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Modern Imaging in Neurooncology

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ABSTRACT

Imaging of intracranial neoplasms has significantly changed over the past two decades. This overview discusses the current state of diagnostic imaging for the three most common tumor types, namely gliomas, metastases and meningiomas, and describes the underlying technical principles as well as their application in diagnosis, treatment planning and follow-up.

Introduction

The diagnosis and treatment of intracranial space-occupying lesions are frequently challenging. The first step is to determine what type of space-occupying lesion is present. Here, neuroimaging is capable of providing important information which may, in some circumstances, even allow to omit histological confirmation, especially when meningiomas are suspected or when brain metastases occur within the context of already previously metastasized disease. Nevertheless, biopsy remains the gold standard for the diagnosis of intracranial space-occupying lesions. For biopsy planning, timely image datasets are used, much in the same way as with the planning of surgical treatment or radiation therapy. Finally, response to treatment needs to be assessed and CNS imaging has proven to be an indispensable tool for following up patients after treatment.

Given the significant complexity into which diagnostic imaging has evolved—from computed tomography (CT) to magnetic resonance imaging (MRI) to nuclear imaging—there is a need to summarize and explain the current evidence as well as the principles of evaluating neuroimaging studies of the most common malignant tumors of the CNS.

This article is the result of a collaboration between diagnostic specialists and treating clinicians. It is intended for neurologists, neurooncologists, oncologists, and radiotherapists responsible for the treatment of primary and secondary malignancies of the CNS, as an introduction to the indications and the significance of the imaging techniques currently used in neuro-oncology. Firstly, today's diagnostic techniques will be introduced in the following. Secondly, the three major intracranial tumor types—gliomas, meningiomas and metastases—will be discussed along the pathway from initial diagnosis to imaging-guided treatment to follow-up care.

Sequences and Tracers

Computed tomography

Computed tomography (CT) depicts radiographic density values (Hounsfield units, HU) as shades of gray in a three-dimensional matrix. Being fast to perform and widely available, this imaging modality is often the first diagnostic tool used in patients with newly

developed neurological signs and symptoms to rule out hemorrhage or—in the form of CT angiography—to rule out acute vascular occlusions. However, in the diagnosis of CNS tumors, CT imaging is regarded as the modality of second choice. This is mostly due to the method's low soft-tissue contrast, a disadvantage which is aggravated by beam-hardening artifacts especially in the posterior cranial fossa region where these are common. Even though some degree of improvement in soft tissue contrast can be achieved with the addition of iodine-containing contrast agents, CT imaging always falls short of the anatomical accuracy of MRI. Since modern radiation therapies use HU values to calculate dose distribution in the target tissue, today's radiation treatment of primary and secondary CNS tumors still relies on CT imaging. In addition, CT imaging can be used in patients with pacemakers or metallic parts.

Magnetic resonance imaging

T1 and T2, T2 FLAIR

In neuro-oncology, imaging primarily relies on MRI. The basic MRI sequences are T1-weighted scans before and after administration of a contrast enhancement agent and T2-weighted scans (CSF bright, fat dark). With the latter, the bright cerebrospinal fluid (CSF) signal typical for T2-weighted imaging can be suppressed, enhancing the sensitivity for water "trapped" in the form of edema or tighter arranged cell bodies in the sequence then referred to as FLuid Attenuated Inversion Recovery (FLAIR).

Contrast-enhanced T1-weighted sequences visualize areas with impaired blood-brain barrier (blood-brain barrier disrupted area, BBBDA). These then hyperintense (bright) areas show in the native T1-weighted sequence as iso- or hypointense. By contrast, residual blood is hyperintense both in the native and contrast-enhanced T1-weighted sequence, especially about 3 days after the hemorrhagic event. Another differential diagnosis, especially in the postoperative course after a surgical procedure, is ischemia which may also present as blood-brain barrier disruption. Thus, to be able to differentiate post-ischemic blood-brain barrier disruption from tumor recurrence, postoperative diagnostic studies must always include diffusion-weighted imaging (DWI) [1].

Navigation dataset

For intraoperative neuronavigation, a so-called navigation dataset is required in the preoperative diagnostic evaluation. This is a thin-slice 3D sequence, visualizing, besides brain parenchyma, the entire head, including nose, eyes, skin. Thus, it can be used for intraoperative neuronavigation. Here, the standard procedure is to use a Magnetization-Prepared Rapid-Acquisition Gradient Echo (MP-RAGE) sequence before and/or after contrast administration, especially with malignant contrast-enhancing lesions. This is a three-dimensional, T1-weighted, gradient-echo sequence with high spatial resolution. However, depending on the query, all other 3D-weighted sequences, such as, for example, a Volume Interpolated Breath-hold Examination (VIBE) sequence, a 3D-FLAIR sequence or a 3D T2-weighted sequence, can be used as well.

