

Role of Neuroimaging in Brain Radiosurgery

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1. Introduction

Radiosurgery is a therapeutic technique to deliver high dose radiation to the target. It induces radiobiological responses of lesions while minimizing radiation effect to the surrounding area. Gamma knife is one of the representative devices for stereotactic radiosurgery, which is exclusively designed for treatment of cerebral disorders. Gamma knife was developed as the first radiosurgical device in 1967. Professor Lars Leksell at the Karolinska Institute in Sweden developed a stereotactic frame for functional neurosurgery in early 1950s and combined the technique of frame fixation with focused irradiation. The primary role of gamma knife radiosurgery is to control small well-demarcated lesions such as metastatic brain tumors, meningiomas, schwannomas, and pituitary adenomas while preserving function of surrounding brain tissue. It has been used as a primary treatment or in combination with surgery, and some applications have been accepted as standard treatment. Treatment of cerebral arteriovenous malformations has also been drastically changed after emergence of this technology. Arteriovenous malformation in deep locations such as the basal ganglia, thalamus and the brainstem came to be safely treated by radiosurgery. Stereotactic radiosurgery is also employed in the control of functional disorders such as mesial temporal epilepsy and trigeminal neuralgia. As such, gamma knife has been widely accepted in clinical practice in the field of neurosurgery (Koga et al., 2010). On the other hand, the risk of radiation-induced adverse events is not negligible and puts limitations to this technology. Accurate target definition is one of the most important factors to reduce complications because it can reduce unwanted radiation to surrounding normal tissue. The target of radiosurgery is primarily visualized by radiological studies such as angiography, computed tomography and magnetic resonance imaging. Owing to this, the accuracy of treatment largely depends on neuroimaging technology. After introduction of gamma knife, technology of neuroimaging has also been drastically changed as an example of magnetic resonance imaging. Not only neuroimaging itself, but also software to utilize different kinds of imaging modalities for treatment planning of radiosurgery has been developed in the past decades. During almost a half century since treatment of gamma knife radiosurgery was applied for the first patient, technology of radiosurgery has progressed in line with the advances in neuroimaging technology. In this chapter, we discuss technological advances in neuroimaging and consider i) how these have driven more sophisticated radiosurgical treatments and ii) the impact on post radiosurgical outcomes.



Fig. 1. Structure of gamma knife

Treatment machinery of gamma knife (left). The helmet has approximately 200 portals (collimator, right) through which gamma rays from ^{60}Co are emitted. Those finely narrowed beams of radiation meet at the focal point of gamma knife and give a high target dose.

Diagnosis	Number of Treatment
Metastatic brain tumor	185,070 (36.8%)
Glioma	26,437 (5.3%)
Other malignant tumor	9,389 (1.9%)
Meningioma	64,115 (12.8%)
Vestibular schwannoma	46,835 (9.3%)
Pituitary adenoma	38,553 (7.7%)
Other benign tumor	26,816 (5.3%)
Vascular lesion	65,084 (12.9%)
Trigeminal neuralgia	32,798 (6.5%)
Epilepsy	2,399 (0.5%)
Other functional disorder	3,264 (0.6%)
Ocular lesion	1,966 (0.4%)
Total	502,726

Table 1. Number of gamma knife treatment in the world until 2008

2. Integration of three-dimensional images into treatment planning

Arteriovenous malformation has been treated by gamma knife radiosurgery since it was introduced at first. Emergence of gamma knife has improved treatment outcomes of cerebral arteriovenous malformations, especially deeply located lesions (Sasaki et al., 1998). The goal of radiosurgery for arteriovenous malformations is obliteration of nidus and prevention of devastating hemorrhage. Histopathological study of arteriovenous malformation after radiosurgery showed damage of endothelial cells, followed by thickening of the intimal layer caused by smooth-muscle cell proliferation, and finally obliteration of the lumen by cellular degeneration and hyalinization (Schneider et al., 1997). Minimum dose of 20 Gy to the nidus could completely obliterate nidus in approximately 90% in the dose response analysis for arteriovenous malformations (Flickinger et al., 2002). In our experience, the rates

of nidus obliteration confirmed by angiography were 72% at 3 years and 83% at 5 years (Shin et al., 2004). In early years of gamma knife treatment, treatment planning for arteriovenous malformation was made based only on angiogram. Because conventional angiogram was two-dimensional projection image, it was difficult to comprehend three-dimensional structure of lesions only by angiogram especially when nidus was large or morphologically complicated. Computed tomography or magnetic resonance imaging could depict three-dimensional structure of nidus of arteriovenous malformation, although angiography could show more precise angioarchitecture. Therefore, use of computed tomography or magnetic resonance imaging jointly with angiography for treatment planning facilitated recognizing three-dimensional structure of nidus and reduced the morbidity associated with gamma knife radiosurgery (Shin et al., 2004). More recently, integration of three-dimensional rotational angiography into treatment planning of radiosurgery for arteriovenous malformation has been attempted (Conti et al., 2011). Because three-dimensional rotational angiography can provide both sufficient temporal and spatial resolution, three-dimensional angioarchitecture of nidus can be easily understood by using this technology, and reports of outcomes including obliteration rates and morbidity after treatment with integration of three-dimensional rotational angiography are awaited.

