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Advances in imaging modalities for spinal tumors

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Abstract

The spinal cord occupies a narrow region and is tightly surrounded by osseous and ligamentous structures; spinal tumors can damage this structure and deprive patients of their ability to independently perform activities of daily living. Hence, imaging is vital for the prompt detection and accurate diagnosis of spinal tumors, as well as determining the optimal treatment and follow-up plan. However, many clinicians may not be familiar with the imaging characteristics of spinal tumors due to their rarity. In addition, spinal surgeons might not fully utilize imaging for the surgical planning and management of spinal tumors because of the complex heterogeneity of these lesions. In the present review, we focus on conventional and advanced spinal tumor imaging techniques. These imaging modalities include computed tomography, positron emission tomography, digital subtraction angiography, conventional and microstructural magnetic resonance imaging, and high-resolution ultrasound. We discuss the advantages and disadvantages of conventional and emerging imaging modalities, followed by an examination of cutting-edge medical technology to complement current needs in the field of spinal tumors. Moreover, machine learning and artificial intelligence are anticipated to impact the application of spinal imaging techniques. Through this review, we discuss the importance of conventional and advanced spinal tumor imaging, and the opportunity to combine advanced technologies with conventional modalities to better manage patients with these lesions.

Key Points

1. Imaging guides diagnosis, treatment planning, and follow-up of spinal tumors.
2. Advanced imaging has the potential to improve spinal tumor management.

Role of Imaging to Diagnose Spinal Tumors

Spinal tumors, which are classified as extradural, intradural extramedullary, and intradural intramedullary, are relatively uncommon. There are various types of spinal tumors as presented in Table 1. Among them, metastatic epidural spinal tumors are most common and account for > 90% of all spinal tumors.[1] However, metastatic spinal cord compression, which is an important clinical presentation, is associated with only 2.5% to 5% of solid tumors, with an incidence rate of 8 per 100 000 individuals.[2,3] As for intradural spinal tumors, annual incidence rates were much less than extradural; around 1 per 100 000 individuals.[4,5] Among them, nerve sheath tumors, including schwannoma and neurofibroma, are the most common followed by meningioma.[6] Due to their rarity, most clinicians are not familiar with spinal tumors, and they are sometimes diagnosed after significant delay.[7]

Additionally, the variety of spinal tumors makes it difficult to diagnose them precisely. For accurate and prompt diagnosis, diagnostic imaging plays an important role for spinal tumors.

For metastatic spinal tumors, diagnostic imaging is critical to evaluate if surgery is indicated, and if so, the required surgical approach. The surgical indications for metastatic spinal tumors should be determined based on the patient's predicted prognosis and a number of other factors including predictive models such as revised Tokuhashi score, Tomita score, the neurologic, oncologic mechanical, and systemic (NOMS) framework, Oswestry Spine Risk Index, the Spinal Instability Neoplastic Score (SINS), and the New England Spinal Metastasis Score.[8] The SINS was developed to evaluate

Table 1. The Classification of Spinal Cord Tumors

	Extradural	Intradural extramedullary	Intramedullary
Primary	Hemangioma Osteoid osteoma Osteoblastoma Osteochondroma Giant Cell Tumor Chordoma Multiple myeloma Osteosarcoma Chondrosarcoma Primary spinal epidural malignant lymphoma Ewing sarcoma	Meningioma Nerve sheath tumors Schwannoma Neurofibroma Solitary fibrous tumor Dermoid/Epidermoid	Gliomas Ependymal tumors Astrocytic tumors Hemangioblastoma Cavernous angioma Ganglioglioma Paraganglioma Primary spinal cord malignant lymphoma Primitive neuroectodermal tumor
Metastatic	Metastatic spinal tumors	Leptomeningeal metastasis	Metastatic spinal cord tumors

Table 2. The Spinal Instability Neoplastic Score (SINS)

Element	Score				
	4	3	2	1	0
Location		Junctional	Mobile spine	Semi-rigid	Rigid
Pain		Yes (mechanical)		Occasional (not mechanical)	No
Bone lesion quality			Lytic	Mixed	Blastic
Spinal alignment	Subluxation		Deformity		Normal
Vertebral body collapse		>50%	<50%	No collapse >50% body involved	None
Posterolateral involvement		Bilateral		Unilateral	None
Total score	18–13		12–7	0–6	
Assessment	Unstable		Indetermined	Stable	
Recommendation	Consider surgical treatment			Conservation	

the instability of lesions and helps surgeons to determine whether surgical stabilization should be combined or not.[9] The SINS score is comprised of (1) location of the lesions, (2) mechanical or postural pain, (3) bone lesion quality (lytic/blastic), (4) radiographic spinal alignment, (5) vertebral body collapse, and (6) posterolateral involvement of spinal elements (Table 2), with some of these elements requiring radiological evaluation. The NOMS framework was presented to determine the use of systemic therapy, surgery, and radiation for the treatment of metastatic spinal tumors.[10] This framework consists of the neurologic (the degree of epidural spinal cord compression and clinical symptoms), oncologic (the radiosensitivity of the primary tumor), mechanical (the spinal stability assessed by the SINS), and systemic considerations (the patient's fitness for surgery), which also require radiological evaluation. Thus, diagnostic imaging for spinal tumors is necessary for adequate assessment of the optimal mangement.

Not all spinal lesions are neoplastic in nature, often demyelinating, vascular, inflammatory, or infectious lesions, including tuberculosis, can minic neoplastic conditions.[11] Multiple sclerosis as well as neuromyelitis optica spectrum disorders represent demyelination caused by immune-mediated inflammation.[12] Acute disseminated encephalomyelitis is also classified as a demyelinating disease, and is suggested to be associated with viral infection.[11] Vascular pathologies including spinal arteriovenous malformations also need to be differentiated from spinal tumors because they are often accompanied by cord edema.[13] Spinal infections such as bacterial spinal cord abscess and spinal tuberculosis should be differentiated from spinal tumors.[11]

Due to the many differential diagnoses of spinal tumors, as mentioned above, a biopsy is occasionally necessary for diagnosis, especially for extradural lesions when a primary spinal neoplasm is being considered. However, accurate and precise use of diagnostic imaging also plays a significant role. In order to narrow the differential diagnosis of the spinal lesion, it is crucial to confirm the cross-sectional location, segmental length, and enhancement pattern of the lesion.[14,15] For instance, multiple sclerosis lesions are usually located in a lateral or posterior aspect of the spinal cord and involve 1–2 vertebral body lengths, whereas neuromyelitis optica spectrum disease lesions are generally located in a central part of the cord and exist as a longer segment.[16,17] Conversely, acute disseminated encephalomyelitis commonly involves long segments without gadolinium enhancement,[18] whereas cauda equina roots are usually enhancing in Guillain-Barré syndrome.[16] Thus,

spinal tumor-like lesions have some radiographic characteristics that help to distinguish them from spinal tumors. Similarly, spinal tumors also have some common features, which are described later in this manuscript.

