Treatment of Brain Tumor

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9.1 Treatment Options

Brain tumor treatment requires a multidisciplinary approach. Symptoms appear in the patient according to the area in which the tumor is located. A variety of therapies are used to treat brain tumors. The type of treatment recommended depends on the size, type, growth rate, and location of the tumor and performance status (PS) of the patient. Treatment options include surgery, radiation therapy, chemotherapy, targeted biological agents, or a combination of these.

9.1.1 Surgery

Brain tumors comprise a wide range of different neoplasms that grow within the central nervous system (CNS) [1]. The aim of neurosurgery in most brain tumors is maximal safe tumor resection. However, in selected cases such as certain deep-seated brain tumors or suspected brain lymphomas, either an open or stereotactic tumor biopsy is indicated. To optimize resection of brain tumors, specific intraoperative techniques were established in recent decades. The application of neuronavigation is nowadays considered as standard for preoperative approach planning, intraoperative localization, and guidance during surgery of brain tumors [2]. In recent years, the use of "advanced navigation" additionally enables the inclusion of multimodality image data such as magnetic resonance spectroscopy (MRS), perfusion magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and functional MRI in order to increase the precision of tissue sampling and patient safety [3, 4]. Furthermore, intraoperative ultrasound and MRI constitute the methods for visualization of brain tumors during surgery [5, 6].

9.1.2 Radiation Therapy (RT)

RT has been established as a mainstay of treatment for brain tumors, and for many brain tumor subtypes such as germinoma, may be curative [7]. Use of RT can also prolong survival or provide palliative relief and is a treatment modality used for both primary and metastatic tumors [8].

9.1.3 Chemotherapy

Chemotherapy, along with radiation (concurrent therapy), has become the standard of care for primary malignant brain tumors. It can be used before, during, or after surgery and/or radiotherapy to help.

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9.1.4 Targeted Therapy

The focus on a specific element of a cell, such as molecules or pathways required for cell growth, in order to use them as a target.

9.2 Treatment Recommendations

9.2.1 Gliomas

Low-grade tumors (grade I and II), which are not aggressive, are treated with watchful monitoring or surgery alone. Surgery may be the only treatment needed especially if all of the tumor can be removed. Radiation therapy and chemotherapy is used for high risk patients. Radiotherapy has been the mainstay of treatment for glioma since the 1980s when it was established that postoperative treatment improves survival [9, 10]. No consensus exists regarding the proper timing of postoperative external beam radiation therapy (EBRT) in low-grade glioma. Although delaying RT in young, healthy patients without progressive neurologic decline can be controversial, there is a consensus to proceed with immediate postoperative RT in older patients after a less than total resection, because their survival is as poor as patients with anaplastic astrocytoma. High-risk patients with low-grade gliomas benefit with respect to both progression-free survival and overall survival with early up-front RT [11].

The standard RT dose for low-grade astrocytoma is 45–54 Gy, delivered in 1.8–2.0 Gy fractions [12]. Consider RT dose escalation to 59.4–60 Gy for isocitrate dehydrogenase (IDH)-wild-type low-grade gliomas, as these patients may have a more aggressive course of disease. Chemotherapy is not a traditional mainstay of upfront treatment for low-grade gliomas. There are some data that support temozolomide or PCV (procarbazine, lomustine, and vincristine) as adjuvant therapy especially in high-risk patients (age ≥40 following any resection or younger patients who were subtotally resected) [13, 14].

Higher grade tumors (grade III and IV), which are malignant and grow quickly, are more difficult to remove and require additional treatments beyond surgery, followed by RT and chemotherapy. Fractionated EBRT after surgery is standard adjuvant therapy for patients with high-grade astrocytoma [15]. The typical dose is 60 Gy in 1.8–2.0 Gy fractions. Use of hypofractionated courses of RT has been shown to be efficacious in poorly performing or older patients with glioblastoma. Typical schemes are 34 Gy in 10 fractions, 40 Gy in 15 fractions, or 50 Gy in 20 fractions. Alternatively, a shorter fractionation schedule of 25 Gy in 5 fractions may be considered for elderly and/or frail patients with smaller tumors for whom a longer course of treatment would not be tolerable [16–18]. Studies including a radiosurgery or brachytherapy boost to conventional RT did not show a survival benefit [19, 20].

