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REVIEW

Machine learning in neuro-oncology: toward novel development fields

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Abstract

Purpose Artificial Intelligence (AI) involves several and different techniques able to elaborate a large amount of data responding to a specific planned outcome. There are several possible applications of this technology in neuro-oncology.

Methods We reviewed, according to PRISMA guidelines, available studies adopting AI in different fields of neuro-oncology including neuro-radiology, pathology, surgery, radiation therapy, and systemic treatments.

Results Neuro-radiology presented the major number of studies assessing AI. However, this technology is being successfully tested also in other operative settings including surgery and radiation therapy. In this context, AI shows to significantly reduce resources and costs maintaining an elevated qualitative standard. Pathological diagnosis and development of novel systemic treatments are other two fields in which AI showed promising preliminary data.

Conclusion It is likely that AI will be quickly included in some aspects of daily clinical practice. Possible applications of these techniques are impressive and cover all aspects of neuro-oncology.

Keywords Artificial intelligence · Deep learning · Machine learning · Brain tumors · Central nervous system malignancies

Introduction

Tumors of the central nervous system (CNS) account for a small proportion (around 1%) of all invasive cancers cases [1]. Malignant (29.7%) and nonmalignant (70.3%) brain tumors employed over a hundred different molecular subtypes with each of them presenting their own clinical and biological behaviors [1]. Overall, these are rare tumors with an overall incidence of 0.8% annually. Nonetheless, these malignancies are associated with a high mortality rate, permanent disability, and high public health costs [1]. In recent years important improvements toward a better diagnosis and treatment of these tumors have been made. The 2021 World Health Organization (WHO) Classification of CNS malignancies offers a comprehensive picture of the important progress achieved in the last years [2]. Despite this, several

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important challenges awaiting researchers and clinicians in the field of neuro-oncology. For example, the prediction of disease course and progression, the research of predictive treatment response factors, an improved tumor diagnosis, the research of novel effective treatments, and a no invasive diagnoses of disease molecular features are clinical needs that have not yet been answered. Artificial intelligence (AI) is any computer method that performs tasks normally requiring human intelligence. Machine learning (ML) is one form of artificial intelligence consisting of developing algorithms to enable computers to learn from existing data the function that relates input and output in order to use this function for future analysis on new data. In other words, ML is a subfield of AI that develops algorithms that allow the computer to adapt to a new problem without being reprogrammed. That is, a machine learning system "learns" to solve a problem directly from data. This is done by applying statistical methods to recognize patterns from a set of provided data without human instruction. Most ML algorithms can be viewed as mathematical models that map a set of observed variables, called features or predictors, of a data point or sample, into a set of outcome variables, called labels or targets [3]. The most used machine learning approaches used in medical field are classification/segmentation methods. These methods split up in two families: (i) supervised learning methods, when the partition of data is known; and (ii) unsupervised learning methods, when the partition of data is unknown. Table 1 shows the principal supervised and unsupervised classification methods with the corresponding (open source) R packages to perform them. Notice that between the round brackets a data.frame object must be entered; whereas, when the symbol ~ is found, this means that the function requires a formula object [4]. The most cited supervised learning methods applied in neuro-oncology field are the Artificial Neural Network (ANN) and Convolutional Neural Network (CNN), also called deep learning approaches. The power of these techniques is in their scalability, which is largely based on their ability to automatically extract relevant features from data [5–7].

In particular, Artificial Neural Networks (ANNs) and Convolutional Neural Networks (CNNs) are a form of AI, roughly modeled on the structure of neurons in the brain, which has shown tremendous promise in solving many problems in computer vision, natural language processing, and automatic image segmentation [8]. These neural networks are supervised machine learning methods that use a specific architecture, namely some form of neural network loosely inspired by how the brain is structured, with hidden layers representing interneurons. The choice of how many layers and how many neurons per layer to include is a crucial step in the ANN/CNN model specification. Each neuron stores a numeric value, and each connection between neurons represents a weight. Weights connect the neurons in different layers and represent the strength of connections between the neurons. A fully connected neural network (i.e., when all neurons in one layer are connected to all neurons in the next can be interpreted and implemented as matrix multiplication) is represented in Fig. 1. These emerging techniques are going to be employed in different fields of neuro-oncology ranging from early phases of radiological and pathological diagnosis to surgery, radiation therapy, and prediction of systemic treatment responses. In this review, we discussed principal studies assessing AI focusing our attention on possible future applications of these techniques in clinical practice (Table 2).

Table 1 Principal supervised and unsupervised classification machine learning methods and the corresponding open-source R-package

Supervised learning	Unsupervised learning
Artificial Neural Network	*K*-Means Clustering
neuralnet(~)	stats::kmeans()
Support Vector Machine	Hierarchical Clustering
e1071:svm(~)	stats::hclust(dist())
Random Forest	DBSCAN Clustering
randomForest(~)	dbscan()
K-Nearest Neighbors	Gaussian Mixture
class::knn(~)	mclust::Mclust()
Naive Bayes Classifier	Mean-shift Clustering
e1071::naiveBayes(~)	meanShiftR::knn_meanShift()

Evicence acquisition

We adopted the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines to conduct this study (PRISMA report attached as supplementary file 1). We reported the keywords adopted for the research on Pubmed/MEDLINE, Scopus, and Cochrane library at the beginning of each paragraph specifying the studies included and excluded from this review. We selected original articles published until the 1st March 2022. We selected only English-written original articles reporting data about the application of deep learning in neuro-oncology. In the case of multiple publications on the same cohort of patients, we included the most updated version with a longer follow-up. Six authors (VDN, MF, AT, LG, SB, PC) carried out the narrative review and selected articles of interest. The other authors validated and reviewed the articles selected for each paragraph (neuroradiology: RA, CT, RL; pathology: SA; neurosurgery: AC, DM; radiation therapy: GM, DB;

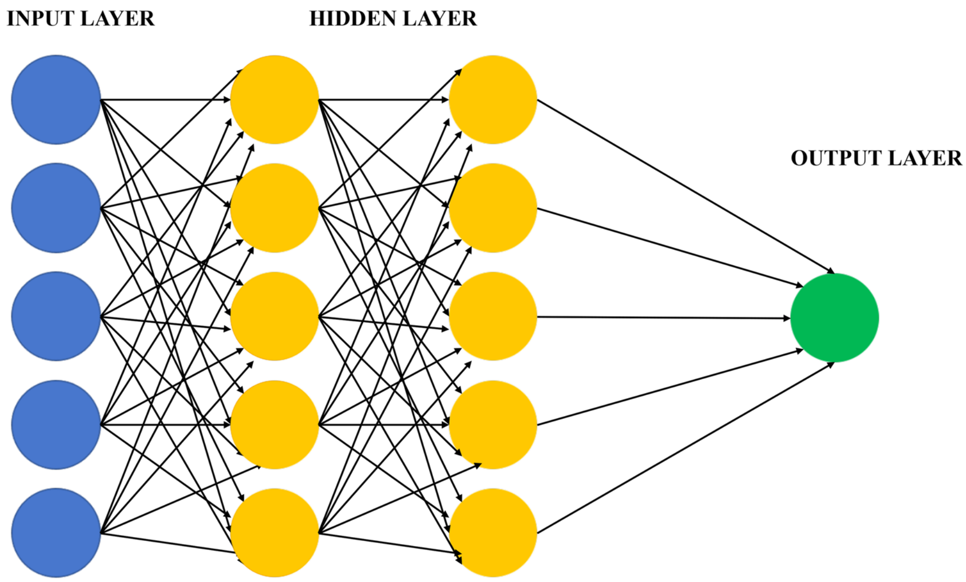

Fig. 1 Example of fully connected neural network architecture consisting of two hidden layers

Table 2 Applications of AI in different fields of neuro-oncology

Neuro-radiology	
	No invasive diagnosis of specific mutations including IDH status [2, 33], MGMT [10, 16] and 1p19qcodeletion [19]
	Differentiating true progression from pseudo-progression [24]
	Differential diagnosis from brain metastases and glioblastoma [18]
	Prediction of meningioma clinical evolution [20, 21, 26, 27]
	Optimizing longitudinal measurement of tumors including those spreading to leptomeninges [22]
	Molecular characterization of medulloblastoma [14]
	Estimation of high qualitative images (like those achieved by a 7 Tesla MRI) starting from 3 Tesla images [37]
Pathological diagnosis	
	Classification of glioma's subtypes [40]
	Estimation of glioma tumor grade [47]
	Molecular alterations prediction [54, 55]
Surgery	
	Intraoperative diagnosis [56, 59]
Radiation therapy	
	Prediction of high-grade toxicity [66]
	The dose administered [63]
	Treatment delivery [63]
	Contouring and segmentation of treatment fields [65]
	Synchronization between MRI and linear accelerator [94–96]
Systemic treatment	
	Selection of most promising compounds to test [93]
	Personalized treatment protocols [91]
Predictive response/resistance factor to systemic treatment [92]	

IDH Isocitrate dehydrogenase, *MGMT* O6-methylguanine-DNA Methyltransferase

systemic treatment: EF). The article selection algorithm has been summarized on supplementary Fig. 1.