Role of Imaging in Planning and Undertaking Surgical Treatment

The spine has unique anatomical characteristics compared with other structures; it not only supports the body, but is also paramount for neurological function. Therefore, spinal cord tumors must be resected with a great deal of caution to preserve spine stability as well as neurological function. Specifically, surgeons must avoid excessively removing vertebrae and surrounding tissues, which can lead to spinal instability and exacerbate neurological symptoms in the future. Additionally, intramedullary spinal tumors cannot be resected with negative margins unlike other internal organs because extended resection will result in neurological sequelae. In order to achieve such a challenging mission, surgeons have to develop an approach using preoperative imaging. As mentioned above, the SINS scoring system for patients with metastatic spinal tumors requires a preoperative radiographical assessment.[9] A low SINS score means that the lesion will be stable, and then the surgeons will choose a decompressive strategy including laminectomy. On the other hand, a decompression and fixation will be performed if the SINS score is high. In the case of intramedullary spinal tumors, preoperative imaging is also essential to determine which approach should be used. There are some sulci (posterior median sulcus and posterolateral sulcus) and fissures (anterior median fissure) in the spinal cord that allow for access to the spinal cord with minimal damage,[19] and some surgical approaches—posterior median sulcus approach,[20] posterolateral sulcus approach,[21] and anterior median fissure approach[22]—are reported to be effective. The optimal approach can be selected depending on the axial location of the tumor.

Pre- and peri-operative imaging plays an ancillary role in tumor resection. For extradural tumors, intraoperative O-arm or computed tomography (CT)-based image navigation for spinal column tumors will contribute to minimally invasive surgery when the operating room is well-equipment.[23,24] As for intradural spinal lesions, intraoperative ultrasonography can be used to confirm tumor location, guide myelotomy, and make sure that tumor resection is appropriately completed.[25,26] Additionally, navigation using fusion images of preoperative magnetic resonance imaging (MRI) and intraoperative O-arm images will help to ensure the safe and precise resection of intramedullary spinal tumors.[27,28] Furthermore, augmented reality (AR) can be used for intraoperative assistance, which is described in a later section.

Postoperative imaging is required to plan for adjuvant therapy. Although there is controversy regarding postoperative irradiation and chemotherapy for spinal tumors, postoperative radiation therapy can be recommended depending on the degree of resection.[29] Even if gross-total resection is achieved, physicians should closely monitor whether local recurrence and distant metastasis occur.[30]

As described above, imaging is crucial throughout the whole period of spinal tumor management. Although the optimal modality varies depending on the therapeutic phase and its purpose, it plays an important role throughout a patient's care journey.

Types of Imaging Modalities and Advances in the Field

Computed Tomography

Metastatic osseous disease is most prevalent in the spine, as mentioned above, and CT is the optimal modality for characterizing these lesions.[31,32] CT allows for differentiating between osteolytic and osteoblastic lesions, thereby providing additional information for differential formation.[33] Moreover, CT images are instrumental in stereotactic body radiation therapy dose calculations, and therefore are part of the usual patient management pathway. When osseous lesions extend into the spinal canal, MRI will need to evaluate the compression of neural tissue; however, myelography can also supplement information obtained with CT for those who are unable to undergo MRI.

Non-osseous lesions of the spine are best evaluated on MRI; however, there are features of certain tumors that can lend to a preliminary differential diagnosis prior to MRI evaluation. For instance, meningioma and schwannoma occasionally have distinguishable CT imaging features.[6] Meningiomas sometimes appear hyperdense due to their calcification. According to previous reports, the incidence of grossly calcified spinal meningiomas that can be detected by plain radiography was only 1%–5% of cases.[34] Conversely, Kobayashi et al. reported that CT could effectively detect calcification in spinal meningiomas, which accounted for 75%.[35] Importantly, spinal meningiomas with calcification have a risk of surgical morbidity due to adhesion[35,36]; therefore, it is crucial to assess if the lesion contains calcifications. Schwannomas seldom have calcification; thus, CT findings will be helpful for distinguishing between schwannomas and meningiomas. On one hand, spinal schwannomas can present as an enlargement of the intervertebral foramen, a pedicular thinning, and posterior vertebral scalloping due to increasing intraspinal pressure.[37,38]

Regarding intramedullary spinal tumors, specific CT findings are limited[39]; therefore, CT is less useful in diagnosis. However, preoperative CT aids in planning the surgical approach in intramedullary spinal tumors. In particular, CT angiography for hemangioblastomas is essential to identify feeding arteries and draining veins, and to determine the sequence of vessel division for a safety resection. Although spinal angiography is the gold-standard for the vascular assessment of spinal hemangioblastomas from the view of spatial resolution, three-dimensional CT angiography has some advantages such as lower invasion, lower X-ray dosage, and fewer complications.[40]

Magnetic Resonance Imaging

MRI is indispensable not only for diagnosing spinal tumors but also for operative planning.[31,32] We can obtain pertinent information such as nerve root and cord compression,

and cord signal change resulting from tumoral lesions. Additionally, we can ascertain the extent of tumor extension precisely using preoperative MRI, which is helpful in determining the surgical approach.

For extradural/bony tumors, MRI can distinguish marrow tumors from normal bone marrow. T1 and T2 weighted images (WI) detect the tumor replacement of normal marrow, fat suppression T1 sequences, and short tau inversion recovery sequences further increasing the contrast between tumor (hyperintense) and normal marrow (hypointense). These sequences allow for tumor delineation; however, the anatomic details are obscured compared to other sequences, hence standard T1 and T2WI should be combined in surgical planning.[32] In addition, vertebral metastasis with extradural extension should be evaluated using contrast and non-contrast T1WI to detect compartmental involvement.[31]

Regarding intradural extramedullary spinal tumors, meningiomas are usually T1 iso- to hypointense with T2 hyperintensity and homogenous enhancement with a dural tail sign, which refer to the tapered enhancement of the tumor and are reported to be noted in 57%–67% of patients with spinal meningiomas.[6,41,42] When the dural tail sign is obscured in intradural extramedullary tumors, the 'ginkgo leaf sign', which is the finding of a stretched dentate ligament involved with meningioma, is also helpful for the preoperative diagnosis.[43] Schwannomas tend to be well-demarcated, T1 iso- to hypointense with T2 hyperintensity and avid enhancement.[6] Spinal schwannomas sometimes present a dumbbell shape with intra- and extradural components, the surgical strategy for dumbbell-shaped spinal tumors will be different depending on their locations. MRI can identify the precise location, which is important to determine the surgical strategy preoperatively.

