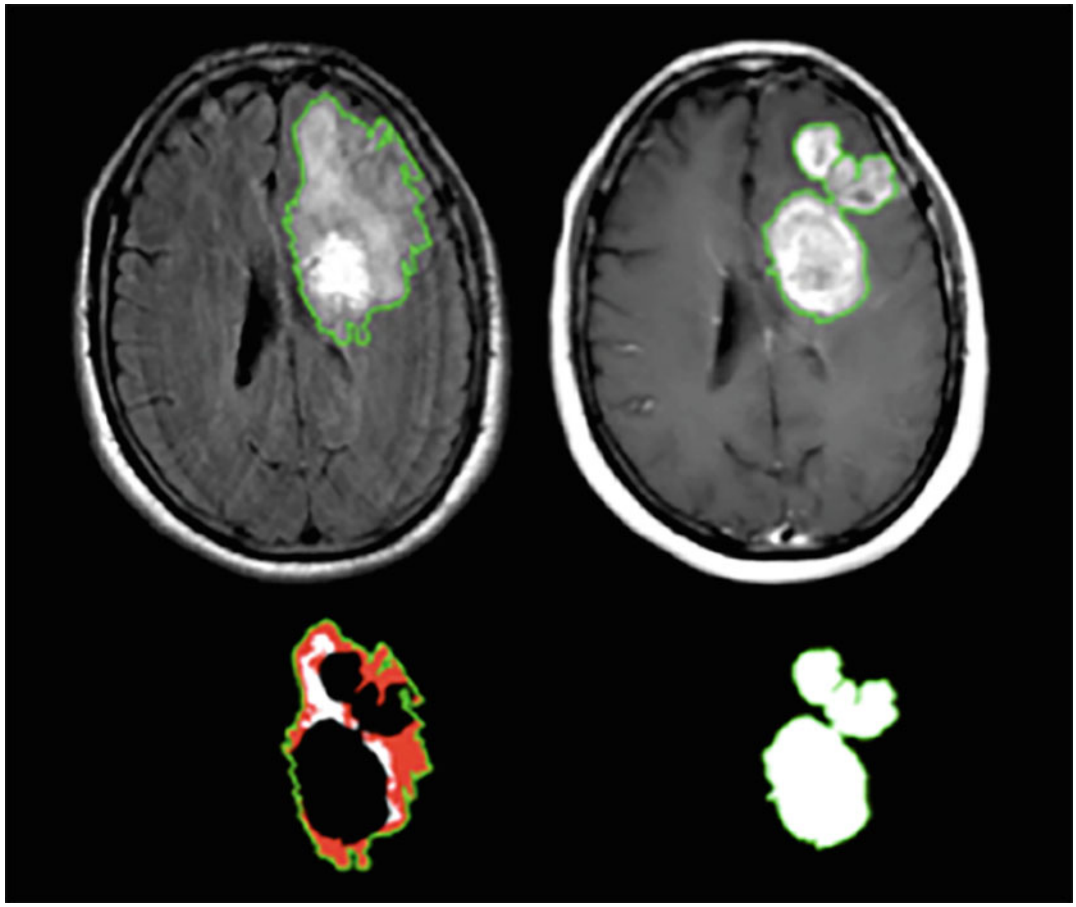

Fig. 3 Example of automated glioma segmentation using deep learning showing FLAIR edema segmentation (left) as well as segmentation of enhancing tissue (right). *(Courtesy Peter Chang, MD)*

BraTS has partnered with the Radiological Society of North America (RSNA) and the American Society of Neuroradiology (ASNR) [53].

4.2 Surveillance

As described previously, psPD cases are not reliably distinguished from true progression using RANO criteria with a recent meta-analysis suggesting that upward of 36% are underdiagnosed [54]. In fact, the only accepted methods to distinguish true PD from treatment-related psPD are invasive tissue sampling and short interval clinical follow-up with imaging, which may delay and compromise disease management in an aggressive tumor [16, 17].