Neuroradiology

Research protocol

We adopted the following keywords for this topic: "Machine learning OR Deep Learning OR Artificial intelligence AND Neuroradiology OR Brain Tumor MRI". Overall, we selected 1752 potential relevant abstracts. After the revision process 19 articles [9–27] have been selected for the following issues of interest:

- Prediction of the different molecular features of the diseases [9–11, 14, 16, 19];
- Distinction of progression from pseudo-progression or radiation necrosis [17, 24];
- Assessment of tumor response [15];
- Predicting grading and biological behaviors of selected tumors including meningioma and pituitary malignancies [20, 21, 23, 25–27];
- Pediatric brain tumors assessment [14, 22, 25].
- Survival [13], glioma tumor grade [12], and metastatic primary tumor type [18] prediction by the use of deep learning.

Discussion

Neuroradiology represents the optimum candidate to test AI. This is mainly due to the high amount of data provided by neuro-radiological examinations and the no-invasive nature of radiological assessments. Because of the high volume and wealth of multimodal imaging information acquired in typical studies, neuroradiology is poised to be an early adopter of machine learning. Brain tissue segmentation is one of the most sought-after research areas in medical image processing. It provides detailed quantitative brain analysis for accurate disease diagnosis, detection, and classification of abnormalities [6, 28, 29]. Brain tissue segmentation and volume estimation of white matter (WM), grey matter (GM), and cerebrospinal fluid (CSF) are important in many neuroradiological applications [28, 30–32]. Volume estimation and segmentation of the brain tissue can be used to assess local and global brain atrophy that is present in different diseases and to monitor its progression. Figure 2 represents an example of 3-class brain tissue segmentation of one slice in one healthy subject. In recent years, also brain lesion detection and segmentation have created an interest in different research areas [28, 29]. Magnetic Resonance Image (MRI) scan analysis is a powerful tool that makes effective detection of the abnormal tissues from the brain. For this, recently more and more new machine learning techniques were proposed for brain image segmentation and automatic lesion detection. Neural networks are ideally trained using large numbers of cases that are divided into several groups. The training cases are looped through multiple times until the accuracy of the model converges. At first, predictions will be poor. However, the relevance of this setup is that you can compare the output of the model with the ground truth via the use of a cost function, i.e., a single number that quantifies how far off the model is. Finally, the testing set is used to assess the model accuracy in terms of prediction on data that has not been used for training. For brain image segmentation, a simple neural network has the image data input as a vector composed of voxel intensities in the case of CNN, or a matrix of intensity values in the case of ANN. The input can consist of entire imaging series, multiple series, or even multiple modalities. Figure 3 represents an example of a lesion detection procedure obtained via 5-class segmentation. Identifying and delineating the margins of a lesion is important because neuroradiologists are often tasked with

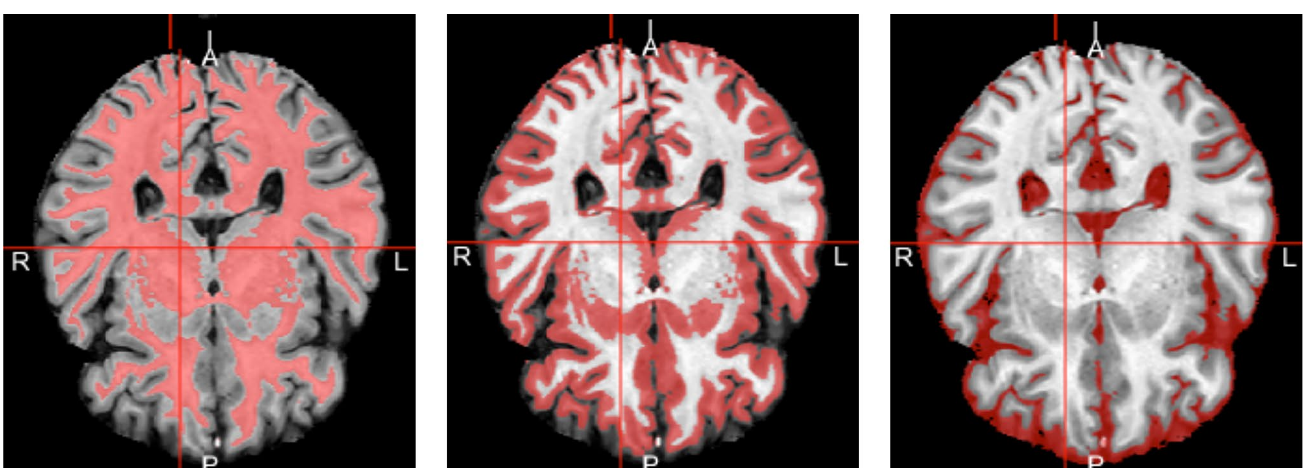

Fig. 2 Brain tissue segmentation, of one slice in one healthy subject. Left plot: white matter (WM); center plot: grey matter (GM); right plot: cerebrospinal fluid (CSF). The three brain regions were calculated automatically by a machine learning technique

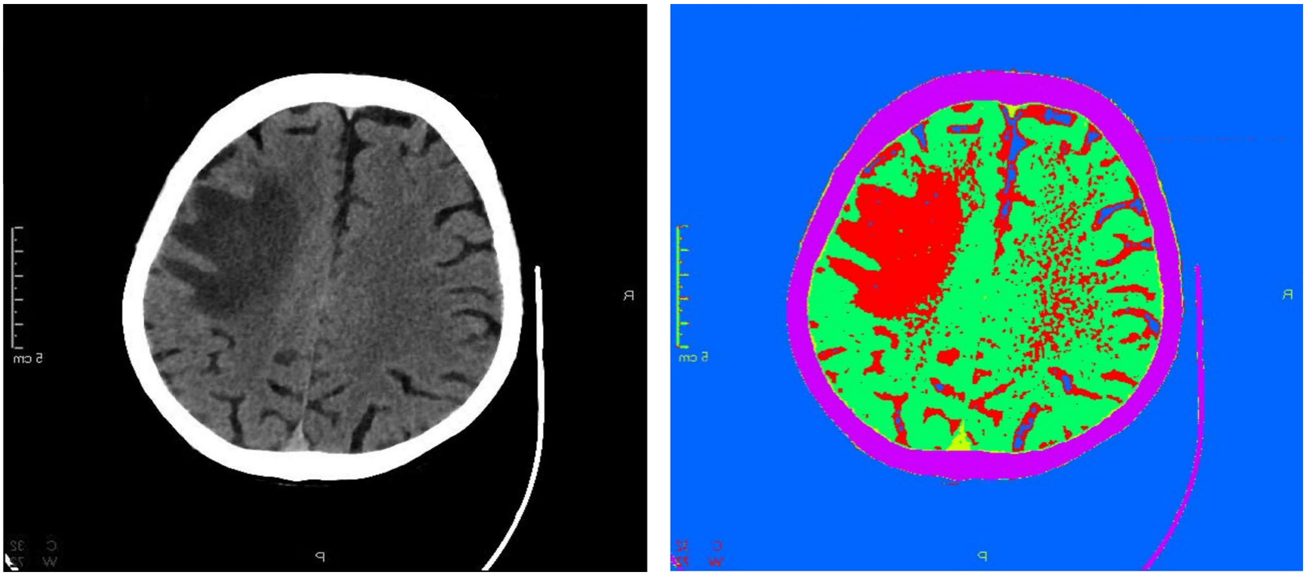

Fig. 3 Brain segmentation of one slice in one 76-year-old man with established diagnoses of glioblastoma multiforme (GBM). Left plot: original magnetic resonance image (input); right plot: automatically 5-class segmented image via ANN. The lesion is the abnormal substance that is highlighted in red