Intramedullary spinal cord lesions typically enhance intensely and have adjacent hyperintense edema. Gadolinium enhancement is related to the vascularity of the lesion, which is not necessarily correlated to the tumor grade,[39] and also identifies cystic, solid, and necrotic portions of the tumor.[44] Contrast-enhanced MRI also allows for the detection of leptomeningeal involvement for further diagnostic and prognostic benefit.[39,44] Ependymomas are T1 iso- to hypointense (hyperintense in the case of intratumoral hemorrhage) and T2 iso- to hyperintense.[39] They are intensely enhancing with cord edema, a cleavage plane, and often with a "cap sign" with T2 hypointensity secondary to hemosiderin deposition.[39,45] Astrocytomas are ill-defined, T1 iso- to hypointense and hyperintense on T2WI with heterogenous contrast enhancement, whose pattern is typically patchy with a focal nodule.[39,46] However, Seo et al. reported that 32% of spinal astrocytomas, including 2 cases of high-grade astrocytomas, were not enhancing at all.[47] Hemangioblastomas manifest iso- to hyperintensity on T1WI, and hyperintense with flow voids on T2WI. These are intensely homogeneous enhancing lesions.[39]

Previous studies demonstrate that MRI was successful in correctly matching the pathologic diagnosis of intramedullary spinal neoplasms.[39] Cysts are identified as intratumoral or non-tumoral; where non-tumoral cysts do not enhance and do not require resection. Intratumoral cysts are enhancing and contain tumor cells requiring resection when amenable.

Thus, MRI provides considerable information to diagnose spinal tumors and to plan for treatments; however, it is not a universal modality for all cases. Patients with instrumentation, for example, previous resection or biopsy necessitating fusion, will have resultant artifacts on MRI. To reduce such metal artifacts, advanced techniques including slice encoding for metal artifact correction and multi-acquisition variable-resonance image combination have been reported in the literature.[48]

Positron Emission Tomography/PET-CT

Nuclear medicine scans are commonly used to assess the extent of metastatic disease, which allows for disease staging. Among them, positron emission tomography (PET) with ^{18}F-fluoro-deoxy-glucose (^{18}F-FDG) is a fundamental modality to detect the activity of metastatic disease. Often, spinal metastases present as "hot" lesions due to the increased vascularity of metastasis resulting in increased tracer uptake.[31] In patients with progressive disease resulting in diffuse metastasis, scans can be interpreted as false negative due to the uniform uptake. A sensitivity ranging from 74% to 98% has been noted in the literature for the detection of spinal metastasis.[31] PET and CT can be fused to allow for increased sensitivity in the detection of bony metastases, comparable to the sensitivity of MRI.[49] This fused modality is able to differentiate between non-pathological and pathologic compression fractures.[49]

Spinal Angiography

Spinal angiography is helpful to facilitate presurgical embolization for hyper-vascular spinal tumors, such as metastatic renal cell carcinoma and thyroid cancer[50]. Although there are other non-invasive diagnostic imaging modalities, spinal angiography remains the gold-standard to evaluate tumor vascularity. Gadolinium-enhanced spinal MRI might be able to assess tumor vascularity; however, some reports have shown that MRI enhancement was not always predictive of tumor hyper-vascularity.[51,52] Therefore, spinal angiography should be considered in patients with spinal tumors that are suspected to be hyper-vascular.

The purpose of presurgical embolization for hyper-vascular tumors is to reduce intraoperative blood loss, which consequently makes surgery easier and facilitates the radical removal of tumors.[53] A meta-analysis regarding blood loss in spinal tumors concluded the mean estimated perioperative blood loss was more than 2000 mL.[54] Excessive intraoperative blood loss could lead to complications due to poor visibility and surgery occasionally being discontinued due to a life-threatening volume of blood being lost.[55] Therefore, it is quite important to take measures to reduce intraoperative blood loss. Presurgical embolization has been widely used for various spinal hyper-vascular tumors. There are some reports regarding embolization for primary spinal tumors such as hemangioblastoma,[56,57] vertebral hemangioma,[58,59] aneurysmal bone cyst,[60,61] osteoblastoma,[62,63] sacral chordoma,[64,65] angiosarcoma,[66] angiolipoma,[67] and

hemangiopericytoma.[68] On one hand, preoperative embolization for metastatic spinal tumors has been performed 3 times as often as primary spinal tumors.[69] Some authors have suggested that presurgical embolization could significantly reduce intraoperative blood loss in cases of hyper-vascular metastatic spinal tumors compared with non-embolization.[70–73] Clausen et al. showed in their randomized control trial that the embolization group had less intraoperative blood loss as compared to the non-embolization group when focusing on hyper-vascular metastatic spinal tumors.[74] Based on these results, surgeons should consider spinal angiography and presurgical embolization for hyper-vascular metastatic spinal tumors, including renal cell and thyroid cancers.

Although complications seldom occur, presurgical embolization has some rare risks including spinal cord infarction and cranial embolic infarction.[75] To prevent such complications, surgeons have to meticulously review the indications and risks/benefits of spinal angiography before a potential embolization procedure. It is vital to confirm the anatomy of the anterior spinal arteries, including the Adamkiewicz artery, and radiologists as well as surgeons should notice that there might be longitudinal and retrocorporeal anastomoses connected with the anterior arteries as well.[50,55] Additionally, the surgical team and endovascular team should thoroughly discuss their treatment plans to maximize the benefits and minimize the risk of presurgical embolization.[75]