Traditional machine learning models have been previously utilized for psPD characterization from radiologic imaging. Hu et al.'s [55] SVM approach examining multi-parametric MRI data yielded an optimized classifier for psPD with a sensitivity of 89.9% and specificity of 93.7%. Though deep learning methods have been leveraged less frequently, they are showing promise for

characterizing psPD versus true PD [56–58]. Jang et al. [56] assessed a deep learning, a long short-term memory network combined with a CNN (CNN-LSTM), to determine psPD versus tumor PD in GBM. Their dataset consisted of clinical and MRI data from 2 institutions, with 59 patients in the training cohort and 19 patients in the testing cohort. Their CNN-LSTM structure, utilizing both clinical and MRI data, outperformed the two comparison models of CNN-LSTM with MRI data alone and a random forest structure with clinical data alone, yielding an AUC (area under the curve) of 0.83, an AUPRC (area under the precision-recall curve) of 0.87, and an F-1 score of 0.74 [56]. More recently, Lee et al. [58] also utilized a CNN-STM to distinguish PD from psPD with an accuracy range of 0.62–0.75. These examples indicate that utilization of a deep learning approach can outperform a more traditional machine learning approach in analyzing images.

4.3 Molecular Classification

Radiogenomics focuses on bridging the associations between medical imaging and gene expression data in order to aid in the understanding of underlying disease mechanisms and improve diagnostics [59]. Certain molecular and genetic alterations in tissue can be observed computationally in terms of radiological appearance, including shape and texture of tissue. Radiogenomics, which leverages the interplay between radiological and genetic features in oncology, is important to improve patient treatment decisions, and artificial intelligence has become a key player that has led to significant advancements in these areas. AI-based radiogenomics has the potential to better characterize diagnosis, prognosis, and survival prediction by detecting key features in images that identify molecular characteristics of disease.

In gliomas, one of the earliest groups that used neural networks to predict tumoral genetic subtypes from imaging features was Levner et al. [60]. In this study, features were extracted from space-frequency texture analysis on the S-transform of brain MRIs to predict MGMT promoter methylation status in newly diagnosed GBM patients. Levner's group achieved an accuracy of 87.7% across 59 patients, among which 31 patients had biopsy-confirmed MGMT promoter methylated tumors. Residual CNN methods have also been used to predict MGMT promoter methylation status [61], as well as IDH mutation status. For example, Chang et al. developed a CNN to simultaneously classify IDH1, 1p19q codeletion, and MGMT promoter methylation status with high accuracy from imaging data derived from 259 patients in the Cancer Imaging Archives dataset [35]. Chang et al. also developed a principal component analysis approach to disentangle the final feature layer and determine the most influential features for each classification (Fig. 4). These features largely overlap with what has been described in the literature by subjective visual assessment. Ryu et al. [62] evaluated glioma heterogeneity via textural analysis and