Diffusion tensor imaging (DTI)

Diffusion tensor imaging makes allows to visualize intracerebral fiber tracts. This technique is part of routine pre-operative imaging in patients with gliomas where, among others, the following questions are addressed: How closely does the space-occupying lesion approach important fiber tracts, such as, for example, the corticospinal tract? Does the space-occupying lesion shift or invade the fiber tracts? How can vital fiber tracts be spared during surgery? In addition, DTI plays an important intraoperative role. By means of fusion of further sequences with neuro-navigation, it is possible to exactly locate important fiber tracts so that they can be spared intraoperatively [2, 3].

Functional MRI (fMRI)

In patients with gliomas, functional MRI is used for the preoperative, non-invasive visualization of areas of the brain which are responsible for essential functions, such as speech and movement. The elementary principle of fMRI depends on the blood oxygenation level dependent (BOLD) effect. The biophysical basis of this effect is that the magnetic properties of hemoglobin vary with varying blood oxygenation levels [4]. This phenomenon is exploited to non-invasively visualize active brain regions [5–7]. An important goal of preoperative imaging is to determine the exact location of space-occupying lesions in relation to the central region or the language center to help with operability evaluation and perioperative risk assessment. Thus, today the standard procedure is to preoperatively perform functional MRI in patients with lesions in the vicinity of an eloquent brain area.

Diffusion-weighted imaging (DWI)

Diffusion-weighted sequences are important for both the detection of postoperative ischemia, which has a significant impact on neurological outcome, and imaging follow-up where they help to avoid the potential misinterpretation of ischemia-related barrier disruptions as tumor recurrences [8–10]. Restrictions in diffusion, resulting from e.g. ischemia-related intracellular edema, show as hyperintensities. Likewise, an increase in the cellular portion—where fluid is bound—augments the signal in DWI.

SWI and T2 *

Susceptibility weighted imaging (SWI) is useful for the visualization of iron and consequently blood within or outside of vessels. It plays an important role, especially in postoperative imaging where it is used in the early stage of hemorrhage workup.

Nuclear medicine

FET and MET

O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) is an ^{18}fluor-labled amino acid. In Europe, it is the most frequently used tracer in nuclear medicine for the evaluation of brain tumors. Up-regulated amino acid transporters are assumed to be involved in the uptake of FET into tumor cells which can then be visualized with the help of the radioactive labelling [11]. Tracer uptake by a tumor is typically quantified as the tumor-to-brain ratio (TBR); hence the uptake of amino acids by tumor is compared with the uptake by healthy brain tissue. The most commonly used TBR_{mean} is calculated by dividing the mean activity values in an area around the maximum tracer uptake by the mean uptake in healthy contralateral tissue; in addition, tracer uptake kinetics can be analyzed to answer specific questions.

DOTANOC

Meningeal tumors typically exhibit over-expression of somatostatin receptors. Using a 68-gallium-labelled somatostatin receptor ligand (such as [68Ga]-DOTA-TATE, -TOC or –NOC), this receptor can be visualized in positron emission tomography (PET) studies. The various tracer materials differ in their affinity to various somatostatin receptor subtypes; however, a preference for a specific tracer cannot be derived from literature and the choice of a substance is usually determined by the local circumstances and synthesis capabilities. The visual assessment by an examiner is facilitated by the comparatively low enhancement of somatostatin receptor ligands in the background tissue.

Gliomas

Belonging to the group of neuroepithelial tumors, gliomas are classified into four malignancy grades according to the current 2016 World Health Organization Classification of Tumors of the Central Nervous System [12]. The diagnosis of these entities nowadays heavily relies on molecular markers; thus, a biopsy is needed to confirm the diagnosis in most cases. MRI is the standard modality for follow-up imaging studies as well as for biopsy and treatment planning. Here, the following sequences should be included in the standard procedure: a 2D- or 3D-weighted FLAIR sequence (FLuid Attenuated Inversion Recovery), a T2-weighted sequence, a diffusion-weighted sequence, a T1-weighted sequence before and after contrast administration. In addition, pre-operative imaging requires diffusion tensor imaging (DTI) studies and, in some cases, functional MRI (fMRI). Perfusion-weighted sequences are increasingly used in glioma imaging and are of particular importance in higher-grade glioma [13]. In addition, MR spectroscopy is used to distinguish glioma from other intracranial lesions or for tumor grading [14].

Morphologic and nuclear medicine characteristics

Pilocytic astrocytoma (WHO I)

Pilocytic astrocytomas primarily occur in children and adolescents and are characterized by slow growth. Most of these tumors are located infratentorially or within the 3rd ventricle. On imaging studies, tumors present with a broad spectrum of morphological features. Typical features of the tumor's MRI morphology are cystic components (T2-hyperintensive) as well as solid components with strong, frequently inhomogeneous contrast uptake [15].