Single-Photon Emission CT

In the field of spinal tumors, Single-photon emission CT (SPECT) is used to distinguish malignant spinal tumors from benign lesions. 99m-Tecnetium (^{99m}Tc)-methylene diphosphonate (MDP), which binds to hydroxyapatite crystals during bone synthesis, is generally used as the radiotracer. The uptake of ^{99m}Tc-MDP increases depending on local blood flow and osteoblastic activity; therefore, ^{99m}Tc-MDP is one of the best markers of bone turnover.[76] It can sensitively detect a change in osteoblastic turnover—a 5% change could be detected via ^{99m}Tc-MDP thanks to its sensitivity, whereas conventional radiographic methods could only detect a 50% change in bone mineralization.[77] On the other hand, SPECT has a low specificity due to its lack of anatomical information, and sometimes misdiagnoses a vertebral fracture or degenerative disease as a malignant lesion. Hence, ^{99m}Tc-MDP SPECT and CT are often simultaneously performed to support SPECT with morphological information and improve its diagnostic accuracy. Previous studies have reported that ^{99m}Tc-MDP SPECT/CT has better accuracy and/or specificity than ^{99m}Tc-MDP SPECT alone.[78–80]

Although ^{99m}Tc-MDP SPECT and ^{99m}Tc-MDP SPECT/CT can be used for a preoperative diagnosis of undetermined spinal lesions, there are lots of other diagnostic imaging modalities such as MRI, PET, and bone scintigraphy (BS); therefore, SPECT and SPECT/CT are not necessarily the optimal modalities among them.[81] However, ^{99m}Tc-MDP SPECT assists other imaging tools to increase their diagnostic accuracy. According to a meta-analysis comparing the diagnostic value of various imaging modalities in detecting vertebral metastases, BS with SPECT had a better diagnostic odds ratio than BS alone.[81] In addition, summary receiver operating characteristic curves also showed that BS with SPECT had better diagnostic accuracy than BS alone. Hence, it would be better to say that ^{99m}Tc-MDP SPECT plays a complementary role in the evaluation of spinal metastases rather than stating it can be used to diagnose malignant lesions as a standalone.

In particular situations, especially for osteosclerotic lesions including breast cancer, SPECT might be more sensitive than other diagnostic modalities.[82,83] Sensitivity is largely due to the characteristics of the radiotracer. Thus, the optimal diagnostic imaging method for metastatic spinal tumors varies depending on the primary lesion and the purpose of examination. The most important thing is to use the best imaging option according to the circumstance.

Diffusion-Tensor Imaging

Diffusion-weighted MRI (DW-MRI) is predicated on the diffusion patterns of water molecules in the nervous system. The technique leverages the various patterns of diffusion affected by the microstructural environment within different nervous system tissues to allow their visualization and in-depth microstructural characterization.[84] DW-MRI has been extensively used for brain tumors to improve in vivo characterization, surgical planning, and prognostication using biomarkers.[85,86] Similarly for spinal cord tumors, DW-MRI techniques have been studied to improve diagnosis as well as surgical planning, and to understand the pathophysiology of the disease.

Fractional anisotropy (FA) is a parameter of diffusion-tensor imaging (DTI)—a form of DW-MRI—that quantifies the degree of anisotropy, or diffusion, on a scale of 0–1. Zero implies unrestricted diffusion in all directions, and 1 implies diffusion restricted to a single direction (for example, in white matter where water diffusion is largely restricted along the direction of the axonal pathways). In a study seeking to illustrate the DTI characteristics of cervical astrocytomas,[87] FA values within the lesions were significantly decreased compared to healthy controls. Comparatively, mean apparent diffusion coefficient was increased in the same lesions, which is suggestive of an overall increase in the rate of diffusion irrespective of direction. These findings indicate that white matter pathways are destroyed in infiltrative astrocytomas in the spinal cord. Similar findings of decreased FA and increased apparent diffusion coefficient values have been reported in other studies.[88,89] Perhaps more important clinically, FA values behave variably depending on the intramedullary neoplastic pathology. Maj et al. found peritumoral FA values to be higher in non-infiltrating spinal cord ependymomas than in infiltrative astrocytomas, indicating the presence of destructive underlying pathology outside the lesion defined by conventional structural MRI.[15] Therefore, though spinal cord DW-MRI studies are still lacking, early results demonstrate promise in their future utility to characterize and diagnose spinal cord intramedullary tumors.

DTI also enables visualization of fibers in the spinal cord that can be used for surgical planning. A preliminary study

investigated the value of DTI in predicting the resectability of intramedullary tumors by comparing it to intraoperative findings.[90] The study found high interrater reliability between preoperative classifications of tumor resectability using DTI fiber tracking and the presence of a surgical plan found intraoperatively. Preoperative surgical planning is crucial in patients suffering from spinal cord tumors. Using DTI, the white matter anatomy surrounding the tumor can be delineated to define tumor margins and resectability. In a case series by Choudhri et al., tumors that splayed spinal cord tracts on preoperative fiber tracking underwent gross-total resection.[91] Infiltrative tumors, however, had extensive involvement of white matter and the patient underwent a biopsy of their lesion. As such, evidence points towards the use of DTI in the preoperative phase of intramedullary tumor surgical management. Larger studies are needed to establish the clinical benefit of DTI in fiber tracking. Further advances in DTI and adjuncts such as intraoperative ultrasounds and neuro-electrophysiological monitoring can aid in the surgical management of spinal cord tumors.

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is an advanced MRI technique that probes various metabolites and the chemical composition of tissue. Unlike conventional MRI techniques that focus on nervous system structure, MRS provides information regarding the underlying neurochemical milieu. Through MRS, concentration of various nuclei, or metabolites, can be quantified and studied. In theory, they represent the underlying mechanisms for various biological processes such as metabolism, inflammation, and myelination, among many others. Clinical studies typically use a region-of-interest-based approach to investigate neurochemical concentrations within small areas in the brain or spinal cord. MRS has been used extensively to study neuroinflammation,[92] neurodegeneration,[93,94] and brain tumors.[95] MRS' applications in the spinal cord, however, are still in their infancy. Most of the research has focused on the cervical spine in multiple sclerosis[96] and myelopathy.[97,98]

N-acetyl-aspartate (NAA) is a frequently utilized metabolite that is present only in neurons—not in glial cells. Multiple lines of evidence suggest that it is a viable biomarker for neuronal integrity.[99] Other metabolites that have been frequently studied in the human brain include glutamate, glutamine, creatinine, choline, and myo-inositol.[100] Primary intra-axial tumors are typically of glial origin and, not surprisingly, have low NAA concentrations within the lesions compared to healthy white matter.[101] Lactate, on the other hand, is found to be markedly increased in glioblastomas and metastatic tumors, reflecting necrosis. Other groups have made attempts to use raw spectroscopy data to classify tumors between meningiomas, gliomas, and metastatic tumors[102] and to predict histopathological grade from preoperative scans.[103] Despite these efforts, MRS techniques have not yet found momentum within the neuro-oncological literature. This is more apparent within the spinal cord tumor literature; this area is still an emerging field, and currently, no formal studies exist demonstrating the viability of MRS-based biomarkers to aid in the diagnosis or prognosis of spinal cord tumors.