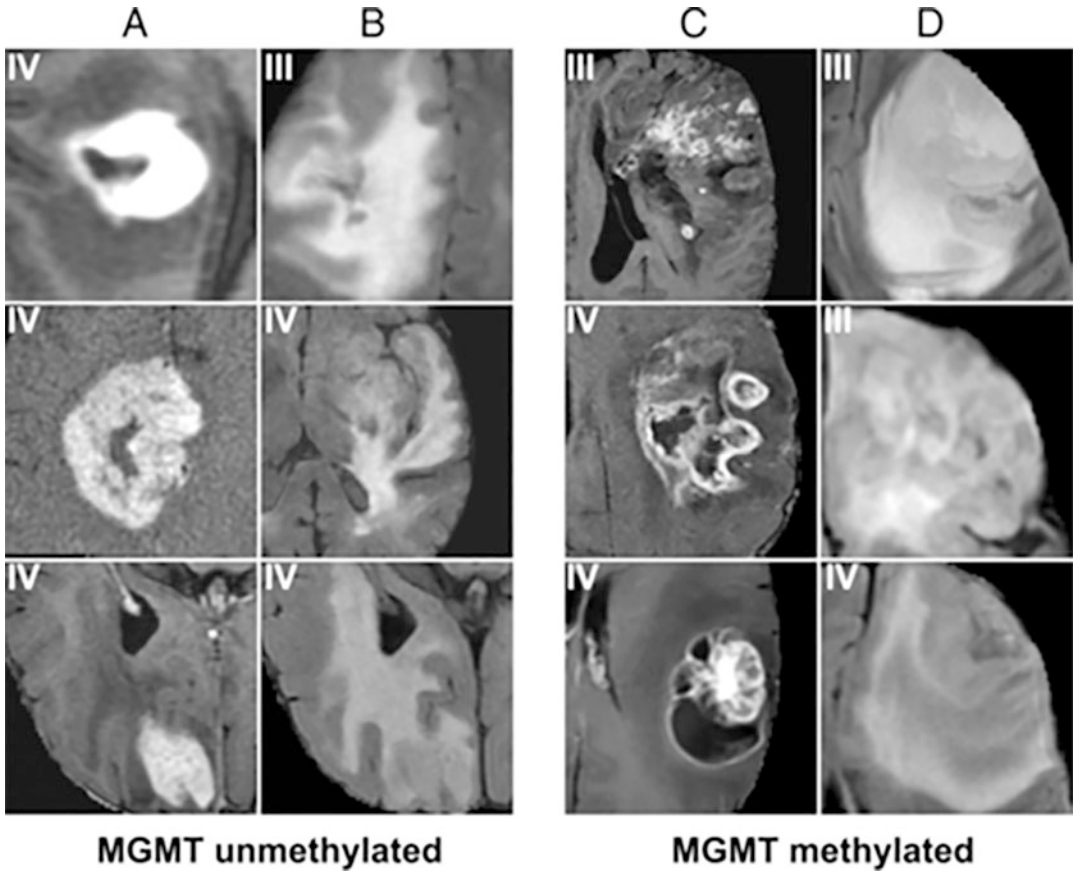

Fig. 4 MRI separating gliomas by MGMT methylation status. Features include thick enhancement with central necrosis (**a**) with infiltrative edema patterns (**b**). In contrast, features predictive of MGMT promoter methylated status include nodular and heterogeneous enhancement (**c**) with masslike FLAIR edema (**d**). (Copyright American Journal of Neuroradiology, adapted, with permission, from reference [35])

distinguished low- and high-grade gliomas with 80% accuracy. Additionally, Drabycz et al. [63] were able to classify MGMT promoter methylation status in glioblastoma patients with 71% accuracy using a textural analysis approach.

5 Summary

In summary, present challenges in brain tumor imaging in part stem from the heterogeneity of the disease, which results in challenges related to disease characterization. However, the application of novel AI, ML, and DL approaches for brain tumor imaging aims to improve many of these areas due to its ability to accurately and reliably detect imaging patterns beyond human perception. Numerous public competitions (e.g., BraTS) have also spurred the field and have recently begun collaborations with multiple

imaging societies, including the RSNA and ASNR. Ultimately, there is optimism that these tools will continue to yield new opportunities to enhance discovery and care in the future.

Acknowledgments

The authors wish to acknowledge Jack Grinband, PhD (Columbia University, New York NY); Brent Weinberg, MD PhD (Emory, Atlanta GA); and Peter Chang, MD (University of California, Irvine, Irvine CA), for their expertise and support. The authors also acknowledge the supportive administrative team from the Center for Artificial Intelligence in Diagnostic Medicine at the University of California, Irvine.

References

1. Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS (2020) CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2013–2017. Neuro Oncol 22(12 Suppl 2):iv1–iv96. https://doi.org/10.1093/neuonc/noaa200
2. Lapointe S, Perry A, Butowski NA (2018) Primary brain tumours in adults. Lancet 392(10145):432–446. https://doi.org/10.1016/S0140-6736(18)30990-5
3. Wrensch M, Minn Y, Chew T, Bondy M, Berger MS (2002) Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro Oncol 4(4):278–299. https://doi.org/10.1093/neuonc/4.4.278
4. Ostrom QT, Gittleman H, Stetson L, Virk SM, Barnholtz-Sloan JS (2015) Epidemiology of gliomas. Cancer Treat Res 163:1–14. https://doi.org/10.1007/978-3-319-12048-5_1
5. McNeill KA (2016) Epidemiology of brain tumors. Neurol Clin 34(4):981–998. https://doi.org/10.1016/j.ncl.2016.06.014
6. Kayabolen A, Yilmaz E, Bagci-Onder T (2021) IDH mutations in Glioma: double-edged sword in clinical applications? Biomedicines 9(7):799. https://doi.org/10.3390/biomedicines9070799
7. Louis DN, Perry A, Wesseling P et al (2021) The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol 23(8):1231–1251. https://doi.org/10.1093/neuonc/noab106
8. Urbańska K, Sokołowska J, Szmidt M, Sysa P (2014) Glioblastoma multiforme - an overview. Contemp Oncol (Pozn) 18(5):307–312. https://doi.org/10.5114/wo.2014.40559
9. Ostrom QT, Gittleman H, Xu J et al (2016) CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2009–2013. Neuro Oncol 18(suppl_5):v1–v75. https://doi.org/10.1093/neuonc/now207
10. Braganza MZ, Kitahara CM, Berrington de González A, Inskip PD, Johnson KJ, Rajaraman P (2012) Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review. Neuro-Oncology 14(11):1316–1324. https://doi.org/10.1093/neuonc/nos208
11. Ostrom QT, Bauchet L, Davis FG et al (Jul 2014) The epidemiology of glioma in adults: a "state of the science" review. Neuro-Oncology 16(7):896–913. https://doi.org/10.1093/neuonc/nou087
12. Nobusawa S, Watanabe T, Kleihues P, Ohgaki H (2009) IDH1 mutations as molecular signature and predictive factor of secondary glioblastomas. Clin Cancer Res 15(19):6002–6007. https://doi.org/10.1158/1078-0432.CCR-09-0715
13. Reardon DA, Galanis E, DeGroot JF et al (2011) Clinical trial end points for high-grade glioma: the evolving landscape. Neuro-Oncology 13(3):353–361. https://doi.org/10.1093/neuonc/noq203
14. Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG (Jul 1990) Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8(7):1277–1280. https://doi.org/10.1200/jco.1990.8.7.1277
15. de Wit MC, de Bruin HG, Eijkenboom W, Sillevis Smitt PA, van den Bent MJ (2004) Immediate post-radiotherapy changes in