Diffuse astrocytoma and oligodendroglioma (WHO II)

Diffuse astrocytomas mainly occur in young adults; malignization, i.e. transformation to a high-grade glioma, is common. In MRI studies, they present as homogenous FLAIR-hyperintense tumors, usually being located in the frontal and temporal region; therefore, seizures are a common initial symptom of diffuse astrocytomas. Although contrast enhancement is not typical for low-grade glioma, diffuse or punctiform contrast enhancements are described in almost half of low-grade gliomas [16]. Further imaging methods can help to distinguish between higher-grade and low-grade gliomas. Compared with higher-grade gliomas, low-grade gliomas have higher apparent diffusion coefficient (ADC) values in diffusion-weighted sequences due to their lower overall cell content [17]. In addition, low-grade gliomas have a comparatively lower cerebral blood volume (CBV) in perfusion-weighted sequences as well as low choline values in spectroscopy, reflecting the lower cellular turnover [14, 15, 18].

Even though MRI is no substitute for histology, it provides—in combination with spectroscopy and additional surrogate parameters—a rough estimation of certain markers. For instance, a recent study has shown that cerebral blood volume is significantly lower in IDH-mutated gliomas compared with wildtype gliomas [19]. Furthermore, IDH1/2 mutation can be demonstrated non-invasively using IDH spectroscopy [20]. Apart from the characteristics of WHO grade II tumors described above, oligodendrogliomas typically show calcifications. Gradient-echo sequences are used to detect theses tumors based on their CT-morphological and MR-morphological features (here hypointense).

Anaplastic gliomas (WHO III)

Anaplastic gliomas mostly occur in middle-aged adults and tend to progress to a higher-grade malignancy; overall, they have a poor prognosis. In most cases, imaging reveals nodular, occasionally annular, strong contrast enhancement; not all WHO Grad III tumors show contrast enhancement [16]. In anaplastic gliomas, the 2007 WHO classification differentiated between astrocytoma, oligodendroglioma and oligoastrocytoma, based on morphological criteria. Tumors with predominately oligodendroglial component frequently show calcifications. Based on the histopathological classification, anaplastic astrocytoma are characterized by increased vascular proliferation which is reflected in the increased perfusion/vascularization observed in imaging studies. At present, it remains unclear to what extent the updated WHO classification will change the specificity of imaging classification. Apart from that, anaplastic gliomas often show, besides frequently observed blood-brain barrier disruption, an increased cerebral blood volume, differentiating them from low-grade gliomas [13, 14]. In the presence of decreased ADC values and increased choline values, diffusion imaging and spectroscopy may also help to distinguish anaplastic gliomas from low-grade gliomas [14].

Glioblastomas (WHO IV)

In adults, glioblastoma is the most common type of malignant tumors originating in the brain. Despite modern diagnostic and therapeutic strategies, survival times are markedly reduced (the overall survival ranges between 1 and 2 years); furthermore, recurrences are very common even after surgery and combined chemoradiotherapy [21, 22]. Typical MR-morphological features of glioblastoma include marginal, gyriform contrast enhancement, central necrosis and surrounding T2/FLAIR hyperintense edema [15]. Here, differentiation from cerebral abscesses is of particular importance which, in contrast to glioblastomas, show marked central diffusion restriction [23]. Differentiation from cerebral metastases is usually difficult, and the patient's history as well as a broader diagnostic workup can give important information. Furthermore, multiple intracranial space-occupying lesions not linked by an edema are more suggestive of metastases. However, glioblastoma may present with multifocal lesions, too. More recent studies have demonstrated that diffusion tensor imaging (DTI) can help to differentiate glioblastomas from metastases. Here, glioblastomas typ-

ically show increased fractional anisotropy (FA) in the contrast-enhancing tumor components, i.e. the isotropic white matter tracts are destroyed by tumor growth [24]. By contrast, metastases displace white mater tracts. On perfusion imaging, glioblastomas typically demonstrate increased cerebral blood volume (CBV) in contrast-enhancing tumor components and studies revealed a correlation between cerebral blood volume and prognosis [25]. Similarly, perfusion imaging plays an important role in differentiating glioblastoma from other brain tumors. For example, glioblastomas show a higher cerebral blood volume compared with lymphomas and hypovascularized metastases [19, 26]. Because of this higher degree of vascularization, susceptibility-weighted (SWI) sequences represent an essential part of glioblastoma-related imaging studies. Characteristic of glioblastoma are signal losses which differentiate them from other malignant brain tumors, such as cerebral lymphomas [27].