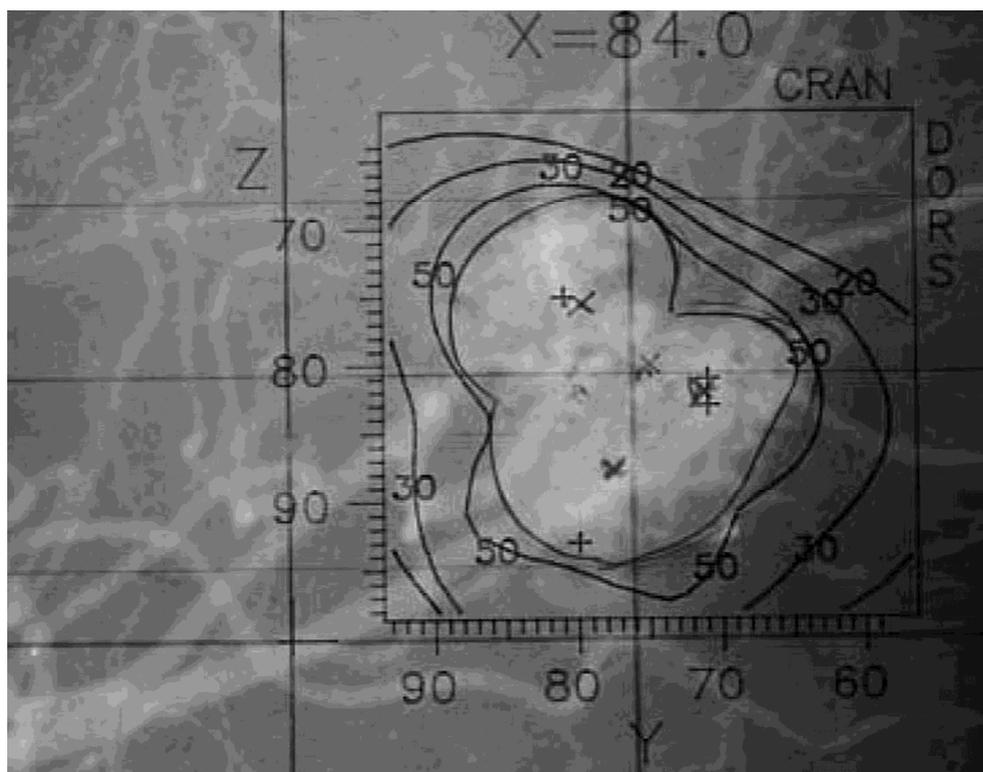


Fig. 2. Treatment planning for arteriovenous malformation based on angiogram. Two-dimensional isodose lines (black) were superimposed to the image. It was difficult to recognize three-dimensional angioarchitecture from angiogram only.