MRS studies of the spinal cord are marred by technical challenges and demand significant expertise to develop protocols and analytical pipelines, therefore limiting their widespread utility.[104] Anatomically, MR imaging the spinal cord poses challenges because (1) it has a relatively small cross-sectional diameter resulting in low signal-to-noise ratios, and (2) it is surrounded by bone, soft tissue, and cerebrospinal fluid, which distorts and alters the spectroscopic data. These challenges can partially be mitigated with the use of higher magnetic field strength scanners; however, that is unsurprisingly limited by resource availability. Sufficiently powered studies need larger sample sizes that are often only possible with multicenter collaborations. Homogenizing acquisition, data processing, and analysis protocols across multiple centers adds another layer of complexity in MRS studies of the spinal cord. Despite these limitations, efforts are underway and MRS is an emerging tool for improving the characterizing of intramedullary spinal lesions.[105]

Emerging Diagnostic Imaging Modalities for Spinal Tumors

Ultrasound Imaging

Ultrasonography is not useful for evaluating spinal tumors in daily clinical practice due to overlying osseous artifacts. However, ultrasonography is effective intraoperatively. Unlike the other modalities, intraoperative ultrasonography provides real-time information for the surgeons with relatively straightforward preparation. Thus, some authors report that intraoperative ultrasonography is helpful for the guidance of dura opening and myelotomy, assessing the extent of tumor excision, and confirming that no hematoma formation exists after closing the dura.[25,26]

When the target lesion is a mobile tumor such as spinal schwannoma, it is sometimes difficult to determine the appropriate vertebral level to expose because there can be a discrepancy between the preoperative finding and the surgical findings, which range from a half vertebra to 5 vertebrae.[106] In such a case, surgeons could perform minimal laminectomy to apply the probe, and then confirm whether the tumor exists there or not. If the exposure of the dura is not enough, they could add laminectomies as needed. This procedure would help to avoid excessive laminectomies.

Rightly, surgeons have to perform a myelotomy to remove intramedullary tumors; however, identification of the exact location of the tumor is often difficult, especially for small intramedullary lesions. If surgeons dissect the surface of the spinal cord only based on preoperative MRI, unnecessary myelotomy could cause damage to the spinal cord and consequently lead to postoperative sequelae. Using intraoperative ultrasonography before myelotomy helps to precisely understand the location of lesions and minimize damage to the neural tissue. The sagittal view would be better to determine the cranial and caudal ends of the tumor, whereas an axial scan would provide anatomical information such as the posterior midline, which is sometimes distorted due to the tumor.[107]

When the intramedullary tumors are infiltrating and not well-circumscribed, it is often difficult to distinguish

the tumor from normal tissue. To excise such tumors is stressful for surgeons because they can damage the normal spinal cord and bring about neurological deterioration. In order to avoid injuring the normal spinal cord, repeated intraoperative ultrasonography is also useful. Li et al. reported that intraoperative ultrasonography combined with neuro-electrophysiological detection in the spinal cord during glioma surgery contributes to the protection of neurological function and thorough tumor resection.[108]

Additionally, intraoperative contrast-enhanced ultrasonography for vascularized spinal tumors, including hemangioblastoma and hemangiopericytoma, is effective in visualizing the feeding arteries and draining veins.[109,110] This method can identify vascular structures in the spinal cord by intravenously injecting sulfur hexafluoride-filled lipidic microbubbles contrast agent. It is also used to identify the residual brain glioblastoma[111]; therefore, intraoperative contrast-enhanced ultrasonography has the potential to enhance spinal cord high-grade glioma for maximal resection.

Optical Imaging

Intraoperative optical imaging can provide valuable information to achieve safe and certain resection of spinal tumors. Indocianine Green (ICG) and 5-aminolevulic acid (5-ALA) are 2 representative substances to visualize tumors or their surrounding structures.

ICG is usually used in the ICG videoangiography for hyper-vascular spinal tumors such as hemangioblastoma. Approximately 0.1–0.3 mg/kg of ICG is intravenously injected just before intraoperative observation and clearly reveals the feeding arteries and draining veins, as well as the borders between the lesions and normal spinal cord. The ICG videoangiography helps to identify the structure of lesions and determine the order of vascular obliterations. The appropriate coagulation of the feeding arteries makes a blood-less surgical field, which is crucial for the safe resection of tumors. Furthermore, some authors reported that intraoperative ICG videoangiography was useful to identify the posterior median sulcus for midline myelotomy.[112,113]

Recently, a novel method using ICG, which is called Second-Window ICG, was reported.[114,115] In this technique, much more ICG, reported as 0.5–2.5 mg/kg, is injected at the beginning of surgery or 24 hours before surgery, and then the accumulation of ICG in the lesion is visualized because the vascular permeability of the tumor is enhanced.[116] The fluorescence in Second-Window ICG can be detected through the dura and parenchyma, unlike with ICG videoangiography,[117] which allows for the identification of the intramedullary lesion location before myelotomy.[114] However, this method hasn't been fully examined in the field of spinal tumors, and it remains uncertain which type of lesions become positive in Second-Window ICG.

Fluorescence-guided resection of tumors using 5-ALA has been increasingly reported, not only in intracranial tumors but also in spinal tumors.[118] Protoporphyrin IX (PpIX), which is excited with a purple light (400–410 nm) and emits a red fluorescence, is accumulated in tumors after 5-ALA administration due to the downregulation of the metabolism of PpIX to heme.[119] Therefore, tumors are intraoperatively visualized using an excitation light when patients orally receive 5-ALA before surgery. In the field of spinal tumors, 5-ALA-induced fluorescence-guided surgery is useful in meningiomas, ependymomas, high-grade gliomas, drop metastases of cerebral neoplasms, and hemangiopericytomas.[118] Fluorescence-guided surgery could facilitate more complete resection of tumors[120] and might lead to a more favorable prognosis. Of course, 5-ALA-induced fluorescence-guided resection cannot be applied to all spinal tumors. Lower proliferating tumors might be PpIX fluorescence-negative,[120] which is the limitation of this method; however, it is certainly useful for specific intramedullary tumors.