monitoring the change in the size of lesions across time and/or in response to some treatment. There are a lot of possible applications of ANN within tumor radiological assessment (Table 2). As known, gliomas represent the most frequent primary malignant solid tumors of the CNS [2]. Among these patients, the presence/absence of isocitrate dehydrogenase (IDH) is important for diagnosis, prognosis estimation, and treatment planning thanks to the availability of specific IDH inhibitors [2, 33]. The assessment of this factor is available only by performing an immunohistochemical and complete sequencing of the tumor specimens (to recognize also rare IDH mutations) [34]. In a study assessing 1166 preoperative MRI images (T1 with contrast and FLAIR sequences) of gliomas, the adoption of an artificial convolutional neural networks system allowed the accuracy of over 90% to predict IDH status with imaging alone [11]. The possibility to predict molecular alterations of tumor specimens is one of the most attractive applications of deep learning and has been already adopted to estimate O6-methylguanine-DNA Methyltransferase (MGMT) [10, 16], 1p19q codeletion [19] and Epidermal growth factor receptor (EGFR) expression [9]. To date, no studies predicting BRAF status with ANN have been performed. In addition, machine learning could be also employed to predict the glioma grade. In a small study composed of 23 patients, an artificial intelligence algorithm using 4 inputs (T2, ADC, CBV, and transfer constant from dynamic contrast-enhanced imaging) demonstrated a very high accuracy (96%) in predicting tumor grade [12]. Pseudo-progression is defined as an increased contrast or T2/FLAIR enhancement on MRI occurring 12 weeks after radiotherapy or combined radio-chemotherapy. This phenomenon is associated with a spontaneous resolution/stabilization and involves over 15–30% of patients especially those with MGMT methylated gliomas [35]. Artificial intelligence has been employed in this setting within small clinical studies showing a promising predictive value in differentiating pseudo-progression from true progression [17]. The distinction between radionecrosis and tumor recurrence is another issue that has been investigated with the use of ANN [24]. Surely, there are other important applications of deep learning also in tumors different from gliomas. Also, brain metastases could be differentiated from primary glioblastoma and discriminated according to their tumor of origin. However, a study adopting MRI and ANN to discriminate metastases of origin reached AUCs of 0.64 and 0.82 for the detection of non-small cell lung cancer and breast brain metastases [18]. Meningioma is a frequent tumor that could be clinically aggressive due to a high recurrence rate and dismal prognosis in some cases [36]. In these tumors, the prediction of tumor's grade and the associated risk of progression is essential to plan follow-up or loco-regional treatment strategies. Deep learning showed to be effective on discriminate low from high-grade meningioma [20, 21, 26, 27]. Differentiating pituitary adenoma from craniopharyngioma and prediction of grade and proliferation index of pituitary macroadenomas are also fields of development for deep learning with ANN [23, 25]. A longitudinal measurement is essential to estimate an adequate tumor burden. This is crucial especially in pediatric and young adult patients affected by CNS tumors [22]. To date, expertise is essential to obtain an adequate tumor size estimation and there is a significant variability. In a large study carried out on pediatric patients with high-grade gliomas, medulloblastoma, and other leptomeningeal seeding tumors authors tested a fully automatized deep learning technique to estimate response assessment in these patients with promising results which should be validated in an external cohort [22]. In addition to tumor measurement, deep learning has been shown to recognize specific imaging alterations associated with a worse clinical outcome in pediatric patients [13]. The molecular characterization of medulloblastoma is important for prognosis stratification and also for therapeutic implications thanks to the increasing availability of tailored treatment. A study of 109 pediatric patients with medulloblastoma assessed images provided by T1, T1 plus contrast, and T2WI MRI examination. Deep learning allowed the identification of group 3, group 4, and sonic hedgehog (SHH) molecular groups with an estimated AUC of 0.70, 0.83, and 0.79 respectively [14]. The use of AI could also improve quality of the studies performed. Indeed, AI can provide high-quality images (like those provided by a 7-Tesla MRI) elaborating images from 3 Tesla MRI [37]. Finally AI could be employed to estimate tumor response after treatment sparing the use of contrast gadolinium [15]. There are a lot of opportunities and fields of development with deep learning in neuro-radiology. To date, these techniques have been assessed in different diseases and settings showing promising results. Unfortunately, there are no validated studies that have allowed to translation of these techniques into clinical practice. In addition, the need for experts able to set and configure adequately ANN are a possible limitation.

Molecular-pathological diagnosis

Research protocol

We adopted the following keywords for this topic: ''Machine learning OR Deep Learning OR Artificial intelligence AND Neuro-oncology Pathology OR Tumor Neuropathology''. Overall, we selected 1027 potential relevant abstracts. After the revision process 4 articles [38–41] have been selected for the following issues of interest:

- Automated grade, molecular and tumor classification diagnosis [38–41].

Discussion

The possible applications of deep learning techniques in clinical practice are multiple and not limited to neuro-radiology. Indeed, even if deep learning could provide several clinical data from MRI imaging a pathological assessment is still required before planning surgical and post-surgical treatments. The application of deep learning in pathological diagnosis has been less assessed as compared to neuro-radiology. Nonetheless, there are some possible applications of these techniques in this field. The histomorphological diagnostic process is based on the experience and expertise of the pathologist in a specific field. Moreover, in the molecular era, the evaluation of the quality and quantity of the bioptic sample is the sole responsibility of the pathologist. The morphological and histological valuation is necessary: (i) to verify that the sample is representative of the disease, evaluating the presence of tumor necrosis, sampling errors, or presence of an exuberant inflammatory component that can affect the molecular results; (ii) to confirm the histotype and to evaluate the morphological heterogeneity of the tumor, which it may have analytical fallout; (iii) for the triage of the material available for molecular analysis of the markers prognostic/predictive in the lesion; (iv) to select the most appropriate area for the investigation molecular; (v) to guide the choice of the correct method based on the technical sensitivity of the molecular device used; (vi) to define artifacts caused by pre-analytical passages inaccurate [42]. Automated computer vision is a branch of artificial intelligence that has seen dramatic successes in natural image classification in recent years [41]. In particular, with the practice of Whole-Slide Imaging (WSI), which is another name for virtual microscopy [43], the field of digital pathology is growing and has applications in diagnostic medicine, to improve diagnostic accuracy, and to identify new prognostic and predictive factors, even if more expensive, due to the success in AI and ML. In gastrointestinal cancer, for example, the application of deep learning techniques can predict microsatellite instability directly from H&E histology [44] while in breast cancer the application of machine learning improved grade staging [45]. In neuro-oncology AI has been employed to classify glioma subtypes [40]. In brief, a CNN trained with over 79,990 histological patch images provided by a slide scanner differentiated gliomas into the most frequent subtypes according to the WHO 2016 classification: glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, diffuse astrocytoma, and oligodendroglioma. Notably, this algorithm required a molecular assessment of the codeletion 1p19q and IDH [40]. Estimation of glioma's grade could be essential to estimate the prognosis of these patients [46]. Ertosum MG et al. developed an automated algorithm trained through the digitalized images obtained from The Cancer Genome Atlas (TCGA) [38]. This algorithm achieved an accuracy of 96% to differentiate GBM from other gliomas. However, this study was carried out on a small proportion of patients ($n=22$) and did not employ molecular assessment to estimate grade and glioma subtype [38]. More recently Pei L et al. proposed a novel algorithm and computational model estimating glioma's grade [47] showing that the type of deep learning adopted and the method employed to select the region of interest (ROI) of images to include into the algorithm are critical as different methods are associated to a significant difference in terms of diagnostic accuracy [47]. Histopathological analysis of brain tumor continues to remain an important tool for both clinical management and neuro-oncology research. The complexity of these analyses has however greatly increased in the molecular era with a growing number of immunohistochemical studies that need to be interpreted in a tandem and parallel manner. Applications of AI in pathology could address this issue by automating alignment of multiple tissue sections generated from different immunohistochemistry-based molecular studies and they could improve the diagnostic quality in neuropathology [39]. Moreover, as known, molecular assessment of CNS malignancies assumes critical importance for diagnosis [48] and also for treatments due to the increasing availability of tailored target therapies [33, 49–52]. In this optic, the use of deep learning could be helpful in the evaluation of the quality of the bioptic sample by the neuropathologist thought predicting the possible presence/absence of a distinct molecular alteration and allowing to adopt advanced molecular investigation on selected cases more likely to present a specific target mutation. Although interesting, there are several limitations to the application of AI in pathology. The first obstacle is represented by the digitalization of pathological slides and images. Indeed, some centers are orphans of a digitalized system able to store imagines from tumor specimens. To overcome this limitation, a digitalized system named: the WSI has been developed in Canada [53]. This system has been approved in 2017 by FDA after demonstrating an equivalent error rate between manual diagnoses made on a digital and standard glass slide. However, several centers do not adopt a digitalized system for slide storage and consultation. The second limitation is represented by postprocessing procedures. Indeed, whole digital slides can be too large to be processed (each image could be larger than 1 GB) thus it is essential to optimize images and segment of the specimens to be incorporated in the algorithm. The optimal segmentation techniques and the most appropriate selection of the ROI have still not been identified [54, 55]. In conclusion, the application of AI is an emerging field of improvement in the pathological and molecular diagnosis of gliomas. Unfortunately, there are some limitations to the inclusion of these techniques in clinical practice and to date, only one validated study adopting this technique has been published [40].

Artificial intelligence and treatments

Surgery

Research protocol

We adopted the following keywords for this topic: ''Machine learning OR Deep Learning OR Artificial intelligence AND Neurosurgery''. Overall, we selected 131 potential relevant abstracts. After the revision process articles, 5 articles [56–60] have been selected for the following issues of interest:

- Presurgical planning [57];
- In vivo tissue assessment [56, 58–60].