Combined chemoradiation has emerged as a new standard of care for patients with 1p/19q co-deleted anaplastic oligodendroglioma or oligoastrocytoma as well as good PS non-elderly glioblastoma [21, 22]. Survival improves when chemotherapy is added to postoperative RT [23, 24]. Temozolomide, an alkylating agent, is now the standard of care in conjunction with postoperative RT for younger, good performance patients with glioblastoma [25, 26]. For frail patients, temozolomide or RT alone may be administered in old age [27].

Bevacizumab, an antiangiogenic agent, can be used for recurrent glioblastoma. Bevacizumab in combination with irinotecan, carmustine or lomustine, carboplatin or temozolomide has also been used in anaplastic gliomas. These combinations may be considered for patients who have failed bevacizumab monotherapy.

Alternating electric field therapy is a type of electromagnetic field therapy using low-intensity electrical fields to treat for recurrent glioblastoma [28].

9.2.2 Ependymoma

Surgery is the primary treatment for ependymoma. For more aggressive tumors or for

tumors that can't be removed completely with surgery, additional treatments, such as radiation therapy or chemotherapy, may be recommended. Whole brain and spine receive 36 Gy in 1.8 Gy fractions, followed by limited field to spine lesions to 45 Gy [29, 30]. For intracranial ependymomas, the primary brain site should receive a total of 54–59.4 Gy in 1.8–2.0 Gy fractions. To reduce toxicity from craniospinal irradiation (CSI) in adults, consider the use of intensity-modulated radiotherapy (IMRT) or protons if available. Stereotactic radiosurgery (SRS) has been used as a boost after EBRT or to treat recurrence with some success, although long-term results are still lacking [31]. Research on chemotherapeutic regimens has also centered on pediatric ependymomas, while the role of chemotherapy in the treatment of adult patients remains poorly defined.

9.2.3 Adult Medulloblastoma and Supratentorial PNET

There is consensus that surgical resection should be the routine initial treatment to establish diagnosis, relieve symptoms, and maximize local control. Complete resection is associated with improved survival. Adjuvant RT following surgery is the current standard of care. The conventional dose is 23.6–36 Gy of CSI and a boost to a total 54–58.8 Gy to the primary brain site with or without adjuvant chemotherapy. The use of post-irradiation chemotherapy to allow RT dose reduction is becoming increasingly common especially for children, but optimal use of adjuvant chemotherapy is still unclear for adult patients [32, 33].

9.2.4 Primary CNS Lymphomas

Methotrexate is the most effective agent in systemic therapy. It is commonly used in combination with other drugs such as vincristine, procarbazine, cytarabine, rituximab, and ifosfamide, but it may also be administered as monotherapy if toxicity tolerance is a concern [34, 35]. Chemotherapy is usually followed by consolidation RT to maximize response and improve outcome [36]. When used, low-dose whole brain radiation therapy (WBRT) should be limited to 23.4 Gy in 1.8 Gy fractions following a complete response (CR) to chemotherapy. For less than CR, consider WBRT to 30–36 Gy followed by a limited field to gross disease to 45 Gy.

9.2.5 Benign Brain Tumors

9.2.5.1 Meningiomas

Asymptomatic tumors 30 mm or larger should be surgically resected or observed. If neurologic impairment is imminent, surgery or RT (EBRT or SRS) is feasible. Complete surgical resection may be curative. Both the tumor grade and the extent of resection impact the rate of recurrence. Meningiomas may be treated by fractionated RT with doses of 45–60 Gy. The use of stereotactic RT in the management of meningiomas continues to evolve [37–39].

9.2.5.2 Vestibular Schwannomas

Tumors may be managed with microsurgical resection, SRS to 12–13 Gy, or fractionated stereotactic radiation therapy (FSRT) using either a standard approach (i.e., 45 Gy at 1.8 Gy per fraction) or a hypofractionated approach (i.e., 20 Gy at 4 Gy per fraction). Local control is more than 90% with all treatment modalities. There are no prospective randomized trials to guide treatment decisions, and multidisciplinary evaluation of each patient is an integral component of appropriate management [40, 41].