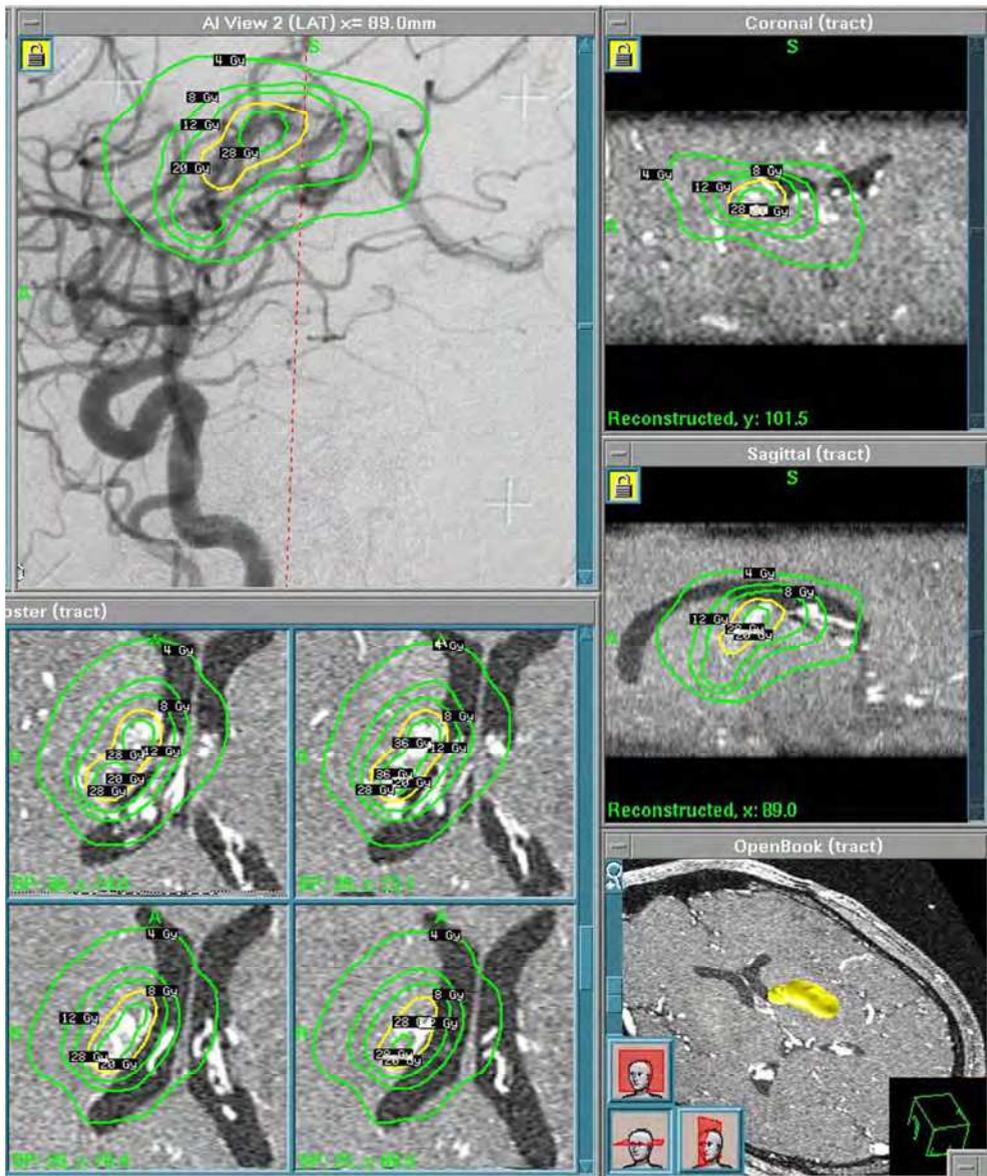


Fig. 3. Treatment planning for a patient with right thalamic arteriovenous malformation. Isodose lines (yellow and green) were simultaneously superimposed to digital subtraction angiogram and magnetic resonance images. Coronal and sagittal images (right upper two images) were simultaneously visible in combination with dose distribution and made recognition of three-dimensional angioarchitecture easier.

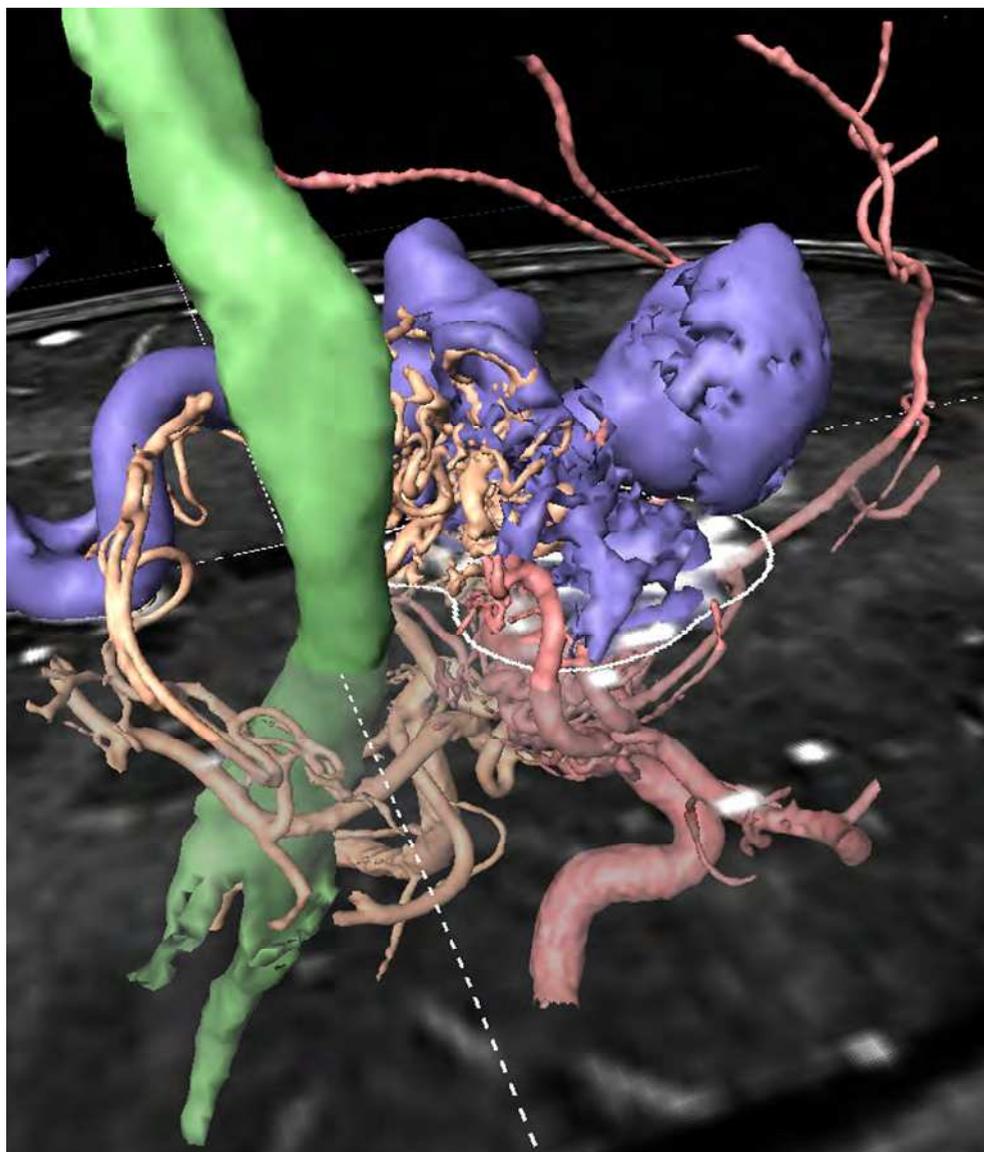


Fig. 4. Three-dimensional rotational angiography in treatment planning for arteriovenous malformation. Nidus and feeder from internal carotid artery (red) and basilar artery (orange) was visible in three-dimensional manner. Drainers (purple) were distinguished from nidus. Isodose line of treatment planning (white line) was superimposed to the image and sufficient coverage by treatment dose was visually confirmed. In this view tractography of the corticospinal tract (green) based on diffusion tensor magnetic resonance imaging was also integrated.