Nuclear medicine aspects

FET PET can contribute further information for differential diagnostic considerations. Here it is important to note that lesions other than tumors—for example abscesses (mostly lower levels)—may show increased uptake levels [28]. FET uptake beyond a specific TBR threshold ($TBR_{mean} > 1.6$) into the lesion is indicative of malignant tissue. However, in about 50 % of cases, low-grade tumors do not demonstrate increased FET uptake; consequently, their presence cannot be ruled out based on negative PET findings [29]. This correlation between FET uptake and tumor grade gave rise to the idea to use FET PET to differentiate LGG from HGG, as this is another question in the primary diagnostic workup of brain tumors which may be important to treatment planning in some cases, depending on the overall constellation of findings. As described above, contrast uptake in MRI represents a potential criterion for the presence of higher-grade brain tumor tissue, but its sensitivity is low [16, 30, 31]. Unfortunately, the sensitivity of static FET uptake with regard to the differentiation between LGG und HGG is not good. Instead, studies of ^{18}F-FET uptake kinetics can be used to differentiate subgroups of gliomas [32, 33]. The dynamics of ^{18}F-FET uptake is depicted in time activity graphs. While HGGs frequently show an early FET-uptake peak after tracer injection, followed by a decline, LGGs demonstrate a steady rise of the time-activity curve [33]. One study showed that FET kinetics for the detection of HGGs among lesions evaluated as LGGs based on morphological MRI criteria had a specificity of 95 %, even in cases with low or diffuse tracer uptake [34].

Aspects of treatment planning

Preoperative imaging and biopsy planning

Preoperative imaging does not only as part of the diagnostic workup, but it also of importance for due to its role in surgical planning. Besides the standard sequences (T1-weighted with or without contrast, T2- or FLAIR-weighted), the following special imaging modalities are needed, too: navigation dataset, diffusion tensor imaging (DTI) and, in certain cases, functional imaging (fMRI).

Furthermore, the use of FET PET may help to identify the tumor components with active metabolism prior to resection and for radiation planning [35, 36]. Especially in patient with a history of unsuccessful biopsy attempts, it is recommended to perform FET PET prior to biopsy because the percentage of valid biopsies is higher in biopsy material obtained from areas with high tracer uptake and because the anaplastic tumor components can be identified using PET [37]. However, despite the theoretical advantages of a more precise PET-supported diagnosis, the impact of this approach on prognosis has not been demonstrated so far [38].

Post-resection follow-up

The extent of tumor resection is an important prognostic parameter, both in low-grade and higher-grade gliomas [10, 39]. The standard imaging procedure to assess and visualize the residual tumor is the early post-operative MRI [40, 41].

Post-resection follow-up in higher-grade gliomas/metastases Here, low-grade gliomas are to be differentiated from higher-grade gliomas as they required different strategies of postoperative imaging due to the difference in contrast behavior. In higher-grade gliomas, the extent to which the contrast-enhancing tumor components are resected has a profound impact on decisions regarding the further management and adjuvant therapy [39]. Earlier studies reported that postoperative MRI (1.5 Tesla) performed from about 72 h after surgery onwards showed reactive contrast-enhancing changes, making it difficult to clearly identify residual tumor tissue. Consequently, early postoperative imaging < 72 h after surgery was recommended [42, 43]. More recent studies using 3 Tesla MRI showed that early postoperative changes already occurred earlier than assumed and increased significantly about 45 h after surgery [44, 45]. Therefore, the current recommendation is to perform postoperative imaging studies already during the first 45 h after surgery to stay clear of these reactive changes.

For brain metastases, no conclusive studies are available to support recommendations regarding the best timing of postoperative imaging. Nevertheless, early postoperative imaging has also been recommended for metastases to detect complications and to estimate the extent of resection, because a correlation with prognosis was demonstrated for metastases as well [46, 47].

Post-resection follow-up in low-grade gliomas Low-grade gliomas frequently show no contrast enhancement. Therefore, reactive postoperative contrast-enhancing changes only play a minor role. Here, the decisive question is whether the FLAIR-hyperintense tumor volume was successfully removed and postoperative imaging evaluation should include a thorough comparison of pre- and postoperative images to answer this question. In low-grade gliomas, early postoperative MRI studies are performed as well, not only to assess the residual tumor, but also to detect complications, such as ischemia or hemorrhage. Studies showed that the FLAIR-hyperintense tumor components were over-estimated in early postoperative MRI studies in patients with low-grade gliomas due to postoperative changes and that in many cases FLAIR hyperintensity disappeared in the further course [48, 49]. Hence, the question has been discussed whether it would be advantageous to postpone postoperative imaging in patients with non-contrast-enhancing tumors to about 3 months after surgery [48]. However, it has recently been shown that the dynamic changes of FLAIR-hyperintense volumes between early postoperative imaging and follow-up imaging play an important prognostic role. Therefore—and also in the light of the additional indication of ruling out complications—early

postoperative imaging is recommended even in patients with non-contrast-enhancing tumors [49].

Criteria for response to treatment

Follow-up care in patient with glioma incudes both clinical and imaging follow-up examinations. Currently, cMRI studies at intervals of 2 to 3 months are recommended for glioblastomas and WHO °III gliomas. In patients with low-grade gliomas, MRI studies should be performed at intervals of 3 to 6 months over a period of 5 years. From year 6 onwards, the frequency of follow-up imaging studies can be reduced to one MRI annually, as long as findings remained stable beforehand [50].