9.2.5.3 Pituitary Tumors and Craniopharyngiomas

Primary therapy is optimized by a multidisciplinary approach. Depending on the endocrine abnormality, tumor size, location, and clinical presentation, management strategies can range from observation to surgery, medical management,

radiation therapy, or a combination of these options. The standard surgical approach is transsphenoidal microsurgery. Adjuvant medical and radiation therapy options may be used to manage pituitary adenomas [42]. Gross total resection (GTR) or subtotal resection (STR) followed by EBRT may be used to manage craniopharyngiomas [43].

9.2.6 Brain Metastases

Advances in surgical technique have rendered upfront resection followed by WBRT, the standard of care for solitary brain metastases [44]. The advent of SRS offered a minimally invasive option as opposed to surgery. Accumulating evidence suggests that low disease volume is a better selection criterion for SRS than a low number of metastatic lesions [45, 46]. Additionally, patients with a favorable histology of the primary tumor (such as breast cancer) or controlled primary tumors can often benefit from SRS regardless of the number of brain metastases present [47].

Historically, WBRT was the mainstay of treatment for metastatic lesions in the brain. For WBRT, doses vary between 20 and 40 Gy delivered in 5–20 fractions. For SRS, maximum marginal doses from 24 to 15 Gy based on tumor volume is recommended.

For patients with limited (1–3) metastatic lesions, aggressive management (surgical resection plus postoperative WBRT and for SRS plus WBRT if only one lesion is involved) should be strongly considered. Other options include SRS alone or SRS following resection [48, 49]. All patients diagnosed with more than three metastatic lesions should be treated with WBRT or SRS as primary therapy. Systemic therapy is rarely used as primary therapy for brain metastases.

9.3 Radiotherapy Techniques

Radiation leads to DNA damage in irradiated cells, ultimately leading to cell death by apoptosis or necrosis. RT uses high-energy beams, such as X-rays or protons. A conventional form of radiation treatment delivery uses a specific arrangement of X-ray beams designed to conform to the shape of the tumor to maximize tumor dose and minimize normal surrounding tissue dose. Several techniques can help focus the radiation more precisely.

9.3.1 3-Dimensional Conformal Radiation Therapy (3D-CRT)

A conventional form of radiation treatment delivery that uses a specific arrangement of X-ray beams designed to conform to the shape of the tumor. This form of treatment is tailored to the patient's specific anatomy and tumor location. CT and/or MRI scan is often required for treatment planning. Intracranial tumor volumes are best defined using pre- and postoperative imaging, usually enhanced T1 and/or FLAIR (fluid-attenuated inversion recovery)/T2 (Fig. 9.1) [50, 51].

9.3.2 Intensity Modulated Radiation Therapy (IMRT)

IMRT is a type of 3D-CRT that can more directly target a tumor. In IMRT, the radiation beams are broken up into smaller beams and the intensity of each of these smaller beams can be changed. This means that the more intense beams, or the beams giving more radiation, can be directed only at the tumor (Fig. 9.2) [52, 53].

9.3.3 Volumetric Modulated Arc Therapy (VMAT)

In recent years, the combination of IMRT delivery and optimization methods with arc therapy, VMAT has become an important method for the delivery of conformal therapy. VMAT is a relatively new IMRT method that combines rotational delivery and MLC-based IMRT (Fig. 9.3) [54, 55].