Photoacoustic Imaging

Photoacoustic imaging (PAI) is a novel imaging technology using a laser-generated ultrasound. The basic principle of PAI is as follows: (1) a tissue is exposed to pulsed light from the optical fibers, and then photoabsorbers within the tissue absorb the light, (2) the tissue undergoes a small thermal expansion due to vibrational and collisional relaxation, (3) the thermal expansion causes an acoustic pressure wave, and (4) the acoustic pressure wave is detected as ultrasound signals by an ultrasound probe and reconstructed into a photoacoustic image.[121]

It has the potential to visualize targets hidden by other tissues including bone; therefore, it has been getting attention in the field of spinal surgery.[122] For example, some authors have reported the usefulness of PAI for pedicle screw implantation in human cadavers or the vertebra of animals.[123–125] However, the clinical application of PAI for spinal fusion surgery has never been explored.[122] Furthermore, there is no report regarding the clinical use of PAI for spinal tumors. Still, PAI is a promising imaging modality. It might be able to noninvasively diagnose different types of bones including cancerous ones,[126] or to be applied to the transpedicular approach for the ventral component of epidural spinal tumors.

Illustrative Cases

Case 1: Extradural Tumor (Hemangioma)

An 18-year-old man was referred to our hospital with unremitting low back pain. Neurological examination did not reveal any neurological deficits; however, lumbar X-ray showed the L2 vertebral body was broken with pincer-type fracture morphology (Figure 1A, B). Lumbar CT revealed lace-like trabeculae (Figure 1C) and polka dot sign (Figure 1D) in the L2 vertebral body. The lesion protruded to the spinal canal with low and high signal intensity on T1- (Figure 1E) and T2-weighted MRI (Figure 1F). The lesion was diagnosed with hemangioma, and we planned preoperative embolization followed by surgical treatment.

A catheter was inserted into the L2 vertebral body via the transpedicular approach. After the infusion of dimethyl sulfoxide, Onyx was injected under live fluoroscopy (Figure 1G). The digital subtraction technique was effective to prevent extravasation outside the hemangioma

(Figure 1H). Post-interventional X-ray showed almost complete embolization of the lesion (Figure 1I). After preoperative embolization, total resection of the L2 vertebral body with circumferential stabilization using anterior interbody cage interposition and posterior instrumented fusion was performed.

Case 2: Intradural Extramedullary Tumor (Schwannoma)

A 51-year-old man with a history of radiation therapy for a scalp mass had a cervical spinal tumor accidentally detected. Gadolinium-enhanced MRI revealed the left-sided lobulated large mass at the level of C2/3 (Figure 2A–C). The lesion was composed of a cystic part and an enhanced solid part, and a dumbbell shape with intra- and extradural and paravertebral components. Cervical CT showed the left C2–3 pedicles and lateral masses were thinning due to the mass, and the left C2–3 transverse foramens were involved (Figure 2D). The lesion was diagnosed with schwannoma.

He underwent C1–3 laminectomy and instrumented fusion with gross-total excision of the tumor under neurophysiological monitoring.

Case 3: Intramedullary Tumor (Hemangioblastoma)

A 66-year-old man with von Hippel Lindau disease complained of balance problems and a tingling sensation in his hands. Cervical MRI revealed the intramedullary lesion at the level of C3–5. T2WI showed a high signal intensity mass with flow void and diffuse high intensity of the spinal cord (Figure 3A), whereas the mass was low signal intensity on T1WI (Figure 3B) and avidly enhanced on gadolinium-enhanced T1WI (Figure 3C, D). Spinal digital subtraction angiography demonstrated multiple feeding arteries from bilateral vertebral arteries, and the lesion was globally stained (Figure 3E, F). The lesion was diagnosed with hemangioblastoma.

He underwent C2–T1 laminectomy and instrumented fusion, gross-total excision of the tumor under neurophysiological monitoring, and complex dural reconstruction. Intraoperative ultrasonography was performed to make sure of the tumor location before dural incision, showing an exophytic heterogeneous echogenic tumor (pound) compressing spinal cord (asterisk; Figure 3G). Based on intraoperative sonography, the dura mater was incised, and the tumor was exposed (Figure 3H).

Future Directions

The conventional and emerging diagnostic imaging modalities mentioned above have certainly contributed to improvements in the diagnosis and treatment of spinal tumors. Additionally, recent state-of-the-art technologies are also gaining attention for their ability to complement spinal tumor surgery.