malignant glioma can mimic tumor progression. Neurology 63(3):535–537

16. Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ (2008) Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. Lancet Oncol 9(5): 453–461. https://doi.org/10.1016/S1470-2045(08)70125-6
17. Hygino da Cruz LC Jr, Rodriguez I, Domingues RC, Gasparetto EL, Sorensen AG (2011) Pseudoprogression and pseudoresponse: imaging challenges in the assessment of posttreatment glioma. AJNR Am J Neuroradiol 32(11): 1978–1985. https://doi.org/10.3174/ajnr.A2397
18. Brandes AA, Franceschi E, Tosoni A et al (2008) MGMT promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. J Clin Oncol 26(13):2192–2197. https://doi.org/10.1200/JCO.2007.14.8163
19. Wen PY, Macdonald DR, Reardon DA et al (2010) Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 28(11):1963–1972. https://doi.org/10.1200/JCO.2009.26.3541
20. Huang RY, Wen PY (Nov 2016) Response assessment in neuro-oncology criteria and clinical endpoints. Magn Reson Imaging Clin N Am 24(4):705–718. https://doi.org/10.1016/j.mric.2016.06.003
21. Huang RY, Neagu MR, Reardon DA, Wen PY (2015) Pitfalls in the neuroimaging of glioblastoma in the era of antiangiogenic and immuno/targeted therapy - detecting illusive disease, defining response. Front Neurol 6:33. https://doi.org/10.3389/fneur.2015.00033
22. Okada H, Weller M, Huang R et al (Nov 2015) Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. Lancet Oncol 16(15):e534–e542. https://doi.org/10.1016/S1470-2045(15)00088-1
23. Yan H, Parsons DW, Jin G et al (2009) IDH1 and IDH2 mutations in gliomas. N Engl J Med 360(8):765–773. https://doi.org/10.1056/NEJMoa0808710
24. Louis DN, Perry A, Reifenberger G et al (Jun 2016) The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 131(6): 803–820. https://doi.org/10.1007/s00401-016-1545-1
25. Bartek J Jr, Ng K, Bartek J, Fischer W, Carter B, Chen CC (Jul 2012) Key concepts in glioblastoma therapy. J Neurol Neurosurg Psychiatry 83(7):753–760. https://doi.org/10.1136/jnnp-2011-300709
26. Hegi ME, Diserens AC, Gorlia T et al (2005) MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 352(10):997–1003. https://doi.org/10.1056/NEJMoa043331
27. Auffinger B, Thaci B, Nigam P, Rincon E, Cheng Y, Lesniak MS (2012) New therapeutic approaches for malignant glioma: in search of the Rosetta stone. F1000 Med Rep 4:18. https://doi.org/10.3410/M4-18
28. Patel AP, Tirosh I, Trombetta JJ et al (2014) Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. Science 344(6190):1396–1401. https://doi.org/10.1126/science.1254257
29. Sottoriva A, Spiteri I, Piccirillo SG et al (2013) Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics. Proc Natl Acad Sci U S A 110(10): 4009–4014. https://doi.org/10.1073/pnas.1219747110
30. Belden CJ, Valdes PA, Ran C et al (Oct 2011) Genetics of glioblastoma: a window into its imaging and histopathologic variability. Radiographics 31(6):1717–1740. https://doi.org/10.1148/rg.316115512
31. Kickingereder P, Sahm F, Radbruch A et al (2015) IDH mutation status is associated with a distinct hypoxia/angiogenesis transcriptome signature which is non-invasively predictable with rCBV imaging in human glioma. Sci Rep 5:16238. https://doi.org/10.1038/srep16238
32. Law M, Young RJ, Babb JS et al (2008) Gliomas: predicting time to progression or survival with cerebral blood volume measurements at dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. Radiology 247(2):490–498. https://doi.org/10.1148/radiol.2472070898
33. Price SJ, Allinson K, Liu H et al (2017) Less invasive phenotype found in Isocitrate dehydrogenase-mutated glioblastomas than in Isocitrate dehydrogenase wild-type glioblastomas: a diffusion-tensor imaging study. Radiology 283(1):215–221. https://doi.org/10.1148/radiol.2016152679
34. Xiong J, Tan W, Wen J et al (2016) Combination of diffusion tensor imaging and conventional MRI correlates with isocitrate dehydrogenase 1/2 mutations but not