3. Integration of multimodal neuroimaging studies into treatment planning

Since gamma knife was developed, several refinements on its hardware and software have been made. Collimator helmet was modified when the second generation gamma knife was developed and computer workstation was introduced thereafter. The introduction of GammaPlan (Elekta Instrument AB, Stockholm, Sweden), a software for treatment planning workstation, achieved accurate dose planning (Cheung et al., 2000). The third generation of gamma knife was equipped with automatic positioning system, which was machinery that automatically moved the patient's head through a stereotactic frame during irradiation. This model enabled more conformal treatment in shorter time and reduced unwanted radiation exposure to patients compared with prior models (Horstmann & Van Eck, 2002, Kuo et al., 2004). Thus, the advances in gamma knife radiosurgery greatly depend on the refinement and the development of new devices and software (Kondziolka et al., 2002, Regis et al., 2002). In view of neuroimaging, the significant modification of gamma knife was development of GammaPlan 4C (Elekta Instrument AB, Stockholm, Sweden), which has started to be utilized since 2004. This software enabled coregistration of multimodal neuroimages even taken without frame fixation (Koga et al., 2009). For example, when lesions and bony structures or the orbital fat were indistinguishable on magnetic resonance imaging for planning, coregistered computed tomography helped clearly contour tumor margin along the bony structures.

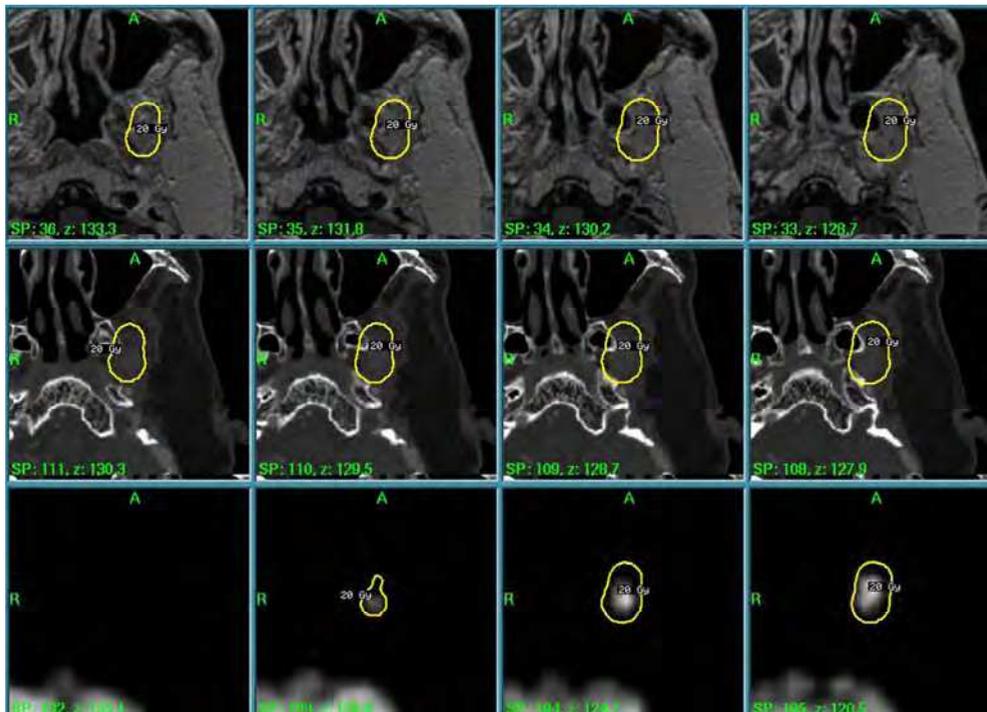


Fig. 5. Treatment planning for a patient with recurrent skull base carcinoma. Computed tomography (middle) and positron emission tomography (lower) was integrated.

Positron emission tomography (PET) enabled access to metabolic information of lesions at the time of treatment planning for radiosurgery (Levivier et al., 2007, Levivier et al., 2000, Levivier et al., 2002). In our experience, we utilized [^{18}F] fluorodeoxyglucose (FDG) PET in patients with malignant tumors to visualize the possibly active component among diffuse enhancement on magnetic resonance images. For example, in a case of recurrent glioblastoma multiforme, ambiguously enhanced lesion on magnetic resonance imaging was suggested to be highly malignant area, because the coregistered FDG-PET showed high uptake at the corresponding area, and this region was irradiated. As another example, 1-11C-acetate PET was utilized for evaluation of extent of meningioma and response of lesions to radiosurgery (Liu et al., 2010).