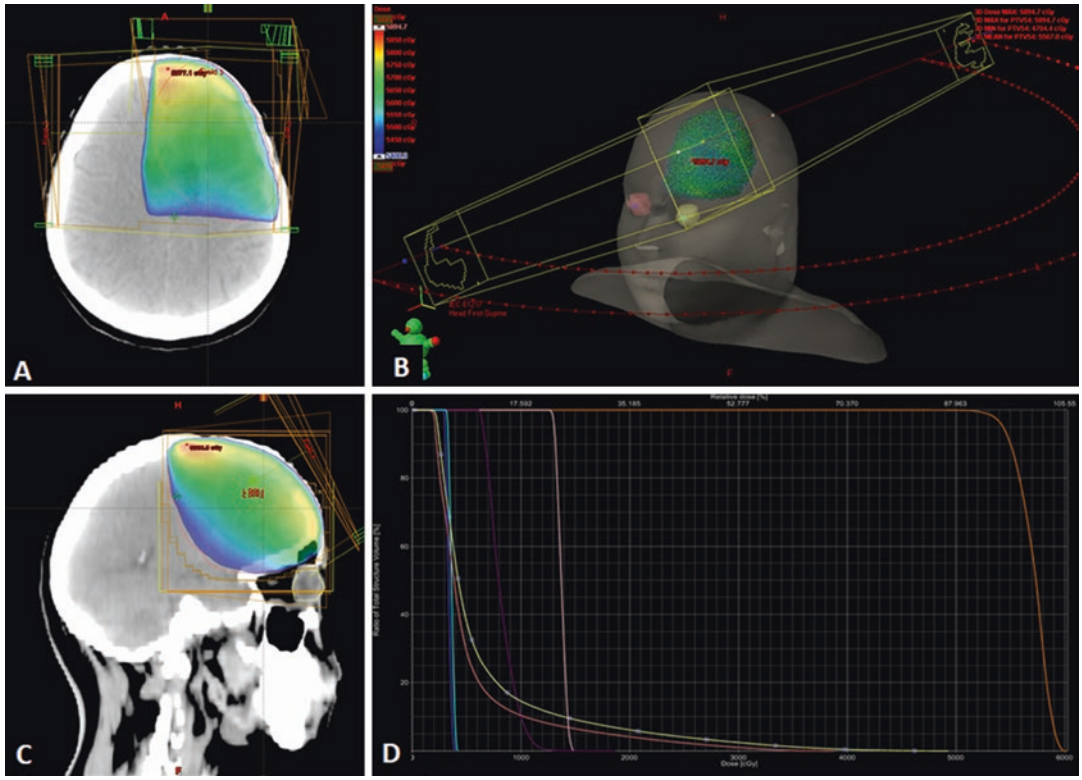

Fig. 9.1 Dose display for 3-D conformal plan. (**a**) Axial computed tomography (CT) with dose color wash. (**b**) Three-dimensional view dose color wash. (**c**) Sagittal CT with dose color wash. (**d**) The planning target volume (PTV) (orange), optic chiasm (pink), brainstem (purple), right eye (yellow), left eye (light orange), right and left lens (blue and dark blue) are shown in the cumulative dose-volume histogram (DVH)

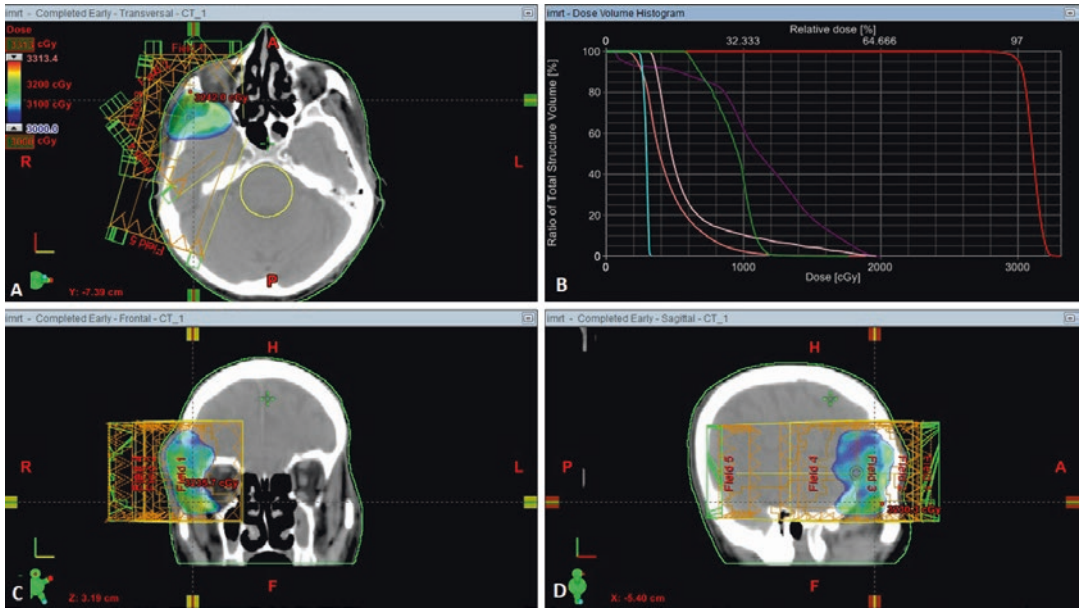

Fig. 9.2 Dose display for IMRT plan. (**a**) Axial CT with dose color wash. (**b**) PTV (red), brainstem (purple), right optic nerve (green), optic chiasm (pink), left eye (light orange), right lens (blue) are shown in the cumulative DVH. (**c**) Coronal and (**d**) sagittal CT with dose color wash