For gliomas, some heterogeneity with regard to the assessment scales used for the assessment of the response to treatment exist [51]. The most commonly used scales are the RANO HGG and LGG as well as the Macdonald criteria [52–54]. The RANO criteria primarily differ from the Macdonald criteria by the inclusion of T2-weighted/FLAIR-weighed sequences into the criteria for treatment responses, while the Macdonald criteria exclusively depend on the evaluation of blood-brain barrier disruptions [22]. Thus, the evaluation of treatment response is not solely based on the increase or decrease of blood-brain barrier disruptions, but relies on the combination of T1, FLAIR and clinical examination. In addition, all three scales incorporate clinical parameters, such as the patient's general condition or use of corticosteroids. Even when imaging studies are not available, a deterioration of the patient's clinical condition can allow to diagnose tumor progression. Especially in patients treated with bevacizumab who may show impressive initial decreases in contrast-enhancement (a phenomenon at times described as tumor pseudoresponse), the actual response to treatment should be evaluated by taking FLAIR sequences into consideration as well. This is of special importance when study results are compared. Studies that include information from FLAIR-/T2-weighted sequences in the evaluation process may detect tumor progression earlier and this, in turn, influences the documented progression-free survival times (PFS). For example, a reduction of PFS from 6.4 to 4.6 months was report which solely resulted from the switch from Macdonald to RANO criteria [55].

Handling of borderline cases

Malignization The occurrence of higher-grade tumor tissue in a known LGG, the so-called malignization, represents an unfavorable prognostic factor and necessitates a change in therapeutic strategy in many cases. Newly developed contrast uptake in a previously non-contrast-enhancing tumor is one MRI sign of progression to a higher-grade malignancy. In patients with suspected malignization, static or dynamic FET PET may be advantageous as an additional imaging modality because of the limitations of conventional MRI resulting from its restricted sensitivity with regard to the presence of HGG tissue [56].

Pseudoprogression Pseudoprogression typically occurs within about 12 weeks after radiation therapy of a HGG and is a relatively common phenomenon (approx. 15–30 % of tumors treated). Thus, the RANO HGG criteria define progression only if the changes occur at least 3 months after the last radiation therapy session. According to the current literature, the first step to differentiate between actual progression and pseudoprogression is to repeat the imaging studies within 4 to 6 weeks [22]. However, since the differentiation between recurrence and treatment-related changes is often challenging despite repeated cMRI studies, additional FET PET studies are performed in many cases [57, 58]. As already during the primary diagnostic evaluation, TBR is calculated to determine the amino acid uptake in lesions suspicious of recurrence; areas with radiation-induced changes should show no or only minimal uptake [59, 60]. For glioblastomas it was demonstrated that a TBR_{mean} value of 2.3 allows to differentiate pseudoprogression from early progression with an accuracy of 96 % (specificity 91 %, sensitivity 100 %) [61]. In addition, FET PET is increasingly used for treatment monitoring because the course of tracer uptake during and after treatment can contribute useful information for the evaluation of treatment response [59, 62, 63].

Radiation treatment planning

In most cases diagnosed with glioma of WHO grade II or higher, radiation therapy, or often chemoradiotherapy, is indicated [64, 65]. Radiotherapy is usually performed as partial-brain treatment as non-inferiority compared to whole brain radiotherapy was shown [66]. Apparently, the highest possible level of imaging data accuracy is desirable for the calculation of the target volume. For this purpose, the radiation treatment CT scan should be complemented by MRI studies. The 3D-weighted T1, T2 and FLAIR sequences are currently recommended as the minimum set of imaging studies for radiation treatment planning. With this approach, all surgical defects, blood-brain barrier disrupted areas and FLAIR hyperintensities are included in the target volume. A safety margin of 10 to 25 mm, depending on histology, is added to these volumes to allow for the infiltrative growth of these tumors and positioning inaccuracies [67, 68].

While the ideal timing of radiation treatment after resection has not yet been established, it seems to be reasonable to start radiotherapy within 6 weeks postoperatively [69, 70]. Since significant anatomical changes may occur during this period, radiotherapy should be based on a separate radiation treatment planning MRI. This frequently helps to better differentiate preoperative FLAIR hyperintensities. Pressure-related edema typically resolves in the further course after resection; by contrast, FLAIR hyperintensities related to tumor infiltration tend to remain stable or to be progressive. The FLAIR hyperintensities in the planning MRI should be part of the target volume [68].

The role played by amino acid PET imaging in radiation treatment planning in patients with previously untreated glioma has not yet been fully established [71]. However, retrospective data suggest that adding PET imaging to the workup for radiation treatment planning may be advantageous. It is known that the addition of amino acid PET to MRI results in a significant increase in target volume. Furthermore, in 13 % of patients treatment of the tumor discernible in PET images would have been incomplete if the nuclear medicine information had not been available [72].