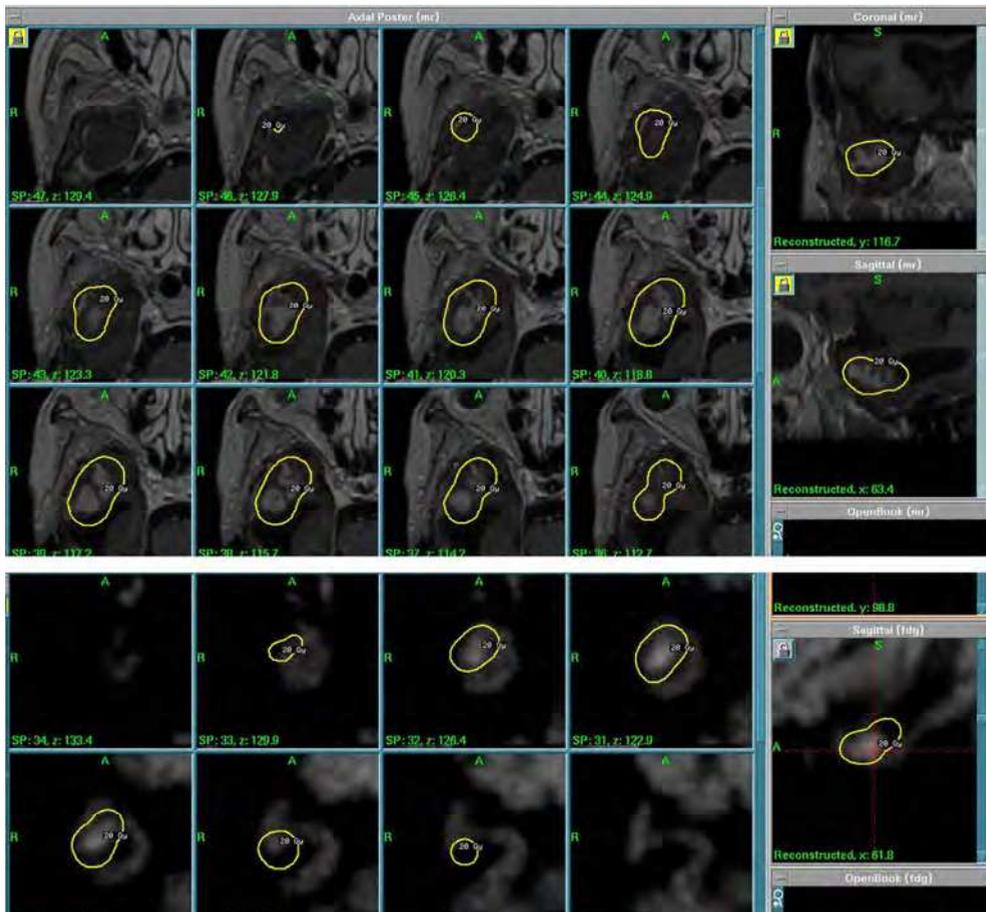


Fig. 6. Treatment planning for a patient with recurrent glioblastoma. An enhanced lesion in the right temporal lobe shown by magnetic resonance imaging (upper). Corresponding area was confirmed as high uptake region by FDG-PET (lower). This lesion was irradiated with margin dose of 20 Gy (yellow line).

4. Integration of structural and functional imaging into treatment planning

Diffusion tensor tractography, one of the major recent advances in neuroimaging, enabled clear visualization of various fibers inside the white matter of the brain, which was not visualized by conventional imaging modalities (Masutani et al., 2003). Clinical application of diffusion tensor tractography were mainly reported as diagnostic tools, and the report on its therapeutic application was quite limited (Maruyama et al., 2005). Although the pointed limitation of tractography is its reliability claiming that there is no guarantee that fibers do not exist where the tracts is not drawn (Holodny et al., 2005, Yamada et al., 2009), intraoperative fiber stimulation analysis proved that tractography reflected functioning pyramidal tracts to some extent (Kamada et al., 2009). Integration of tractography into intraoperative navigation was also developed at our institute (Kamada et al., 2005). However, it contains risks of inevitable brain shift caused by craniotomy or tumor removal, thus leads to poorer accuracy. On the other hand, such a shift does not occur in the setting of integration of tractography into radiosurgery. At our institute, integration of diffusion tensor tractography into radiosurgical treatment planning was started in 2004. While there were a variety of white matter fiber tracts, we considered that the pyramidal tract would be the most important tract in preventing morbidity of radiosurgery because its injury caused motor paresis and led to decline of activity of daily living. (Andrade-Souza et al., 2006, Hadjipanayis et al., 2001) At the same time, the pyramidal tract was practically the easiest one to draw from the technical point of view. (Yamada et al., 2009) The optic radiation and the arcuate fasciculus would be next important and was more difficult to draw. (Catani et al., 2005, Yamamoto et al., 2007) Injury of the optic radiation causes visual disturbance. Verbal function requires participation of a distributed neural system in the dominant hemisphere, and we integrated the arcuate fasciculus tractography in order to preserve this function. For the time being, we are introducing above three tracts, considering them as critical white matter structures to be preserved. By analyzing relationship between occurrence of radiation-induced neuropathy and the maximum dose received by each tract, tolerable doses of each white matter tract were estimated. The estimated tolerable dose for the corticospinal tract was approximately 20 Gy. The dose was 8 Gy for the optic radiation, 8 Gy and 20 Gy for temporal and frontal fibers of the arcuate fasciculus, respectively (Maruyama et al., 2008, Maruyama et al., 2005, Maruyama et al., 2007). Among 144 patients with arteriovenous malformation who underwent radiosurgical procedure after integration of tractography was started, one patient experienced worsening of pre-existing dysesthesia, one patient exhibited mild transient hemiparesis, and the other two patients who were treated before integration of arcuate fasciculus tractography was started experienced transient speech disturbance during median follow-up of 23 months. Overall, the rate of radiation-induced neuropathy was 2.8%. Since the rates of radiation-induced neuropathy were generally reported as five to 20% (Andrade-Souza et al., 2005, Flickinger et al., 1999, Maruyama et al., 2005, Pollock et al., 2004, Sasaki et al., 1998), permanent and transient morbidity was suggested to be potentially reduced by integrating diffusion-tensor tractography into treatment planning of radiosurgery (Koga et al., 2011). Two major concerns regarding this new technique were i) whether integration of tractography significantly reduced morbidity and ii) whether alteration of dose planning using tractography compromised obliteration of arteriovenous malformation, which was regarded as cure of this disease. To unveil these issues, further follow-up and accumulation of data of patients who underwent tractography-integrated radiosurgery are awaited.