Discussion

The AI could improve outcomes and performances of brain tumor surgical resections. An adequate assessment of tumor burden and extension is essential in pre-surgical planning. Applications of deep learning in neuro-radiology allowed us to obtain an optimal estimation of tumor burden also in some difficult settings like pediatric tumors and leptomeningeal spreading malignancies [22]. However, most deep learning techniques are involved in longitudinal assessment and measurement [57] rather than in pre-surgical planning and data in this setting are poor. Of interest, AI can also be involved during surgery improving patient outcomes [61]. In particular, deep learning could replace the intraoperative diagnosis which is currently based on standard H&E fixation and coloration. At least two studies are investigating alternative approaches for intraoperative diagnosis employing CNNs [56, 59]. In 2020 Hollon TC et al proposed a workflow employing Stimulated Raman Histology (SRH) which is a label-free optical imaging method providing label-free sub-micrometer-resolution images of unprocessed biological tissues and a deep CNN to obtain a real-time diagnosis [56]. Authors trained their CNN with over 2.5 million SRH images. In a multicenter prospective trial, authors demonstrated that the SRH-CNN system provided brain tumor diagnosis in 2–3 min comparing the canonical 10–15 min required for conventional techniques. Moreover, the diagnostic performance of SRH-CNN was not inferior to the conventional analysis (94.6% vs 93.9%) [56]. Another similar approach has been assessed by Chen D et al. This group evaluated the multiphoton microscopy (MPM) which is a high-resolution non-destructive technique obtaining subcellular resolution images free from unprocessed surgical specimens [59]. The authors assessed this technique on 19 consecutive patients involving also a deep learning algorithm to elaborate images and provide the final diagnosis. Authors achieved promising results even if this approach remains invalidated due to the small size of patients assessed [59]. It is important to observe that fuorescence-based imaging techniques are emerging tools employed in neuro-surgery. These methods allow a macroscopic visualization of fluorescent areas and an endomicroscopy assessment of a selected areas [58]. The confocal endomicroscopy (CEM) is one of the most promising techniques leading to obtain an high microstructure amplification of a target tissue [58]. Combination between CEM and AI are still poorly investigated [60]. To summarize, AI could help surgical procedures through better planning before surgery and surely can improve intraoperative diagnosis reducing time, economic and human resources. Available data suggest that the intraoperative use of CNN is reliable and could be included in clinical practice in the coming years.

Radiation therapy

Research protocol

We adopted the following keywords for this topic: ''Machine learning OR Deep Learning OR Artificial intelligence AND Brain Radiation Therapy OR Spinal Cord Radiation Therapy. Overall, we selected 428 potential relevant abstracts. After the revision process articles, 7 articles [62–68] have been selected for the following issues of interest:

- Volume, dose and treatment planification employing deep learning [62–68].

Discussion

AI has been proposed to allow automation and optimization of the complex radiotherapy workflows with the aim of increase quality, standardization, and accuracy of each step of the treatment process [66,69,70]. Possible applications include medical image registration, automation of target delineation, treatment planning, patient simulation, quality assurance, radiation dose delivery, patient monitoring, clinical outcomes and prediction of treatment to assist treatment decision making [70–77]. Several review papers have been published on the use of AI, machine-learning and deep-learning in radiotherapy [71–77]. Accurate segmentation of target volumes and organs at risk, and optimization of radiotherapy treatment planning are crucial steps of radiation process which are time-consuming and associated with large user variability [62, 63, 65, 78, 79]. Automated machine-learning to aid target delineation and treatment planning have been employed to improve accuracy and efficiency of radiotherapy plans [64]. In a small study of ten brain tumors candidate to stereotactic treatment where each case was contoured by nine medical professionals, the use of AI assistance significantly improved contouring accuracy reducing variability between physicians and increased treatment efficiency with a median of 30.8% time-saving [65]. A similar approach has also been adopted for the detection and segmentation of brain metastases candidates to stereotactic treatment with encouraging preliminary results [62]. MRI is used for target volume and organs-at-risk delineation for its superior soft-tissue contrast as compared to CT imaging. However, CT images remain the standard in the radiotherapy workflow, as they provide robust information about electron densities in various tissues, expressed in Hounsfield units (HU), which are needed for dose calculations performed by the treatment planning system [78–80]. Several methods of synthetic-CT generation from MRI data based on convolutional neural network algorithm have been developed to improve accuracy of dose calculations on cone-beam CT (CBCT) or MRI images [67, 68, 81–87]. In a review of 57 studies where the most commonly investigated anatomical localization was the brain, the mean dose difference between the synthetic-CT and the reference CT was < 2% [88]. Models of tumor control probability, prediction of clinical outcomes, clinical decision support have emerged as additional focus areas for AI efforts in radiation oncology [67]. In a retrospective study of 150 patients with 308 brain metastases from solid tumors treated by stereotactic radiosurgery, the AI model based on MRI allowed prediction of early response to radiosurgery with an accuracy of 75%, outperforming the visual assessment of patterns of contrast enhancement [67]. A ML-based approach has been employed to identify patients more likely to require advanced medical care in course of radiation therapy. In a single-institution quality improvement, randomized clinical trial 963 (238 with brain primary tumor or brain metastases) outpatient treated with radiation and chemotherapy were triaged by a machine learning approach [66]. The algorithm recognized patients with high (> 10%) risk to acute care in course of treatment. These patients were randomized to a standard once weekly evaluation or twice weekly evaluation. The trial clearly showed that twice-weekly evaluation reduced rates of acute care in course of treatment. The ML accurately triaged patients according to their clinical risk [66]. Other important applications of ML-based prediction models include early recurrence in patients with glioblastoma [81], prediction of treatment toxicity [89], diagnosis of pseudoprogression/radiation necrosis versus progression after radiotherapy [90]. The application of AI has a great potential for improving radiotherapy in patients with malignant brain tumors and high diagnostic accuracies of 80–90% has been reported by different ML approaches. However, despite several independent studies that started to explore the use of AI in radiation oncology none of them lead to the approval of these techniques in clinical practice. It is likely that AI will be evaluated in radiation oncology and could modify the standard of care in coming years.

Systemic treatment

Research protocol

We adopted the following keywords for this topic: ''Machine learning OR Deep Learning OR Artificial intelligence AND Systemic Treatment OR Chemotherapy AND

Table 3 In this table we report a list of software employed to develop artificial neural network

Neural designer	https://www.neuraldesigner.com/
Neuroph	http://neuroph.sourceforge.net/
Keras	https://keras.io/ It is a high-level neural network, written in phyton
Tflearn	http://tflearn.org/
ConvNetJS	https://cs.stanford.edu/people/karpathy/convnetjs/
Torch	http://torch.ch/
Stuttgart neural network simulator (SNNS)	http://www.ra.cs.uni-tuebingen.de/SNNS/welcome.html This package wraps the SNNS functionality to make it available from within R

Neuro-oncology. Overall, we selected 6 potential relevant abstracts. After the revision process articles, 2 articles [91, 92] have been selected for the following issues of interest:

- Personalized treatment dose [91] and identification of predictive response factors [92].

Discussion

Differently from surgery and radiation therapy few studies investigated the potential role of AI within systemic treatments for CNS malignancies. One possible application of machine learning in this setting could be the identification of novel promising drugs to test in pre-clinical studies. Neves BJ et al. elaborated a deep learning algorithm assessing anti-glioma cells activity and blood–brain barrier penetration ability of novel compounds [93]. By this method, authors were able to select more promising compounds within a very large library prioritizing their assessment in vivo. Notably by this approach, they identified two candidates for further clinical assessment [93]. Another possible application of AI is the identification of the optimal dosage and protocol of systemic treatment. This is what investigated Houy N et al. In this study authors utilized AI to identify the optimal personalized protocol for temozolomide administration within a heterogeneous population of patients [91]. This study quantifies in-silico the potential benefit offered by a tailored temozolomide dose protocol. In their simulation, the personalized protocol resulted in greater tumor reduction and a lower rate of adverse events [91]. Finally, the obvious use of AI could be the identification of predictive response factors to systemic treatment. This optic appears of particular interest in a study assessing 906 patients affected by GBM. The authors evaluated the genomic stemness signature of GBM cells. Thanks to this signature specimens were differentiated GBM into two main subtypes named stemness subtype I and II [92]. These two classes differed from overall survival (significantly longer for subtype I), associate tumor microenvironment, and response to treatment. Authors also suggested that subtype I was more likely to benefit from immune-checkpoint inhibitors and be resistant to temozolomide on the contrary of the stemness subtype II [92].