In addition, many cases of recurrence can be treated effectively and safely with re-irradiation; however, studies directly comparing radiation therapy with best supportive care and a chemotherapy regimen have not yet been conducted [73–75]. In general, the requirements for treatment planning are higher in the re-irradiation situation. Therefore, it is crucial to ensure that positioning variabil-

ity is reduced to an absolute minimum, ideally by applying stereotactic positioning. As in primary therapy, MRI is used to define the recurrence's anatomical boundaries. Here, the target volume always comprises the blood-brain barrier disrupted area in the T1-weighted sequence. In the treatment of recurrences, FLAIR sequences play only a minor role as post-treatment gliosis cannot reliably be differentiated from edema or tumor recurrence. Thus, it seems to be obvious to turn to biological imaging in the form of amino acid PET or spectroscopy for this purpose. The GLIAA/NOA-10 study is currently collecting randomized data on the value of amino acid PET for re-irradiation treatment planning. According to the extensive pilot studies conducted in preparation of this trial, amino acid PET may offer a survival-relevant benefit in patients with glioblastoma requiring re-irradiation treatment [72, 76].

Meningiomas

Radiation treatment planning

Meningiomas are the most common primary brain tumors and usually affect middle-aged and older adults. They are also classified according to the WHO classification; 3 grades of malignancy are described [77]. Most meningiomas (> 90 %) are classified as WHO grade I and thus are slow-growing tumors, originating from arachnoid cap cells [77]. Common locations include falx, tentorium and sphenoid wing. In principle, all of the locations mentioned are accessible to treatment with radiation therapy. The range of indications for radiation therapy treatment extends from definitive radiotherapy with or without prior histological confirmation to adjuvant therapy in patients with high-risk constellations to the treatment of recurrences [50]. Especially in skull base meningiomas, radiation therapy is an effective and comparatively well tolerated alternative to surgical resection of the tumor [78–80]. Since in the majority of cases meningiomas are irradiated with the patient in stereotactic positioning, i.e. with at times minimal safety margins, an exact description of the anatomical extent of the tumor is critical for radiation therapy treatment planning. Provided there are no contraindications, this workup should always include a contrast-enhanced, thin-slice MRI (slice thickness of 1 mm; at least one T1-weighted sequence before and after contrast; an additional T2-weighted sequence is desirable). If no histological confirmation—still considered as the gold standard for diagnosis of meningioma—was obtained or in patients with recurrent meningioma, additional nuclear medicine imaging should be performed to substantiate the reliability of the diagnosis. Despite this high diagnostic reliability, resulting from the pathognomonic morphological features and the characteristic enhancement behavior in PET, the patient should be fully informed that radiation therapy planned under the imaging-based assumption of a WHO grade I meningioma would not be sufficiently dosed to treat rare histologies, such as higher-degree meningiomas or a hemangiopericytoma.

Likewise, in patients with recurrent meningioma, an additional PET study should be included in radiation treatment planning. This applies especially if the postoperative changes cannot be differentiated from active tumor tissue by MRI alone.

Morphological characteristics of meningioma

Both CT and MRI morphology of meningiomas is characterized by intense, usually homogeneous contrast enhancements. The tumor arises from the dura mater and is sharply demarcated from the surrounding brain parenchyma which is displaced, not infiltrated by the tumor. Frequently characteristic hyperostosis or osteolysis of the adjacent bone is observed. Another typical feature of meningiomas is the dural tail sign, i.e. an extensive contrast enhancement and thickening of the dura directly adjacent to the mass. Atypical (WHO II) or anaplastic (WHO III) meningiomas are characterized by perifocal edema, infiltrative growth, inhomogeneous morphology, as well as early recurrences/rapid growth [15].

Due to their slow growth, calcifications are very common in meningiomas. With the help of gradient echo sequences, these can be detected in CT-morphological or MR-morphological studies. Since meningiomas are usually highly vascularized tumors, perfusion imaging shows homogeneously increased cerebral blood volume [15].

Follow-up care

Follow-up care of patients treated for meningioma is primarily based on contrast-enhanced MRI. Meningioma patients who received primary radiation therapy and patients with a WHO grade I or grade II meningioma should be followed up with imaging studies at months 3, 6 and 12 after end of treatment. Thereafter, further imaging studies should be performed at intervals of once every 6 to 12 months over a period of up to 5 years. If the disease is stable over this period of time, follow-up intervals may be extended to up to every 3 years [50]. Unfortunately, uniform and meningioma-specific criteria to evaluate response to treatment or clinically significant tumor progression are not available at present [81]. Until this changes, it is recommended to use the MacDonald or RANO criteria for meningioma and metastases as a guidance [51, 52, 54].