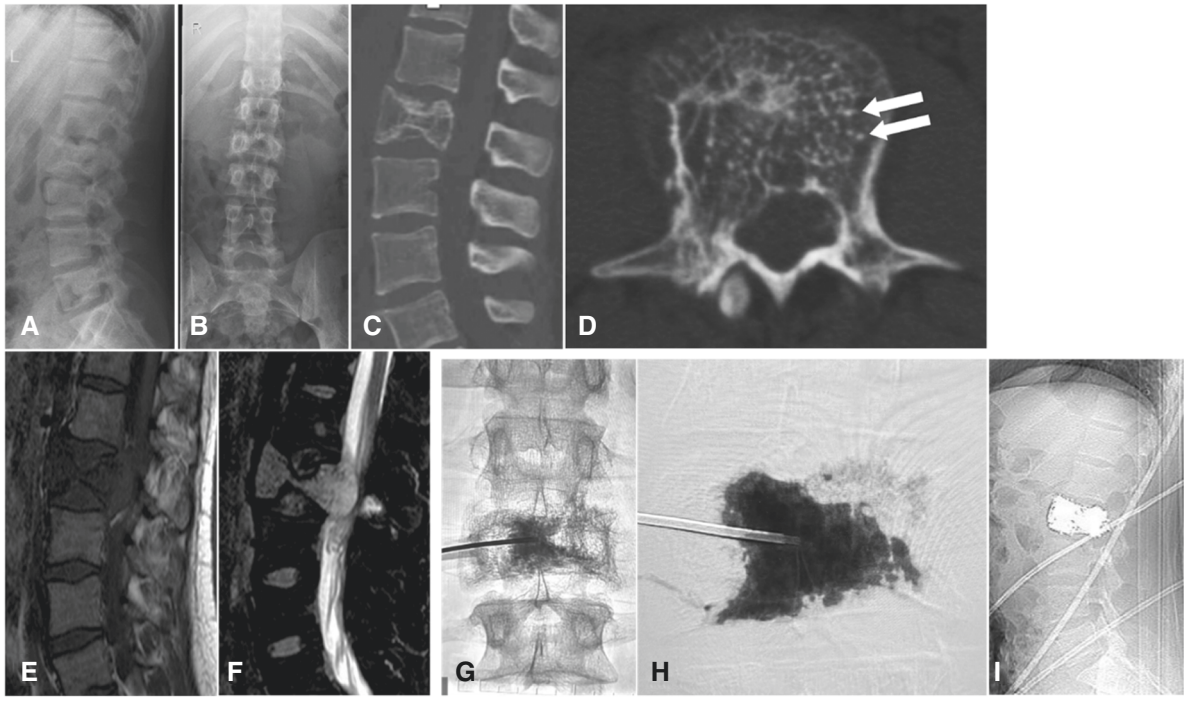

Figure 1. An 18-year-old man with L2 hemangioma. X-ray showed superior and inferior endplate fracture with pincer-type morphology (A, B). The sagittal view of computed tomography (CT) revealed lace-like trabeculae in the L2 vertebral body (C), and the axial view of CT demonstrated polka dot sign (D, arrow). The lesion showed low signal intensity on T1-weighted magnetic resonance imaging (MRI; E) and high signal intensity on T2-weighted MRI (F). Preoperative embolization using Onyx was performed under live fluoroscopy (G) with digital subtraction technique (H) and resulted in almost complete embolization (I).

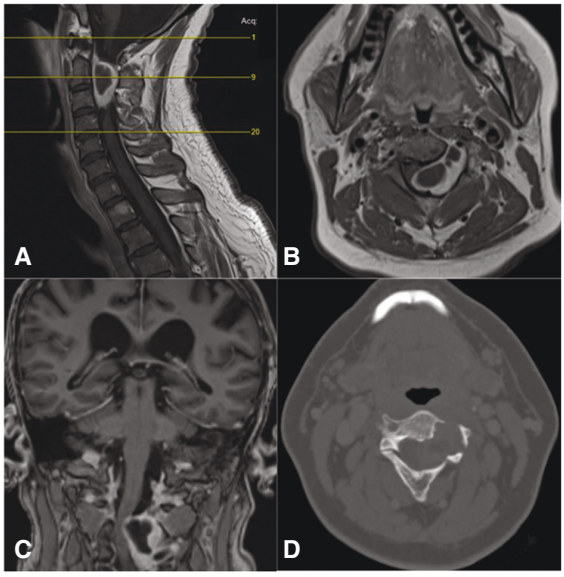

Figure 2. A 51-year-old man with cervical spinal schwannoma. Gadolinium-enhanced MRI revealed the partially cystic enhanced dumbbell shape lesion. The lesion extended at the level of C2–3 on the sagittal view (A) and was left-sided on axial and coronal views with intra- and extradural and paravertebral components (B, C). The computed tomography axial view at the level of C3 showed the left pedicle and lateral mass were thinning and the left transverse foramens were involved by the lesion (D).

Virtual Reality and AR

Virtual reality (VR) and AR are representative examples of such advanced technologies. In VR, the surgical target is placed within the computer-generated virtual environment and surgeons as well as trainees can be immersed in this environment.[127,128] Conversely, AR is a technology that overlays patient-specific information on the real surgical field.[127,128] VR and AR would be effective in various situations including, (1) education for students and trainees, (2) preoperative planning and simulation, and (3) intraoperative assistance.

Some authors have implied that AR could be an accessory teaching tool to assist medical students in learning anatomy.[129] The AR system would be attractive for early-year medical students, and might enhance their motivation to learn anatomy and facilitate understanding it. In addition, AR would be a valuable surgical education tool for both medical students and young doctors.[130]

Preoperative planning is a necessary part of surgery to reduce surgical complications and increase safety. In particular, for complex spinal tumors, surgeons have to meticulously prepare the operative strategy. However, the accuracy of traditional preoperative planning approaches using radiographic images depends on the quality of preoperative images and surgeons' experience. Therefore, it is sometimes troublesome to accurately understand the anatomical structure of the lesion, especially for young surgeons. Three-dimensional (3D) printing models are a recent technological advancement with the capability to facilitate the understanding of anatomical structure, even for inexperienced surgeons,[131] but the cost and time to construct a 3D model are obstacles to widespread adoption. When surgeons, even if they are not experts, use VR or AR, they will intuitively and effectively execute preoperative planning. They can freely rotate the lesion, remove and see through the surrounding structures. In addition, once the devices are equipped the costs are low.

VR and AR have already been used in clinical situations as an intraoperative assistant. Carl et al. used AR intraoperatively for 10 patients with intradural spinal tumors and reported that the target registration error was 0.72 ± 0.24 mm.[132] Anthony et al. presented 5 surgical cases, including a case of spinal cord cavernoma, and reported the advantages of intraoperative 3D navigation using a VR system.[133] Some authors have reported the accuracy of AR navigation in spine surgery[134,135] and less invasiveness.[136] Although reports regarding the clinical use of VR and AR for spinal tumors are lacking, they are promising novel technologies which will steadily progress in the field of spinal tumors.

Artificial Intelligence and Machine Learning

Artificial Intelligence (AI) is one of the most promising technologies in the field of healthcare. Subfields of AI technology, including Machine Learning (ML) and deep learning (DL), have been widely studied in medical imaging.[137] They have the potential to aid in diagnoses,[138,139] the classification/grading of cancer,[140,141] predicting therapeutic responses,[142] detecting diseases,[143] and so on. Radiomics is also an emerging field which aims to provide diagnostic information and tumor characteristics/prognosis based on imaging criteria. Radiomics is defined as "the extraction and analysis of large amounts of advanced quantitative imaging features with high throughput from medical images obtained with CT, PET, or MRI."[144] In other words, the tumor image mentioned is considered as a cluster of enormous pixel data rather than one figure in this research field. Radiomics has been widely used in oncologic research[145,146] and recently combined with ML.