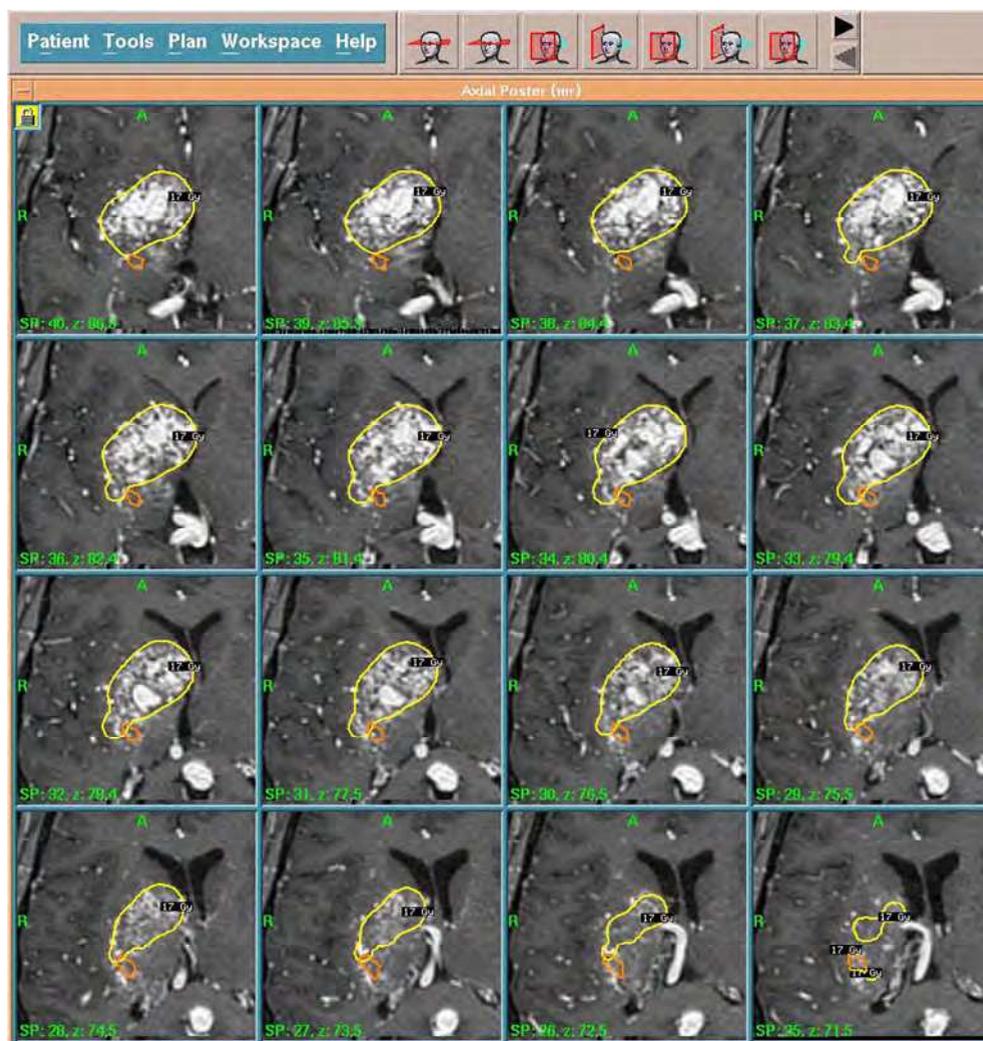


Fig. 7. Treatment planning for a patient with ruptured arteriovenous malformation in the right basal ganglia. Magnetic resonance imaging for treatment planning and integrated diffusion-tensor tractography of the right corticospinal tract showed that the tract (orange) was passing through just behind the nidus of arteriovenous malformation. Therefore, dose distribution at around the posterior portion of the nidus modified so as the dose received by the right corticospinal tract not to exceed 20 Gy, which was considered as tolerable dose of the corticospinal tract. This patient presented mild left hemiparesis at the onset of cerebral hemorrhage. However, no further worsening of hemiparesis was observed until last follow-up at 23 months after gamma knife treatment.