Nuclear medicine diagnostic workup

In the diagnostic workup of both recurrent and newly diagnosed meningioma, radiolabeled somatostatin analogs (such as DO-TA-TATE, DOTA-TOC, and DOTA-NOC) have emerged as PET tracers of choice because of their high affinity to the SSTR2 receptor. Somatostatin receptor PET has a sensitivity of 90 % for vital meningioma tissue, both in newly diagnosed and recurrent meningiomas. The method also shows a strong correlation between tracer enhancement and SSTR2 expression [82]. DOTA PET has been shown to be of advantage especially for planning, re-evaluation after treatment (scar vs. recurrence), and precise visualization of tumor extent (bone infiltration, scar tissue), but also for the diagnosis of meningiomas which are often too small to be detected by MRI. The preparation of target volumes for the resection the or local therapy can be improved by means of somatostatin receptor PET [83].

Brain Metastases

Tomographic imaging

Intracranial metastases are a frequent complication in patients with malignant tumors; in adults, the incidence of brain metastases is higher than that of glioblastomas [84, 85]. Standard imaging

workup of brain metastases should include, besides the above mentioned sequences, a thin-slice 3D-weighted T1 sequence after contrast to ensure small metastases are not missed [86]. The most common primary tumors to metastasize to the brain are lung cancer, breast cancer, melanoma, renal cancer, gastrointestinal cancer, and thyroid cancer [85]. However, intracranial metastasis from other tumors, such as liver cancer, endometrial cancer and thymus cancer, may also occur [87–89]. On imaging, brain metastases present very differently according to their histopathological subtypes. However, strong contrast enhancement is a typical common feature, partly with a gyriform or annular pattern, with central necrosis as in glioblastoma, but frequently with solid tumor components which can help to differentiate them from glioblastoma [84]. In some histopathological subtypes, such as renal cancer and melanomas, areas of hemorrhage are observed more frequently [84].

With regard to brain metastasis differential diagnosis, cerebral lymphoma shall be highlighted here because of its very characteristic MR-morphological features. Cerebral lymphomas typical present with strong, usually solid contrast enhancement; frequently, several intracranial lesions and contact to the subarachnoid space or the ventricular system are observed [90]. Due to their high cellularity, lymphomas typically show ADC reduction and appear hyperdense in CT scans [91, 92].

Biological imaging

PET imaging may be useful for distinguishing brain metastases from benign lesions and pseudoprogression (refer to the corresponding sections regarding primary imaging for gliomas). Here again, a dedicated amino acid PET should be performed. With 18F-fluorodeoxyglucose (FDG), a radiotracer commonly used for whole-body tumor staging PET, it is difficult to distinguish brain metastases from normal glucose metabolism in healthy brain tissue, as the latter is exhibiting pathology-induced variability in glucose metabolism and generally shows a high background FDG-uptake. Static FET PET has demonstrated a good accuracy with regard to brain metastasis diagnosis (sensitivity of 74 % and specificity of 90 %) [56]. Moreover, the kinetic curves known from glioma diagnosis to be suspicious of malignancy (early peak with subsequent plateau or decline) can be used as criteria for recurrence of metastatic brain tumors, further increasing specificity.

Treatment planning and monitoring

The following pattern of lesions are distinguished in the treatment of brain metastases: solitary brain metastasis (a single metastasis of a tumor in the whole body, located in the brain), singulary brain metastases (several metastases of a tumor in the whole body, only one of these in the brain), central oligometastases (with a maximum of 4 brain metastases) and an extensive metastatic spread with multiple metastases. Furthermore, a cerebrospinal fluid (CSF) space involvement/leptomeningeal spread should be evaluated. For this, MRI studies of the entire neuroaxis or repeated lumbar punctures are considered an adequate diagnostic approach. In addition, staging, adapted to the primary disease, should be performed, not least to be able to predict the prognosis.

Symptomatic metastases are frequently located in eloquent brain areas. In cases where a single metastatic lesion can be identified as the cause of the signs and symptoms, resection of this lesion by an experienced neurosurgeon can frequently resolve these complaints. Here, imaging-based preparation of the surgical procedure does not significantly differ from the preoperative imaging strategy in glioma surgery. Early postoperative MRI follow-up after resection of metastases is currently not included in the guideline, but should be considered, not least to identify complications and to determine the extent of the resection.

Resection of solitary or singulary metastases should be supplemented by adjuvant radiation therapy, especially when the location of the tumor prohibited hyper-complete resection [93, 94]. Since metastases tend to displace rather than infiltrate neighboring tissue, the anatomical changes in the area of the former tumor bed after resection can be substantial [95]. A up to date cMRI should be available for treatment planning of a radiation therapy that tightly follows the resection cavity and also to rule out the presence of additional brain metastases. Minimum imagining requirements for target volume definition include a 3D-weighted T1 sequence before and after contrast and a T2-weighed or T2-FLAIR sequence for differential diagnosis in case of newly developed contrast changes. In addition, a SWI sequence to reveal potential hemorrhage is also desirable.