1p/19q genotyping in oligodendroglial tumours. Eur Radiol 26(6):1705–1715. https://doi.org/10.1007/s00330-015-4025-4

35. Chang P, Grinband J, Weinberg BD et al (2018) Deep-learning convolutional neural networks accurately classify genetic mutations in gliomas. AJNR Am J Neuroradiol 39(7): 1201–1207. https://doi.org/10.3174/ajnr.A5667
36. Zlochower A, Chow DS, Chang P, Khatri D, Boockvar JA, Filippi CG (2020) Deep learning AI applications in the imaging of glioma. Top Magn Reson Imaging 29(2):115. https://doi.org/10.1097/RMR.0000000000000237
37. Shaver MM, Kohanteb PA, Chiou C et al (2019) Optimizing neuro-oncology imaging: a review of deep learning approaches for glioma imaging. Cancers (Basel) 11(6):829. https://doi.org/10.3390/cancers11060829
38. Gutman DA, Cooper LA, Hwang SN et al (2013) MR imaging predictors of molecular profile and survival: multi-institutional study of the TCGA glioblastoma data set. Radiology 267(2):560–569. https://doi.org/10.1148/radiol.13120118
39. Chow DS, Qi J, Guo X et al (2014) Semiautomated volumetric measurement on postcontrast MR imaging for analysis of recurrent and residual disease in glioblastoma multiforme. AJNR Am J Neuroradiol 35(3):498–503. https://doi.org/10.3174/ajnr.A3724
40. Sorensen AG, Patel S, Harmath C et al (2001) Comparison of diameter and perimeter methods for tumor volume calculation. J Clin Oncol. 19(2):551–557. https://doi.org/10.1200/JCO.2001.19.2.551
41. Provenzale JM, Mancini MC (2012) Assessment of intra-observer variability in measurement of high-grade brain tumors. J Neurooncol 108(3):477–483. https://doi.org/10.1007/s11060-012-0843-2
42. Provenzale JM, Ison C, Delong D (2009) Bidimensional measurements in brain tumors: assessment of interobserver variability. AJR Am J Roentgenol 193(6):W515–W522. https://doi.org/10.2214/AJR.09.2615
43. Dempsey MF, Condon BR, Hadley DM (2005) Measurement of tumor "size" in recurrent malignant glioma: 1D, 2D, or 3D? AJNR Am J Neuroradiol 26(4):770–776
44. LeCun Y, Bengio Y, Hinton G (2015) Deep learning. Nature. 521(7553):436–444. https://doi.org/10.1038/nature14539
45. Simonyan K, Vedaldi A, Zisserman A (2013) Deep inside convolutional networks: visualising image classification models and saliency maps. CoRR. abs/1312.6034
46. Zhang W, Li R, Deng H et al (2015) Deep convolutional neural networks for multi-modality isointense infant brain image segmentation. NeuroImage 108:214–224. https://doi.org/10.1016/j.neuroimage.2014.12.061
47. Menze BH, Jakab A, Bauer S et al (2015) The multimodal brain tumor image segmentation benchmark (BRATS). IEEE Trans Med Imaging 34(10):1993–2024. https://doi.org/10.1109/TMI.2014.2377694
48. Chang PD (2016) Fully convolutional deep residual neural networks for brain tumor segmentation. In: Crimi A, Menze B, Maier O, Reyes M, Winzeck S, Handels H (eds). Brainlesion: glioma, multiple sclerosis, stroke and traumatic brain injuries: second international workshop, BrainLes 2016, with the challenges on BRATS, ISLES and mTOP 2016, Held in conjunction with MICCAI 2016, Athens, Greece, October 17, 2016, revised selected papers. Springer International Publishing; pp 108–118
49. Bangalore Yogananda CG, Shah BR, Vejdani-Jahromi M et al (2020) A fully automated deep learning network for brain tumor segmentation. Tomography 6(2):186–193. https://doi.org/10.18383/j.tom.2019.00026
50. Ranjbarzadeh R, Bagherian Kasgari A, Jafarzadeh Ghoushchi S, Anari S, Naseri M, Bendechache M (2021) Brain tumor segmentation based on deep learning and an attention mechanism using MRI multi-modalities brain images. Sci Rep 11(1):10930. https://doi.org/10.1038/s41598-021-90428-8
51. Havaei M, Davy A, Warde-Farley D et al (2017) Brain tumor segmentation with Deep Neural Networks. Med Image Anal 35:18–31. https://doi.org/10.1016/j.media.2016.05.004
52. Isensee F, Jager PF, Full PM, Vollmuth P, Maier-Hein KH (2020) nnU-Net for brain tumor segmentation. Int MICCAI. arXiv preprint arXiv:2011.00848
53. Baid U, Ghodasara S, Bilello M, et al (2021) The RSNA-ASNR-MICCAI BraTS 2021 benchmark on brain tumor segmentation and radiogenomic classification. arXiv preprint arXiv:2107.02314, 2021
54. Abbasi AW, Westerlaan HE, Holtman GA, Aden KM, van Laar PJ, van der Hoorn A (Sep 2018) Incidence of tumour progression and pseudoprogression in high-grade gliomas: a systematic review and meta-analysis. Clin Neuroradiol 28(3):401–411. https://doi.org/10.1007/s00062-017-0584-x