Conclusion

There is an increasing availability of artificial neural network software (Table 3) which reflect the increasing use of deep learning in medicine and specifically in neuro-oncology research. Some of these software are totally free (such as R software) and allow to obtain segmentation and accurate big data assessment adopting machine learning algorithm. An example of possible segmentation methods with R is reported in the supplementary material attached (supplementary file 2). There are several applications of artificial intelligence in clinical neuro-oncology. From being tested selectively in neuro-radiology, AI has been included also in other fields including surgery, radiation therapy, systemic therapy, and also pathology. It is probably that surgery and radiation oncology will be the first to benefit from these technologies however it is also likely that this is only the beginning of a coming revolution involving all aspects related to neuro-oncology. Opportunities in neuro-oncology are rich given the advancement in our understanding of the brain, expanding indications for intervention, and diagnostic challenges often characterized by multiple clinical and environmental factors. Supervised learning models appear to be the most commonly incorporated algorithm models for machine learning across the reviewed neuro-disciplines with the primary aim of diagnosis. However, we think that new ML contributions also for treatment and prognosis purposes may enhance current medical best practices while also broadening our understanding of dynamic neural networks and the brain. Accumulating evidence has indeed demonstrated that noninvasive advanced imaging analytics, can reveal key components of tumor phenotype for multiple three-dimensional lesions at multiple time points over and beyond the course of treatment. These developments in the use of computerized tomography (CT), positron emission tomography (PET), ultrasound US, and MR imaging could augment patient stratification and prognostication buttressing emerging targeted therapeutic approaches. Many powerful open-source and commercial platforms are currently available to embark on new research areas of radiomics. However, the quantitative imaging procedures are complex and key statistical principles should be followed to realize its full potential. At the same time, computer science has progressed rapidly to develop techniques that enable the storage, processing, and analysis of these complex datasets, a feat that traditional statistics and early computing technologies could not accomplish.

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References

1. Miller KD, Ostrom QT, Kruchko C, Patil N, Tihan T, Cioffi G, Fuchs HE, Waite KA, Jemal A, Siegel RL (2021) Barnholtz-Sloan JS (2021) Brain and other central nervous system tumor statistics. CA Cancer J Clin 71(5):381–406. https://doi.org/10.3322/caac.21693
2. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW (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
3. Ibrahim A, Gamble P, Jaroensri R, Abdelsamea MM, Mermel CH, Chen PC, Rakha EA (2020) Artificial intelligence in digital breast pathology: techniques and applications. Breast 49:267–273. https://doi.org/10.1016/j.breast.2019.12.007
4. Baştanlar Y, Ozuysal M (2014) Introduction to machine learning. Methods Mol Biol 1107:105–128. https://doi.org/10.1007/978-1-62703-748-8_7
5. Deo RC (2015) Machine learning in medicine. Circulation 132(20):1920–1930. https://doi.org/10.1161/circulationaha.115.001593
6. Dora L, Agrawal S, Panda R, Abraham A (2017) State-of-the-art methods for brain tissue segmentation: a review. IEEE Rev Biomed Eng 10:235–249. https://doi.org/10.1109/rbme.2017.2715350
7. Hassabis D, Kumaran D, Summerfield C, Botvinick M (2017) Neuroscience-inspired artificial intelligence. Neuron 95(2):245–258. https://doi.org/10.1016/j.neuron.2017.06.011
8. Zaharchuk G, Gong E, Wintermark M, Rubin D, Langlotz CP (2018) Deep learning in neuroradiology. AJNR Am J Neuroradiol 39(10):1776–1784. https://doi.org/10.3174/ajnr.A5543
9. Akbari H, Bakas S, Pisapia JM, Nasrallah MP, Rozycki M, Martinez-Lage M, Morrissette JJD, Dahmane N, O'Rourke DM, Davatzikos C (2018) In vivo evaluation of EGFRvIII mutation in primary glioblastoma patients via complex multiparametric MRI signature. Neuro Oncol 20(8):1068–1079. https://doi.org/10.1093/neuonc/noy033
10. Chang P, Grinband J, Weinberg BD, Bardis M, Khy M, Cadena G, Su MY, Cha S, Filippi CG, Bota D, Baldi P, Poisson LM, Jain R, Chow D (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
11. Choi YS, Bae S, Chang JH, Kang SG, Kim SH, Kim J, Rim TH, Choi SH, Jain R, Lee SK (2021) Fully automated hybrid approach to predict the IDH mutation status of gliomas via deep learning and radiomics. Neuro Oncol 23(2):304–313. https://doi.org/10.1093/neuonc/noaa177
12. Gates EDH, Lin JS, Weinberg JS, Prabhu SS, Hamilton J, Hazle JD, Fuller GN, Baladandayuthapani V, Fuentes DT, Schellingerhout D (2020) Imaging-based algorithm for the local grading of glioma. AJNR Am J Neuroradiol 41(3):400–407. https://doi.org/10.3174/ajnr.A6405
13. Grist JT, Withey S, Bennett C, Rose HEL, MacPherson L, Oates A, Powell S, Novak J, Abernethy L, Pizer B, Bailey S, Clifford SC, Mitra D, Arvanitis TN, Auer DP, Avula S, Grundy R, Peet AC (2021) Combining multi-site magnetic resonance imaging with machine learning predicts survival in pediatric brain tumors. Sci Rep 11(1):18897. https://doi.org/10.1038/s41598-021-96189-8
14. Iv M, Zhou M, Shpanskaya K, Perreault S, Wang Z, Tranvinh E, Lanzman B, Vajapeyam S, Vitanza NA, Fisher PG, Cho YJ, Laughlin S, Ramaswamy V, Taylor MD, Cheshier SH, Grant GA, Young Poussaint T, Gevaert O, Yeom KW (2019) MR imaging-based radiomic signatures of distinct molecular subgroups of medulloblastoma. AJNR Am J Neuroradiol 40(1):154–161. https://doi.org/10.3174/ajnr.A5899
15. Jayachandran Preetha C, Meredig H, Brugnara G, Mahmutoglu MA, Foltyn M, Isensee F, Kessler T, Pflüger I, Schell M, Neuberger U, Petersen J, Wick A, Heiland S, Debus J, Platten M, Idbaih A, Brandes AA, Winkler F, van den Bent MJ, Nabors B, Stupp R, Maier-Hein KH, Gorlia T, Tonn JC, Weller M, Wick W, Bendszus M, Vollmuth P (2021) Deep-learning-based synthesis of post-contrast T1-weighted MRI for tumour response assessment in neuro-oncology: a multicentre, retrospective cohort study. Lancet Digit Health 3(12):e784–e794. https://doi.org/10.1016/s2589-7500(21)00205-3
16. Kickingereder P, Bonekamp D, Nowosielski M, Kratz A, Sill M, Burth S, Wick A, Eidel O, Schlemmer HP, Radbruch A, Debus J, Herold-Mende C, Unterberg A, Jones D, Pfister S, Wick W, von Deimling A, Bendszus M, Capper D (2016) Radiogenomics of glioblastoma: machine learning-based classification of molecular characteristics by using multiparametric and multiregional mr