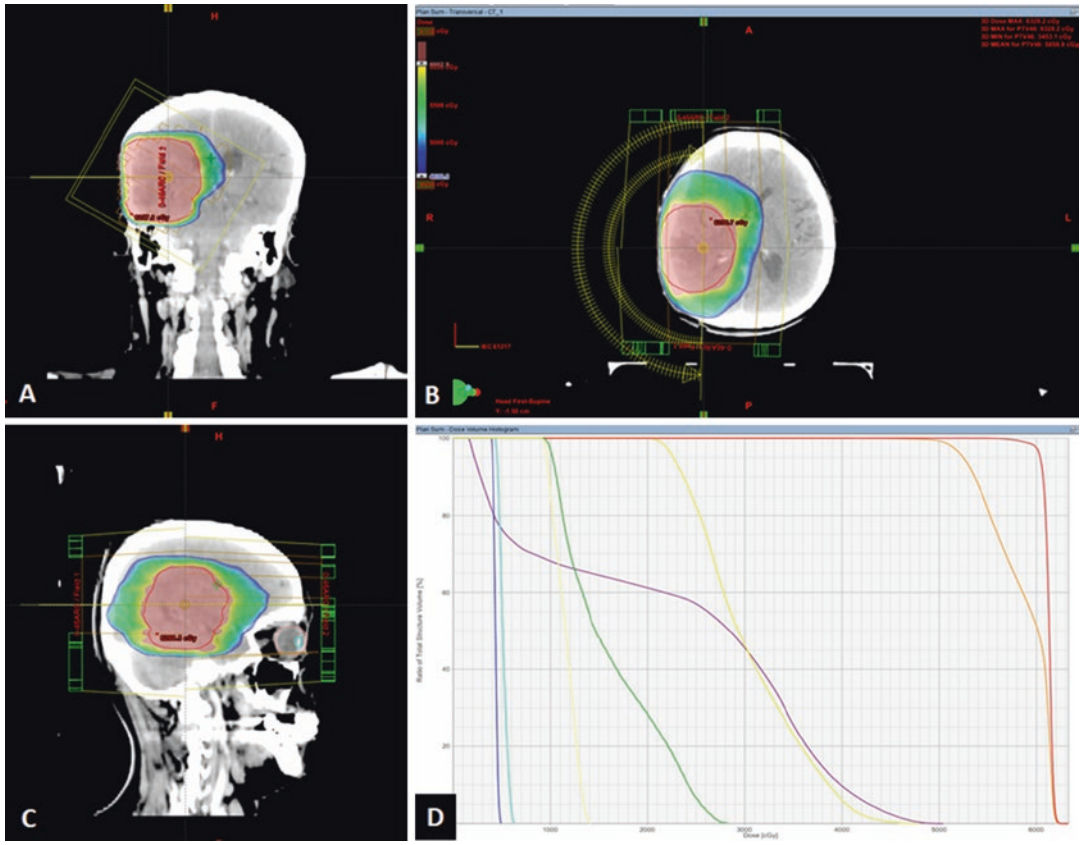

Fig. 9.3 A 63-year-old female patient underwent near-total excision and diagnosed glioblastoma multiforme (GBM). Total dose delivered is 60 Gy, in 2 Gy fractions administered 5 days per week for 5 weeks. In the VMAT plan coronal (**a**), axial (**b**), and sagittal (**c**) dose color wash are shown, along with the DVH (**d**) demonstrating PTV (red), brainstem (purple), right optic nerve (green), optic chiasm (yellow), left lens (dark blue), and right lens (blue)

9.3.4 Stereotactic Radiosurgery (SRS)

A highly precise form of radiation therapy that directs narrow beams of radiation to the tumor from different angles. There are different types of technology used in radiosurgery to deliver radiation to treat brain tumors, such as a Gamma Knife (Fig. 9.4) [56], a cyber knife, [57] or a linear accelerator [58]. In general, there can be many different combinations of technologies used to develop and implement sophisticated conformal therapy. SRS is an established method of ablating brain metastases and AVMs as well as treating certain benign intracranial neoplasms and trigeminal neuralgia.