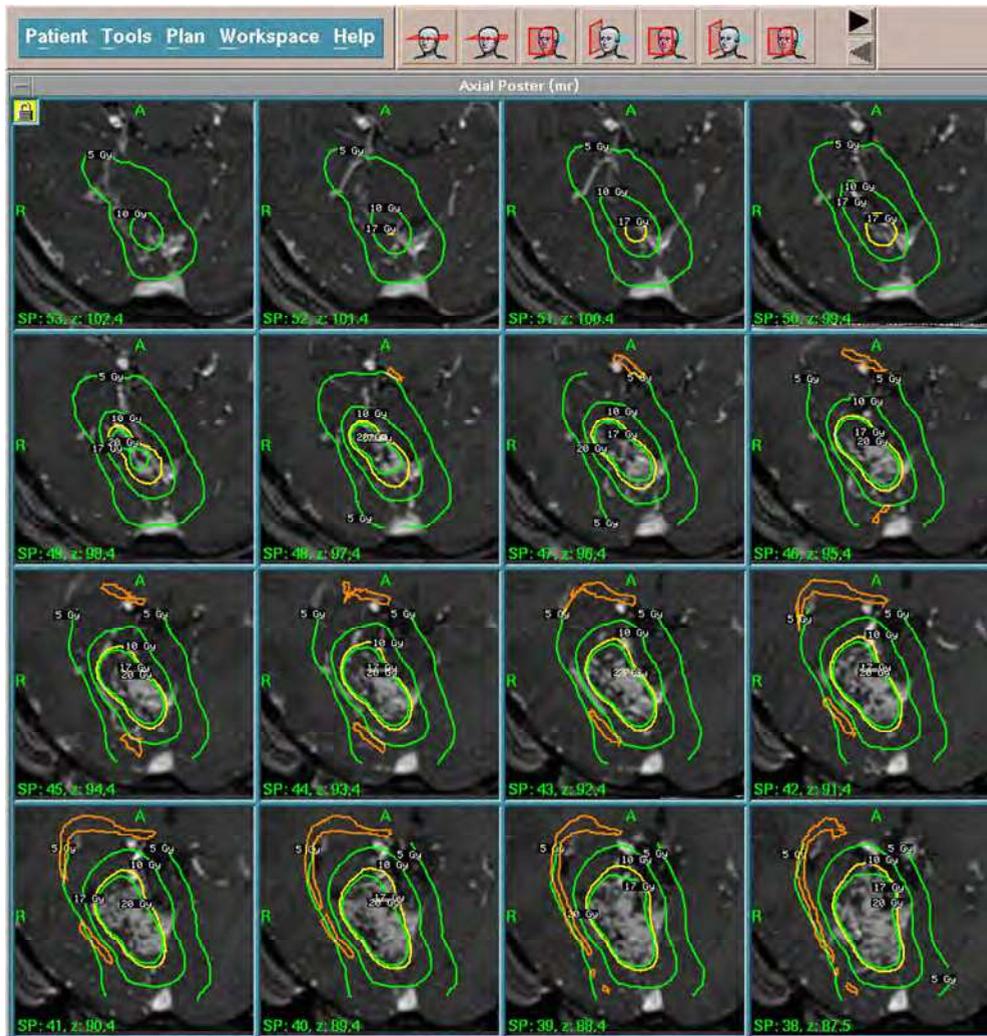


Fig. 8. Treatment planning of gamma knife stereotactic radiosurgery for a patient with unruptured arteriovenous malformation in the right occipital lobe. Magnetic resonance imaging for treatment planning and integrated diffusion-tensor tractography of the right optic radiation showed that the tract (orange) was passing through just lateral to the nidus of arteriovenous malformation. Therefore, dose distribution around the nidus was modified and dose fall-off to the lateral side of nidus was adjusted to be steeper by blocking a part of beams from cobalt sources so as the dose received by the right optic radiation not to exceed 8 Gy, the dose considered as tolerable dose of the optic radiation, while margin of the nidus was irradiated by 20 Gy. This patient presented with headache at the onset. The patient had presented no signs of left visual field defect during the clinical course until the last follow-up at 16 months after radiosurgery.

Diffusion tensor tractography was used for CyberKnife stereotactic radiosurgery as well. The technique was utilized in treatment planning for several kinds of cerebral disorders such as arteriovenous malformation, hemangioma and metastatic brain tumor. They successfully reduced the dose received by the optic tract and the corticospinal tract by integrating diffusion tensor tractography of these fibers. They further utilized blood oxygenation level-dependent functional magnetic resonance imaging to visualize the primary motor cortex and reduced the dose delivered to the cortex (Pantelis et al., 2010). Outcomes of this type of treatment are awaited.

As another example of functional imaging, magnetoencephalography was useful to detect firing neurons not only in the cortex, but also in the deeply located structures (Stefan et al., 1990). Since very early stage of gamma knife radiosurgery, magnetoencephalography was used to visualize epileptic foci in treatment planning for focal epilepsy (Hellstrand et al., 1993). Further, magnetoencephalography was as useful to detect functioning cortex as functional magnetic resonance imaging. Use of magnetoencephalography in combination with magnetic resonance imaging and cerebral angiography enabled understanding the relationship between angioarchitecture of arteriovenous malformation nidus and the adjacent sensorimotor cortex (Kamiryo et al., 2002).