imaging features. Radiology 281(3):907–918. https://doi.org/10.1148/radiol.2016161382
17. Kim JY, Park JE, Jo Y, Shim WH, Nam SJ, Kim JH, Yoo RE, Choi SH, Kim HS (2019) Incorporating diffusion- and perfusion-weighted MRI into a radiomics model improves diagnostic performance for pseudoprogression in glioblastoma patients. Neuro Oncol 21(3):404–414. https://doi.org/10.1093/neuonc/noy133
18. Kniep HC, Madesta F, Schneider T, Hanning U, Schönfeld MH, Schön G, Fiehler J, Gauer T, Werner R, Gellissen S (2019) Radiomics of brain MRI: utility in prediction of metastatic tumor type. Radiology 290(2):479–487. https://doi.org/10.1148/radiol.2018180946
19. Lu CF, Hsu FT, Hsieh KL, Kao YJ, Cheng SJ, Hsu JB, Tsai PH, Chen RJ, Huang CC, Yen Y, Chen CY (2018) Machine learning-based radiomics for molecular subtyping of gliomas. Clin Cancer Res 24(18):4429–4436. https://doi.org/10.1158/1078-0432.Ccr-17-3445
20. Morin O, Chen WC, Nassiri F, Susko M, Magill ST, Vasudevan HN, Wu A, Vallières M, Gennatas ED, Valdes G, Pekmezci M, Alcaide-Leon P, Choudhury A, Interian Y, Mortezavi S, Turgutlu K, Bush NAO, Solberg TD, Braunstein SE, Sneed PK, Perry A, Zadeh G, McDermott MW, Villanueva-Meyer JE, Raleigh DR (2019) Integrated models incorporating radiologic and radiomic features predict meningioma grade, local failure, and overall survival. Neurooncol Adv. https://doi.org/10.1093/noajnl/vdz011
21. Park YW, Oh J, You SC, Han K, Ahn SS, Choi YS, Chang JH, Kim SH, Lee SK (2019) Radiomics and machine learning may accurately predict the grade and histological subtype in meningiomas using conventional and diffusion tensor imaging. Eur Radiol 29(8):4068–4076. https://doi.org/10.1007/s00330-018-5830-3
22. Peng J, Kim DD, Patel JB, Zeng X, Huang J, Chang K, Xun X, Zhang C, Sollee J, Wu J, Dalal DJ, Feng X, Zhou H, Zhu C, Zou B, Jin K, Wen PY, Boxerman JL, Warren KE, Poussaint TY, States LJ, Kalpathy-Cramer J, Yang L, Huang RY, Bai HX (2022) Deep learning-based automatic tumor burden assessment of pediatric high-grade gliomas, medulloblastomas, and other leptomeningeal seeding tumors. Neuro Oncol 24(2):289–299. https://doi.org/10.1093/neuonc/noab151
23. Ugga L, Cuocolo R, Solari D, Guadagno E, D'Amico A, Somma T, Cappabianca P, Basso D, de Caro ML, Cavallo LM, Brunetti A (2019) Prediction of high proliferative index in pituitary macroadenomas using MRI-based radiomics and machine learning. Neuroradiology 61(12):1365–1373. https://doi.org/10.1007/s00234-019-02266-1
24. Zhang Q, Cao J, Zhang J, Bu J, Yu Y, Tan Y, Feng Q, Huang M (2019) Differentiation of recurrence from radiation necrosis in gliomas based on the radiomics of combinational features and multimodality MRI images. Comput Math Methods Med 2019:2893043. https://doi.org/10.1155/2019/2893043
25. Zhang Y, Chen C, Tian Z, Xu J (2020) Discrimination between pituitary adenoma and craniopharyngioma using MRI-based image features and texture features. Jpn J Radiol 38(12):1125–1134. https://doi.org/10.1007/s11604-020-01021-4
26. Zhang Y, Chen JH, Chen TY, Lim SW, Wu TC, Kuo YT, Ko CC, Su MY (2019) Radiomics approach for prediction of recurrence in skull base meningiomas. Neuroradiology 61(12):1355–1364. https://doi.org/10.1007/s00234-019-02259-0
27. Zhu Y, Man C, Gong L, Dong D, Yu X, Wang S, Fang M, Wang S, Fang X, Chen X, Tian J (2019) A deep learning radiomics model for preoperative grading in meningioma. Eur J Radiol 116:128–134. https://doi.org/10.1016/j.ejrad.2019.04.022
28. Chen L, Bentley P, Rueckert D (2017) Fully automatic acute ischemic lesion segmentation in DWI using convolutional neural networks. Neuroimage Clin 15:633–643. https://doi.org/10.1016/j.nicl.2017.06.016
29. Chu R, Tauhid S, Glanz BI, Healy BC, Kim G, Oommen VV, Khalid F, Neema M, Bakshi R (2016) Whole brain volume measured from 1.5T versus 3T MRI in healthy subjects and patients with multiple sclerosis. J Neuroimaging 26(1):62–67. https://doi.org/10.1111/jon.12271
30. Dadar M, Collins DL (2021) BISON: Brain tissue segmentation pipeline using T(1) -weighted magnetic resonance images and a random forest classifier. Magn Reson Med 85(4):1881–1894. https://doi.org/10.1002/mrm.28547
31. Halder A, Talukdar NA (2019) Brain tissue segmentation using improved kernelized rough-fuzzy C-means with spatio-contextual information from MRI. Magn Reson Imaging 62:129–151. https://doi.org/10.1016/j.mri.2019.06.010
32. West J, Blystad I, Engström M, Warntjes JB, Lundberg P (2013) Application of quantitative MRI for brain tissue segmentation at 1.5 T and 3.0 T field strengths. PLoS ONE 8(9):e74795. https://doi.org/10.1371/journal.pone.0074795
33. Gatto L, Franceschi E, Tosoni A, Di Nunno V, Maggio I, Lodi R, Brandes AA (2021) IDH inhibitors and beyond: the cornerstone of targeted glioma treatment. Mol Diagn Ther 25(4):457–473. https://doi.org/10.1007/s40291-021-00537-3
34. Di Nunno V, Franceschi E, Tosoni A, Gatto L, Maggio I, Lodi R, Angelini D, Bartolini S, Brandes AA (2022) Clinical and molecular features of patients with gliomas harboring idh1 non-canonical mutations: a systematic review and meta-analysis. Adv Ther 39(1):165–177. https://doi.org/10.1007/s12325-021-01977-3
35. Brandes AA, Franceschi E, Tosoni A, Blatt V, Pession A, Tallini G, Bertorelle R, Bartolini S, Calbucci F, Andreoli A, Frezza G, Leonardi M, Spagnolli F, Ermani M (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
36. Maggio I, Franceschi E, Tosoni A, Nunno VD, Gatto L, Lodi R, Brandes AA (2021) Meningioma: not always a benign tumor a review of advances in the treatment of meningiomas. CNS Oncol 10(2):72. https://doi.org/10.2217/cns-2021-0003
37. Qu L, Zhang Y, Wang S, Yap PT, Shen D (2020) Synthesized 7T MRI from 3T MRI via deep learning in spatial and wavelet domains. Med Image Anal 62:101663. https://doi.org/10.1016/j.media.2020.101663
38. Ertosun MG, Rubin DL (2015) Automated grading of gliomas using deep learning in digital pathology images: a modular approach with ensemble of convolutional neural networks. AMIA Annu Symp Proc 2015:1899–1908
39. Faust K, Lee MK, Dent A, Fiala C, Portante A, Rabindranath M, Alsafwani N, Gao A, Djuric U, Diamandis P (2022) Integrating morphologic and molecular histopathological features through whole slide image registration and deep learning. Neurooncology 4(1):vdac001. https://doi.org/10.1093/noajnl/vdac001
40. Jin L, Shi F, Chun Q, Chen H, Ma Y, Wu S, Hameed NUF, Mei C, Lu J, Zhang J, Aibaidula A, Shen D, Wu J (2021) Artificial intelligence neuropathologist for glioma classification using deep learning on hematoxylin and eosin stained slide images and molecular markers. Neuro Oncol 23(1):44–52. https://doi.org/10.1093/neuonc/noaa163
41. Ker J, Bai Y, Lee HY, Rao J, Wang L (2019) Automated brain histology classification using machine learning. J Clin Neurosci 66:239–245. https://doi.org/10.1016/j.jocn.2019.05.019
42. Klitzman R (2015) Consenting for molecular diagnostics. Clin Chem 61(1):139–141. https://doi.org/10.1373/clinchem.2014.223404
43. Shafique A, Babaie M, Sajadi M, Batten A, Skdar S, Tizhoosh HR (2021) Automatic multi-stain registration of whole slide images in histopathology. Annu Int Conf IEEE Eng Med Biol