Following conventional whole-brain radiation therapy, follow-up care is initially solely clinical. Imaging follow-ups are scheduled once every 3 months or as required by the individual patient's needs [96]. If cMRI is performed after whole-brain radiation therapy treatment, FLAIR-hyperintense white matter changes and a reduction in brain parenchyma and hippocampal volumes are observed in typical sequence; these changes are in line with post-treatment leukoencephalopathy [97].

If prophylactic treatment of wide areas of the CNS was totally (in case of SFS and RC) or partially (in case of hippocampus-sparing whole-brain radiation therapy) avoided, tight follow-up examinations every 8 to 12 weeks are indicated [98, 99].

Various classification systems are available to determine the response to treatment in patients with brain metastases. Some of the classification systems regard metastatic spread to the brain as an integral component of a systemic disease and define consistent criteria for the whole body. Important representatives of these systems are the RECIST and the WHO system [100]. By contrast, the RANO-BM criteria solely refer to brain metastases [51].

Patients treated with immunotherapy are regarded as a special case. Particularly in the early stage of therapy after treatment for melanoma metastases with Ipilimumab, pseudoprogression with an at times substantial increase in the number of metastases has been reported. Nevertheless, response to treatment, even to the extent of a complete response, was observed in many of these cases in the further course of the immunotherapy. Criteria for treatment response must take this phenomenon into account in order to not jeopardize a successful treatment outcome by diagnosing (apparent) treatment failure too early and subsequently stop treatment. Therefore, the RANO has recently developed a catalog for treatment response under immunotherapy specifically for the brain [101]. The various criteria for treatment response are summarize in ▶ **Table 1**.

▶ **Table 1** Criteria for response to treatment.

	measurable lesion	Measuring technique	Confirmation of progression by re-examination	CR = complete response	PR = partial response	SD = stable disease	PD = progressive disease
Macdonald [54]	not defined	two-dimensional	required, interval at least 1 month	complete resolution of all blood-brain barrier disrupted areas, clinically stable or improved	greater than 50 % reduction in the sum of orthogonal diameters of the blood-brain barrier disrupted areas; stable or reduced corticosteroid use; clinically stable or improved	less than 50 % reduction but/or 25 % reduction in the sum of orthogonal diameters of the blood-brain barrier disrupted areas; clinically stable or improved; stable or reduced corticosteroid use. No new blood-brain barrier disrupted areas	more than 25 % increase in the sum of the orthogonal diameters of the blood-brain barrier disrupted areas; or: substantial clinical deterioration
RANO (HGG)[52]	at least 10 × 10mm in size	two-dimensional	required, interval at least 4 weeks	complete resolution of all blood-brain barrier disruptions; FLAIR hyperintensity stable or getting smaller; fully tapered off corticosteroids; clinical stable or improved	greater than 50 % reduction in the sum of orthogonal diameters of the blood-brain barrier disrupted areas; FLAIR hyperintensity stable or smaller; stable or reduced corticosteroid use; clinically stable or improved	less than 50 % reduction but/or 25 % increase in the sum of orthogonal diameters of the blood-brain barrier disrupted areas; clinically stable or improved; stable or reduced corticosteroid use. No new blood-brain barrier disrupted areas	more than 25 % increase in the sum of the orthogonal diameters of the blood-brain barrier disrupted areas; or: substantial increase in FLAIR hyperintensities; or: substantial clinical deterioration
RANO (LGG)[53]	not defined	two-dimensional	not defined	complete resolution of all blood-brain barrier disruptions and all FLAIR hyperintensities; fully tapered off corticosteroids; clinical stable or improved	greater than 50 % reduction in the sum of orthogonal diameters of FLAIR hyperintensities; stable or reduced corticosteroid use; clinically stable or improved	less than 50 % reduction but/or 25 % reduction in the sum of orthogonal diameters of FLAIR hyperintensities; clinically stable or improved; stable or reduced corticosteroid use. No new blood-brain barrier disrupted areas	more than 25 % increase in the sum of the orthogonal diameters of the FLAIR hyperintensities; or: substantial clinical deterioration
RANO (BM)[51]	maximal diameter at least 10mm in size	one-dimensional	recommended, after 6-12 months	complete resolution of all blood-brain barrier disruptions for more than 4 weeks; no new lesions; no corticosteroids; clinical stable or improved	more than 30 % reduction in the maximal diameter of the target lesions for more than 4 weeks; no new lesions; stable or reduced corticosteroid use; clinically stable or improved	finding not sufficient for PR or PD	more than 20 % increase in the sum of the maximal diameters of the target lesions; or: new lesions; or: substantial clinical deterioration
iRA-NO[101]			required, after 3 months	same as RANO HGG/LGG/BM; immunotherapy should—if no substantial increase in corticosteroid use is required—be continued until confirmation of progression			

Conflict of interest

No conflict of interest has been declared by the authors.

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