All these conformal therapy delivery methods are greatly improved by the use of image-guided radiation therapy (IGRT) techniques to accurately position and set up the patient, using integrated megavoltage or kilovoltage diagnostic imaging, cone beam CT, radiofrequency beacons or radiographic fiducials, and other image-guidance methods.

9.4 Brachytherapy

The temporary placement of radioactive sources within the body, usually employed to give an extra dose or boost of radiation to the area of the excision site or to any residual tumor [59].

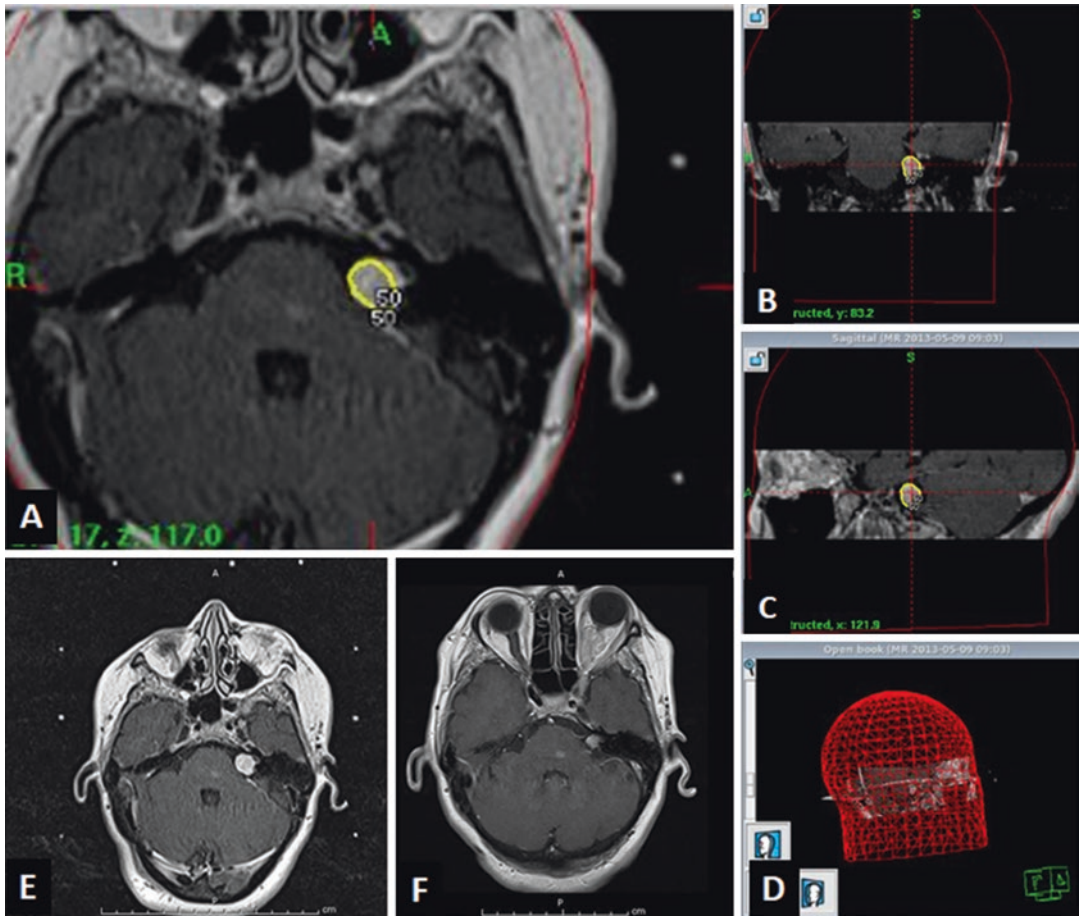

Fig. 9.4 Example of Gamma Knife radiosurgery treatment of a right-side vestibular schwannoma to a prescription dose of 12.5 Gy. The 50% isodose line (yellow) is shown on axial (**a**), coronal (**b**), sagittal (**c**) MRI, three-dimensional view (**d**) planes. MRI axial images of the patient before (**e**) and 55 months after (**f**) the treatment

9.5 Proton Beam

Proton irradiation may offer more localized delivery of radiation than conventional RT, which use photon irradiation. Therefore, it can permit higher radiation doses to the tumor with decreased risk of damage to surrounding tissue; this form of RT may be chosen for tumors with close proximity to important brain structures [60–62].

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