Soc 2021:3622–3625. https://doi.org/10.1109/embc46164.2021.9629970
44. Kather JN, Pearson AT, Halama N, Jäger D, Krause J, Loosen SH, Marx A, Boor P, Tacke F, Neumann UP, Grabsch HI, Yoshikawa T, Brenner H, Chang-Claude J, Hoffmeister M, Trautwein C, Luedde T (2019) Deep learning can predict microsatellite instability directly from histology in gastrointestinal cancer. Nat Med 25(7):1054–1056. https://doi.org/10.1038/s41591-019-0462-y
45. Wang Y, Acs B, Robertson S, Liu B, Solorzano L, Wählby C, Hartman J, Rantalainen M (2022) Improved breast cancer histological grading using deep learning. Ann Oncol 33(1):89–98. https://doi.org/10.1016/j.annonc.2021.09.007
46. Franceschi E, Tosoni A, Bartolini S, Minichillo S, Mura A, Asioli S, Bartolini D, Gardiman M, Gessi M, Ghimenton C, Giangaspero F, Lanza G, Marucci G, Novello M, Silini EM, Zunarelli E, Paccapelo A, Brandes AA (2020) Histopathological grading affects survival in patients with IDH-mutant grade II and grade III diffuse gliomas. Eur J Cancer 137:10–17. https://doi.org/10.1016/j.ejca.2020.06.018
47. Pei L, Jones KA, Shboul ZA, Chen JY, Iftekharuddin KM (2021) Deep neural network analysis of pathology images with integrated molecular data for enhanced glioma classification and grading. Front Oncol 11:668694. https://doi.org/10.3389/fonc.2021.668694
48. Figarella-Branger D, Appay R, Metais A, Tauziède-Espariat A, Colin C, Rousseau A, Varlet P (2021) The 2021 WHO classification of tumours of the central nervous system. Ann Pathol. https://doi.org/10.1016/j.annpat.2021.11.005
49. Gatto L, Franceschi E, Tosoni A, Di Nunno V, Bartolini S, Brandes AA (2022) Molecular targeted therapies: time for a paradigm shift in medulloblastoma treatment? Cancers. https://doi.org/10.3390/cancers14020333
50. Le Rhun E, Preusser M, Roth P, Reardon DA, van den Bent M, Wen P, Reifenberger G, Weller M (2019) Molecular targeted therapy of glioblastoma. Cancer Treat Rev 80:101896. https://doi.org/10.1016/j.ctrv.2019.101896
51. Touat M, Li YY, Boynton AN, Spurr LF, Iorgulescu JB, Bohrson CL, Cortes-Ciriano I, Birzu C, Geduldig JE, Pelton K, Lim-Fat MJ, Pal S, Ferrer-Luna R, Ramkissoon SH, Dubois F, Bellamy C, Currimjee N, Bonardi J, Qian K, Ho P, Malinowski S, Taquet L, Jones RE, Shetty A, Chow KH, Sharaf R, Pavlick D, Albacker LA, Younan N, Baldini C, Verreault M, Giry M, Guillerm E, Ammari S, Beuvon F, Mokhtari K, Alentorn A, Dehais C, Houillier C, Laigle-Donadey F, Psimaras D, Lee EQ, Nayak L, McFaline-Figueroa JR, Carpentier A, Cornu P, Capelle L, Mathon B, Barnholtz-Sloan JS, Chakravarti A, Bi WL, Chiocca EA, Fehnel KP, Alexandrescu S, Chi SN, Haas-Kogan D, Batchelor TT, Frampton GM, Alexander BM, Huang RY, Ligon AH, Coulet F, Delattre JY, Hoang-Xuan K, Meredith DM, Santagata S, Duval A, Sanson M, Cherniack AD, Wen PY, Reardon DA, Marabelle A, Park PJ, Idbaih A, Beroukhim R, Bandopadhayay P, Bielle F, Ligon KL (2020) Mechanisms and therapeutic implications of hypermutation in gliomas. Nature 580(7804):517–523. https://doi.org/10.1038/s41586-020-2209-9
52. Wen PY, Stein A, van den Bent M, De Greve J, Wick A, de Vos F, von Bubnoff N, van Linde ME, Lai A, Prager GW, Campone M, Fasolo A, Lopez-Martin JA, Kim TM, Mason WP, Hofheinz RD, Blay JY, Cho DC, Gazzah A, Pouessel D, Yachnin J, Boran A, Burgess P, Ilankumaran P, Gasal E, Subbiah V (2022) Dabrafenib plus trametinib in patients with BRAF(V600E)-mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial. Lancet Oncol 23(1):53–64. https://doi.org/10.1016/s1470-2045(21)00578-7
53. Têtu B, Evans A (2014) Canadian licensure for the use of digital pathology for routine diagnoses: one more step toward a new era of pathology practice without borders. Arch Pathol Lab Med 138(3):302–304. https://doi.org/10.5858/arpa.2013-0289-ED
54. Kurc T, Bakas S, Ren X, Bagari A, Momeni A, Huang Y, Zhang L, Kumar A, Thibault M, Qi Q, Wang Q, Kori A, Gevaert O, Zhang Y, Shen D, Khened M, Ding X, Krishnamurthi G, Kalpathy-Cramer J, Davis J, Zhao T, Gupta R, Saltz J, Farahani K (2020) Segmentation and classification in digital pathology for glioma research: challenges and deep learning approaches. Front Neurosci 14:27. https://doi.org/10.3389/fnins.2020.00027
55. Levine AB, Schlosser C, Grewal J, Coope R, Jones SJM, Yip S (2019) Rise of the machines: advances in deep learning for cancer diagnosis. Trends Cancer 5(3):157–169. https://doi.org/10.1016/j.trecan.2019.02.002
56. Hollon TC, Pandian B, Adapa AR, Urias E, Save AV, Khalsa SSS, Eichberg DG, D'Amico RS, Farooq ZU, Lewis S, Petridis PD, Marie T, Shah AH, Garton HJL, Maher CO, Heth JA, McKean EL, Sullivan SE, Hervey-Jumper SL, Patil PG, Thompson BG, Sagher O, McKhann GM II, Komotar RJ, Ivan ME, Snuderl M, Otten ML, Johnson TD, Sisti MB, Bruce JN, Muraszko KM, Trautman J, Freudiger CW, Canoll P, Lee H, Camelo-Piragua S, Orringer DA (2020) Near real-time intraoperative brain tumor diagnosis using stimulated Raman histology and deep neural networks. Nat Med 26(1):52–58. https://doi.org/10.1038/s41591-019-0715-9
57. Chang K, Beers AL, Bai HX, Brown JM, Ly KI, Li X, Senders JT, Kavouridis VK, Boaro A, Su C, Bi WL, Rapalino O, Liao W, Shen Q, Zhou H, Xiao B, Wang Y, Zhang PJ, Pinho MC, Wen PY, Batchelor TT, Boxerman JL, Arnaout O, Rosen BR, Gerstner ER, Yang L, Huang RY, Kalpathy-Cramer J (2019) Automatic assessment of glioma burden: a deep learning algorithm for fully automated volumetric and bidimensional measurement. Neuro Oncol 21(11):1412–1422. https://doi.org/10.1093/neuonc/noz106
58. Charalampaki P, Nakamura M, Athanasopoulos D, Heimann A (2019) Confocal-assisted multispectral fluorescent microscopy for brain tumor surgery. Front Oncol 9:583. https://doi.org/10.3389/fonc.2019.00583
59. Chen D, Nauen DW, Park HC, Li D, Yuan W, Li A, Guan H, Kut C, Chaichana KL, Bettegowda C, Quiñones-Hinojosa A, Li X (2021) Label-free imaging of human brain tissue at subcellular resolution for potential rapid intra-operative assessment of glioma surgery. Theranostics 11(15):7222–7234. https://doi.org/10.7150/thno.59244
60. Ziebart A, Stadniczuk D, Roos V, Ratliff M, von Deimling A, Hänggi D, Enders F (2021) Deep neural network for differentiation of brain tumor tissue displayed by confocal laser endomicroscopy. Front Oncol 11:668273. https://doi.org/10.3389/fonc.2021.668273
61. Zoli M, Staartjes VE, Guaraldi F, Friso F, Rustici A, Asioli S, Sollini G, Pasquini E, Regli L, Serra C, Mazzatenta D (2020) Machine learning-based prediction of outcomes of the endoscopic endonasal approach in Cushing disease: is the future coming? Neurosurg Focus 48(6):E5. https://doi.org/10.3171/2020.3.Focus2060
62. Xue J, Wang B, Ming Y, Liu X, Jiang Z, Wang C, Liu X, Chen L, Qu J, Xu S, Tang X, Mao Y, Liu Y, Li D (2020) Deep learning-based detection and segmentation-assisted management of brain metastases. Neuro Oncol 22(4):505–514. https://doi.org/10.1093/neuonc/noz234
63. Xing Y, Nguyen D, Lu W, Yang M, Jiang S (2020) Technical note: a feasibility study on deep learning-based radiotherapy dose calculation. Med Phys 47(2):753–758. https://doi.org/10.1002/mp.13953
64. Tsang DS, Tsui G, McIntosh C, Purdie T, Bauman G, Dama H, Laperriere N, Millar BA, Shultz DB, Ahmed S, Khandwala M, Hodgson DC (2022) A pilot study of machine-learning based automated planning for primary brain tumours. Radiat Oncol 17(1):3. https://doi.org/10.1186/s13014-021-01967-3
65. Lu SL, Xiao FR, Cheng JC, Yang WC, Cheng YH, Chang YC, Lin JY, Liang CH, Lu JT, Chen YF, Hsu FM (2021) Randomized