55. Hu X, Wong KK, Young GS, Guo L, Wong ST (2011) Support vector machine multiparametric MRI identification of pseudoprogression from tumor recurrence in patients with resected glioblastoma. J Magn Reson Imaging 33(2):296–305
56. Jang B-S, Jeon SH, Kim IH, Kim IA (2018) Prediction of pseudoprogression versus progression using machine learning algorithm in glioblastoma. Sci Rep 8(1):12516
57. Jang BS, Park AJ, Jeon SH et al (2020) Machine learning model to predict pseudoprogression versus progression in glioblastoma using MRI: a multi-institutional study (KROG 18–07). Cancers (Basel) 12(9):2706. https://doi.org/10.3390/cancers12092706
58. Lee J, Wang N, Turk S et al (2020) Discriminating pseudoprogression and true progression in diffuse infiltrating glioma using multiparametric MRI data through deep learning. Sci Rep 10(1):20331. https://doi.org/10.1038/s41598-020-77389-0
59. Trivizakis E, Papadakis GZ, Souglakos I et al (2020) Artificial intelligence radiogenomics for advancing precision and effectiveness in oncologic care (Review). Int J Oncol 57(1):43–53. https://doi.org/10.3892/ijo.2020.5063
60. Levner I, Drabycz S, Roldan G, De Robles P, Cairncross JG, Mitchell R (2009) Predicting MGMT methylation status of glioblastomas from MRI texture. Med Image Comput Comput Assist Interv 12(Pt 2):522–530. https://doi.org/10.1007/978-3-642-04271-3_64
61. Korfiatis P, Kline TL, Lachance DH, Parney IF, Buckner JC, Erickson BJ (Oct 2017) Residual deep convolutional neural network predicts MGMT methylation status. J Digit Imaging 30(5):622–628. https://doi.org/10.1007/s10278-017-0009-z
62. Ryu YJ, Choi SH, Park SJ, Yun TJ, Kim JH, Sohn CH (2014) Glioma: application of whole-tumor texture analysis of diffusion-weighted imaging for the evaluation of tumor heterogeneity. PLoS One 9(9):e108335. https://doi.org/10.1371/journal.pone.0108335
63. Drabycz S, Roldán G, de Robles P et al (2010) An analysis of image texture, tumor location, and MGMT promoter methylation in glioblastoma using magnetic resonance imaging. Neuroimage 49(2):1398–1405. https://doi.org/10.1016/j.neuroimage.2009.09.049