5. Role of neuroimaging in follow-up study after radiosurgery

Accumulation of radiological knowledge is also important to appropriately follow-up patients after treatment. One of the most difficult issues regarding follow-up of patients with malignant tumors who underwent radiosurgery is differentiation of tumor recurrence and radiation effect including radiation necrosis. Tumor recurrence necessitates additional treatment including surgical resection. On the other hand, radiation necrosis usually responds to administration of steroid. Therefore, these two pathologies should be appropriately differentiated to be appropriately treated. An analysis of correlation between magnetic resonance imaging after radiosurgery and histopathological data revealed that a distinct lesion margin on T2-weighted images as well as a contrast-enhanced margin on T1-weighted images was highly correlated with tumor recurrence, and that the pathology was associated with a higher rate of necrosis when the lesion border on T2-weighted images did not correspond to the contrast-enhanced T1 lesion volume (Kano et al., 2010).

Another example is the findings that predict the risk of hemorrhage from completely obliterated arteriovenous malformations treated by gamma knife radiosurgery. Although complete obliteration of the nidus can be considered as cure of arteriovenous malformation which was treated by radiosurgery, the risk of hemorrhage from obliterated nidus still slightly remains. The annual bleeding rate from completely obliterated arteriovenous malformation was 0.3% (Shin et al., 2005). A study of contrast-enhanced magnetic resonance imaging findings in angiographically obliterated arteriovenous malformation revealed that increment of the enhanced regions within 1 year of angiographic obliteration compared with the previous measurement was highly associated with hemorrhage after angiographical obliteration. They concluded that patients with this finding should be carefully followed-up by contrast-enhanced magnetic resonance imaging, while contrast-enhanced studies could be reduced for those without the increment of contrast-enhanced area in the first year after obliteration (Kunishima et al., 2010).

6. Conclusion

As described above, radiosurgery using gamma knife was quite dependent on neuroimaging technology because the target of radiosurgery was solely defined by imaging studies. Introduction of basic three-dimensional imaging studies such as computed tomography and magnetic resonance imaging made recognition of three-dimensional structure of the target on planning more feasible compared with the planning solely based on two-dimensional projection images such as angiography. In fact, analyses of patient outcomes after radiosurgery proved that the use of three-dimensional imaging studies for treatment planning had reduced the morbidity associated with unwanted irradiation. Thus, more accurate target definition enabled by advances in imaging technology truly resulted in safer treatment even in this example of simple progress in the very early stage of brain radiosurgery. Technological advances in computed tomography and magnetic resonance imaging themselves achieved not only images of higher resolution but also imaging studies of completely different quality such as images of vessels and wide variety of sequences of magnetic resonance imaging. Further, metabolic imaging such as positron emission tomography became widely accepted in the field of neuroimaging as well. Technological progress of treatment planning software for gamma knife radiosurgery made it possible to utilize wide variety of neuroimaging studies for process of target definition in planning. By this way, technology of gamma knife radiosurgery could incorporate the fruit of development in neuroimaging and more sophisticated treatment planning based on concise target definition became feasibly available. Furthermore, development such as imaging of neural fibers which was “invisible” on ordinary imaging modalities and visualization of neural function was peculiar to the field of neuroimaging. Protecting neural function of the central nervous system is one of the most important goals of brain radiosurgery. Therefore, as most recent advance in imaging technology, these modalities of neuroimaging were indispensable for development of radiosurgery. Although introduction of neurostructural or functional imaging into treatment planning of brain radiosurgery just became realistic, several recent data suggested that modification of treatment planning to protect white matter visible on diffusion tensor magnetic resonance imaging and functioning cortex visualized in functional magnetic resonance imaging from excessive irradiation during stereotactic radiosurgery contributed to preservation of neural function associated with these structures. Since these kinds of new technology are quite recent progress, it is true that outcomes of patients who underwent radiosurgery using new technology must be carefully followed-up for long period after treatment. However, brain radiosurgery has been developed in this manner in line with recent drastic advances in neuroimaging technology, and technological progress in both radiosurgery and neuroimaging is still in continuation. Therefore, development of safer and more effective brain radiosurgery will be continued in the future as long as progress of neuroimaging technology is on its way.

7. Acknowledgment

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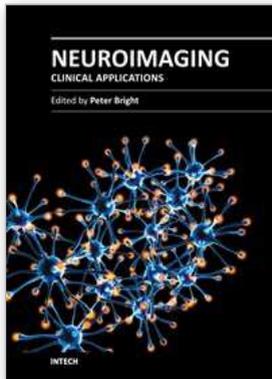
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Modern neuroimaging tools allow unprecedented opportunities for understanding brain neuroanatomy and function in health and disease. Each available technique carries with it a particular balance of strengths and limitations, such that converging evidence based on multiple methods provides the most powerful approach for advancing our knowledge in the fields of clinical and cognitive neuroscience. The scope of this book is not to provide a comprehensive overview of methods and their clinical applications but to provide a "snapshot" of current approaches using well established and newly emerging techniques.

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