Specific to the field of spinal tumors, especially metastatic spinal tumors, ML, DL, and radiomics have been used in various situations.[147–153] For example, Chmelik et al. described a framework based on the deep Convolutional Neural Network for voxel-wise segmentation and classification of lytic and sclerotic spinal metastases using a three-dimensional CT dataset.[148] They showed that their method had high sensitivity—80% for lytic lesions and 92% for sclerotic lesions, even for small metastatic lesions greater than 1.4 mm^3. Fan et al. reported that a DL-based dilated convolutional U-Net model using energy/spectral CT images could detect spinal metastases in lung cancer patients to the same degree as professional doctors.[151] They also reported in another article that DL methods with the AdaBoost algorithm and the Chan-Vese algorithm using MRI images were useful for primary classification of images and image segmentation in spinal metastases of lung cancer patients, respectively.[150]

Unlike metastatic tumors, there are only a few reports regarding ML and DL for intradural spinal tumors, which is

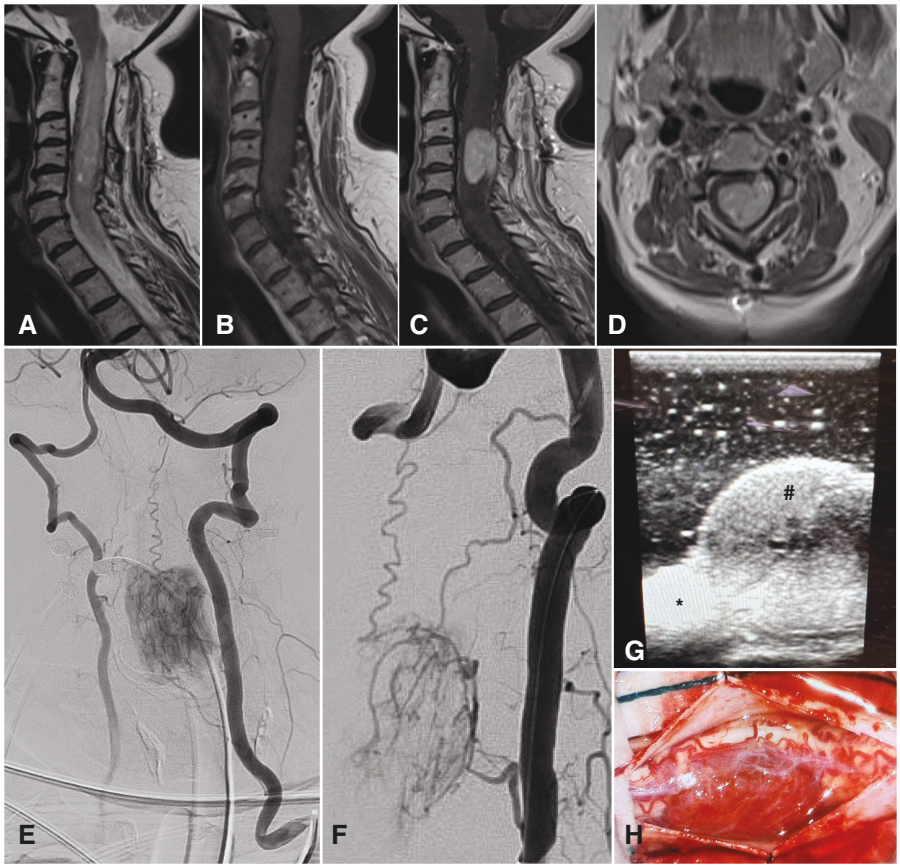

Figure 3. A 66-year-old man with cervical hemangioblastoma. T2 weighed magnetic resonance imaging showing high signal intensity mass at the level of C3–5 with flow void and diffuse cord edema (A). The lesion showed low signal intensity on T1WI (B) and avidly enhanced on gadolinium-enhanced T1WI (C, D). Spinal angiography revealed multiple feeding arteries from vertebral arteries (E, F). Intraoperative ultrasonography showed an exophytic heterogeneous echogenic tumor (pound) compressing the spinal cord (asterisk; G). Based on intraoperative imaging, the lesion was exposed (H).

due to their rarity. Lemay et al. presented a DL model based on a three-dimensional U-Net for the multiclass segmentation of the tumor, cavity, and edema for intramedullary spinal tumors such as astrocytoma, ependymoma, and hemangioblastoma.[154] Zhuo et al. developed an automated classification system for T2 weighted MR images using DL, which demonstrated 96% accuracy for differentiation between tumor and demyelinating lesion, and 82% for astrocytoma versus ependymoma.[137] In addition, Ma et al. suggested that a DL model using MRI images should be able to predict the intramedullary glioma grade.[155]

Personalized Medicine and Diagnostic Imaging

Personalized medicine, or precision medicine, is a medical model to optimize health care for the individual via tailored medicine[156]; whereas, traditional medicine gives all patients a uniform therapy. In personalized medicine, it is crucial to identify patient-specific measurement regimens including imaging, genomics, or epigenomics.[157] If it is applied to the field of spinal tumors, accurate diagnostic imaging is indispensable. For example, the use of separation surgery and stereotactic body radiotherapy for metastatic spinal tumors relies on accurate advanced imaging to plan the treatment and carry it out. Thus, it is not an exaggeration to say that personalized medicine in spinal tumors depends on diagnostic imaging.

To precisely grasp the extent of the lesion and adjacency to normal tissues before surgical resection or radiation therapy, high magnetic field MRI could provide a clear image to inform the following therapy. High magnetic field MRI, such as 7-tesla MRI, has better spatial resolution and will make it easy to delineate the lesion. Although there are some technical issues associated with high-field spinal cord MRI that must be overcome, including a lack of optimized radiofrequency coils, physiological noise, high specific absorption rate, and B_0 field inhomogeneities,[158] it has the potential to enhance personalized medicine for spinal tumors.

Diagnostic imaging could help to estimate the characteristics of tumors, which might lead to personalized therapy. For example, dynamic contrast-enhanced MRI can detect enhanced microcirculation, which results from angiogenesis and changes in blood vessel permeability.[159] Furthermore, dynamic contrast-enhanced-MRI

could identify patients who might benefit from antiangiogenic drugs such as bevacizumab.[159] Apart from that, ^{18}F-fluoromisonidazole (FMISO)-PET can detect hypoxic conditions caused by malignant lesions, and Rockne et al. reported the novel approach of hypoxia-modulated radiation using ^{18}F-FMISO-PET in a brain glioblastoma patient.[160] While hypoxia reduces the efficacy of radiation therapy, they designed hypoxia-escalating dose distribution from the perspective of personalized medicine. There have been few reports regarding ^{18}F-FMISO-PET for spinal tumors to date; however, it remains a promising diagnostic imaging option to promote personalized medicine.

Concluding Remarks

As described in this review, the imaging of spinal tumors is essential throughout the whole management continuum—not only for tumor detection and diagnosis, but also for preoperative surgical planning, intraoperative assistance, and even postoperative follow-up. Both surgeons and radiologists need to be familiar with traditional and emerging imaging modalities for spinal tumors and to use them appropriately, according to their strengths and weaknesses. Furthermore, as advanced imaging for spinal tumors, including VR/AR, advanced MRI sequences, and AI technologies progress dramatically, we should focus on these latest fields and prepare to combine them with conventional modalities to better manage patients with spinal tumors.

Keywords

advanced imaging | artificial intelligence | diagnostic imaging | intraoperative imaging | spinal tumor

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