multi-reader evaluation of automated detection and segmentation of brain tumors in stereotactic radiosurgery with deep neural networks. Neuro Oncol 23(9):1560–1568. https://doi.org/10.1093/neuonc/noab071
66. Hong JC, Eclov NCW, Dalal NH, Thomas SM, Stephens SJ, Malicki M, Shields S, Cobb A, Mowery YM, Niedzwiecki D, Tenenbaum JD, Palta M (2020) System for high-intensity evaluation during radiation therapy (SHIELD-RT): a prospective randomized study of machine learning-directed clinical evaluations during radiation and chemoradiation. J Clin Oncol 38(31):3652–3661. https://doi.org/10.1200/jco.20.01688
67. Gutsche R, Lohmann P, Hoevels M, Ruess D, Galldiks N, Visser-Vandewalle V, Treuer H, Ruge M, Kocher M (2022) Radiomics outperforms semantic features for prediction of response to stereotactic radiosurgery in brain metastases. Radiother Oncol 166:37–43. https://doi.org/10.1016/j.radonc.2021.11.010
68. Dinkla AM, Wolterink JM, Maspero M, Savenije MHF, Verhoeff JJC, Seravalli E, Išgum I, Seevinck PR, van den Berg CAT (2018) MR-only brain radiation therapy: dosimetric evaluation of synthetic cts generated by a dilated convolutional neural network. Int J Radiat Oncol Biol Phys 102(4):801–812. https://doi.org/10.1016/j.ijrobp.2018.05.058
69. Cusumano D, Boldrini L, Dhont J, Fiorino C, Green O, Güngör G, Jornet N, Klüter S, Landry G, Mattiucci GC, Placidi L, Reynaert N, Ruggieri R, Tanadini-Lang S, Thorwarth D, Yadav P, Yang Y, Valentini V, Verellen D, Indovina L (2021) Artificial intelligence in magnetic resonance guided radiotherapy: medical and physical considerations on state of art and future perspectives. Phys Med 85:175–191. https://doi.org/10.1016/j.ejmp.2021.05.010
70. Huynh E, Hosny A, Guthier C, Bitterman DS, Petit SF, Haas-Kogan DA, Kann B, Aerts H, Mak RH (2020) Artificial intelligence in radiation oncology. Nat Rev Clin Oncol 17(12):771–781. https://doi.org/10.1038/s41571-020-0417-8
71. Bibault JE, Giraud P, Burgun A (2016) Big data and machine learning in radiation oncology: state of the art and future prospects. Cancer Lett 382(1):110–117. https://doi.org/10.1016/j.canlet.2016.05.033
72. Boldrini L, Bibault JE, Masciocchi C, Shen Y, Bittner MI (2019) Deep learning: a review for the radiation oncologist. Front Oncol 9:977. https://doi.org/10.3389/fonc.2019.00977
73. Meyer P, Noblet V, Mazzara C, Lallement A (2018) Survey on deep learning for radiotherapy. Comput Biol Med 98:126–146. https://doi.org/10.1016/j.compbiomed.2018.05.018
74. Rattan R, Kataria T, Banerjee S, Goyal S, Gupta D, Pandita A, Bisht S, Narang K, Mishra SR (2019) Artificial intelligence in oncology, its scope and future prospects with specific reference to radiation oncology. BJR Open 1(1):20180031. https://doi.org/10.1259/bjro.20180031
75. Sahiner B, Pezeshk A, Hadjiiski LM, Wang X, Drukker K, Cha KH, Summers RM, Giger ML (2019) Deep learning in medical imaging and radiation therapy. Med Phys 46(1):e1–e36. https://doi.org/10.1002/mp.13264
76. Shen C, Nguyen D, Zhou Z, Jiang SB, Dong B, Jia X (2020) An introduction to deep learning in medical physics: advantages, potential, and challenges. Phys Med Biol 65(5):05tr1. https://doi.org/10.1088/1361-6560/ab6f51
77. Thompson RF, Valdes G, Fuller CD, Carpenter CM, Morin O, Aneja S, Lindsay WD, Aerts H, Agrimson B, Deville C Jr, Rosenthal SA, Yu JB, Thomas CR Jr (2018) Artificial intelligence in radiation oncology: a specialty-wide disruptive transformation? Radiother Oncol 129(3):421–426. https://doi.org/10.1016/j.radonc.2018.05.030
78. Maziero D, Straza MW, Ford JC, Bovi JA, Diwanji T, Stoyanova R, Paulson ES, Mellon EA (2021) MR-guided radiotherapy for brain and spine tumors. Front Oncol 11:626100. https://doi.org/10.3389/fonc.2021.626100
79. Rai R, Kumar S, Batumalai V, Elwadia D, Ohanessian L, Juresic E, Cassapi L, Vinod SK, Holloway L, Keall PJ, Liney GP (2017) The integration of MRI in radiation therapy: collaboration of radiographers and radiation therapists. J Med Radiat Sci 64(1):61–68. https://doi.org/10.1002/jmrs.225
80. Hyun CM, Kim HP, Lee SM, Lee S, Seo JK (2018) Deep learning for undersampled MRI reconstruction. Phys Med Biol 63(13):135007. https://doi.org/10.1088/1361-6560/aac71a
81. Della Pepa GM, Caccavella VM, Menna G, Ius T, Auricchio AM, Sabatino G, La Rocca G, Chiesa S, Gaudino S, Marchese E, Olivi A (2021) Machine learning-based prediction of early recurrence in glioblastoma patients: a glance towards precision medicine. Neurosurgery 89(5):873–883. https://doi.org/10.1093/neuros/nyab320
82. Emami H, Dong M, Nejad-Davarani SP, Glide-Hurst CK (2018) Generating synthetic CTs from magnetic resonance images using generative adversarial networks. Med Phys. https://doi.org/10.1002/mp.13047
83. Han X (2017) MR-based synthetic CT generation using a deep convolutional neural network method. Med Phys 44(4):1408–1419. https://doi.org/10.1002/mp.12155
84. Johansson A, Karlsson M, Nyholm T (2011) CT substitute derived from MRI sequences with ultrashort echo time. Med Phys 38(5):2708–2714. https://doi.org/10.1118/1.3578928
85. Lei Y, Harms J, Wang T, Liu Y, Shu HK, Jani AB, Curran WJ, Mao H, Liu T, Yang X (2019) MRI-only based synthetic CT generation using dense cycle consistent generative adversarial networks. Med Phys 46(8):3565–3581. https://doi.org/10.1002/mp.13617
86. Liu F, Yadav P, Baschnagel AM, McMillan AB (2019) MR-based treatment planning in radiation therapy using a deep learning approach. J Appl Clin Med Phys 20(3):105–114. https://doi.org/10.1002/acm2.12554
87. Lundervold AS, Lundervold A (2019) An overview of deep learning in medical imaging focusing on MRI. Z Med Phys 29(2):102–127. https://doi.org/10.1016/j.zemedi.2018.11.002
88. Boulanger M, Nunes JC, Chourak H, Largent A, Tahri S, Acosta O, De Crevoisier R, Lafond C, Barateau A (2021) Deep learning methods to generate synthetic CT from MRI in radiotherapy: a literature review. Phys Med 89:265–281. https://doi.org/10.1016/j.ejmp.2021.07.027
89. Isaksson LJ, Pepa M, Zaffaroni M, Marvaso G, Alterio D, Volpe S, Corrao G, Augugliaro M, Starzyńska A, Leonardi MC, Orecchia R, Jereczek-Fossa BA (2020) Machine learning-based models for prediction of toxicity outcomes in radiotherapy. Front Oncol 10:790. https://doi.org/10.3389/fonc.2020.00790
90. Kim HY, Cho SJ, Sunwoo L, Baik SH, Bae YJ, Choi BS, Jung C, Kim JH (2021) Classification of true progression after radiotherapy of brain metastasis on MRI using artificial intelligence: a systematic review and meta-analysis. Neurooncol Adv 3(1):vdab080. https://doi.org/10.1093/noajnl/vdab080
91. Houy N, Le Grand F (2019) Personalized oncology with artificial intelligence: the case of temozolomide. Artif Intell Med 99:101693. https://doi.org/10.1016/j.artmed.2019.07.001
92. Wang Z, Wang Y, Yang T, Xing H, Wang Y, Gao L, Guo X, Xing B, Wang Y, Ma W (2021) Machine learning revealed stemness features and a novel stemness-based classification with appealing implications in discriminating the prognosis, immunotherapy and temozolomide responses of 906 glioblastoma patients. Brief Bioinform. https://doi.org/10.1093/bib/bbab032
93. Neves BJ, Agnes JP, Gomes MDN, Henriques Donza MR, Gonçalves RM, Delgobo M, de Souza R, Neto L, Senger MR, Silva-Junior FP, Ferreira SB, Zanotto-Filho A, Andrade CH (2020) Efficient identification of novel anti-glioma lead compounds by machine learning models. Eur J Med Chem 189:111981. https://doi.org/10.1016/j.ejmech.2019.111981

94. Ding J, Zhao R, Qiu Q, Chen J, Duan J, Cao X, Yin Y (2022) Developing and validating a deep learning and radiomic model for glioma grading using multiplanar reconstructed magnetic resonance contrast-enhanced T1-weighted imaging: a robust, multi-institutional study. Quant Imaging Med Surg 12(2):1517–1528. https://doi.org/10.21037/qims-21-722
95. Yin S, Luo X, Yang Y, Shao Y, Ma L, Lin C, Yang Q, Wang D, Luo Y, Mai Z, Fan W, Zheng D, Li J, Cheng F, Zhang Y, Zhong X, Shen F, Shao G, Wu J, Sun Y, Luo H, Li C, Gao Y, Shen D, Zhang R, Xie C (2022) Development and validation of a deep-learning model for detecting brain metastases on 3D post-contrast MRI: a multi-center multi-reader evaluation study. Neuro Oncol. https://doi.org/10.1093/neuonc/noac025
96. Yoganathan SA, Paul SN, Paloor S, Torfeh T, Chandramouli SH, Hammoud R, Al-Hammadi N (2022) Automatic segmentation of MR images for high-dose-rate cervical cancer brachytherapy using deep learning. Med Phys. https://doi.org/10.1002/mp.15506