Radiation Oncology

A Case-Based Review

Gokhan Ozyigit
Ugur Selek
Editors

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ISBN 978-3-319-97144-5 ISBN 978-3-319-97145-2 (eBook)
https://doi.org/10.1007/978-3-319-97145-2

Library of Congress Control Number: 2018967706

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To our parents Gülcan and Bekir Özyiğit and Hacer and Hasan Hüseyin Selek.

Preface

Radiation Oncology: A Case-Based Review provides residents, fellows, and practicing radiation oncologists with an evidence-based guide to the current management of cases in major tumor sites to appropriately decide, delineate, and prescribe tumor volumes/fields for intensity-modulated radiation therapy (IMRT) including volumetric modulated arc therapy (VMAT) and stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT). Each section with an academic expert's perspective includes the most commonly seen cases to clarify different stages and specific clinical concepts in an order of case presentation, literature review, patient preparation, simulation, contouring, treatment planning, image-guided delivery, and follow-up. Every chapter offers practical step-by-step question and answer-based guidelines on clinical target volume (CTV) selection and treatment planning, accompanied with illustrations from slice-by-slice delineations on planning CT images to finalized plan evaluations based on detailed acceptance criteria. We will also provide acute and late toxicity management for each specific tumor site. Each individual chapter will begin with a representative case presentation. Then, we provided evidence-based review for each case from their diagnostic evaluation to radiotherapy. We also provided several high-quality figures for each case.

Case-based approach will prepare the reader for real-time clinical discussion environment in multidisciplinary setting. Furthermore, evidence-based guidance per case from scratch to evaluate the treatment planning and to follow up for toxicity management will provide self-confidence in a great spectrum of tumor sites. Case-based cutting-edge histopathological findings will equip the reader with tumor-specific adaptive immune classifications for future discussions in future oncological environment, along with the standard treatment approaches.

This comprehensive book will support knowledge- and guideline-based confidence, especially to manage the common cancers without outside referral, as well as to help in clinical challenges seen in practice. We hope *Radiation Oncology: A Case-Based Review* will meet the need for a practical and up-to-date review of major tumors for residents, fellows, and clinicians of radiation, medical, and surgical oncology, as well as for medical students, physicians, and medical physicists.

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Acknowledgments

The editors are indebted to Gesa Frese and Wilma McHugh from Springer DE and Samantha Sharmine Steven and SwarnaDivya Chokkalingam from SPi Global/ Springer Nature for their assistance in preparing *Radiation Oncology: A Case-Based Review*. We extend our most sincere gratitude to our colleagues and friends at Hacettepe University, Koç University, and Baskent University as well as our families.

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Central Nervous System Tumors

1

Gozde Yazici, Melis Gultekin, Pervin Hurmuz,
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1.1 Medulloblastoma

Overview

Medulloblastoma accounts for approximately 20% of all primary tumors of the central nervous system among children <19 years of age. The peak incidence is between 5 and 9 years of age, and nearly 70% of patients are diagnosed before 20 years of age.

These tumors occur exclusively in the posterior fossa. Patients with medulloblastoma present with symptoms of increased intracranial pressure, including headaches, nausea, vomiting, and altered mental status. Gait ataxia or truncal instability is seen in midline lesions, whereas tumors in the lateral cerebellar lesions cause limb clumsiness or incoordination.

One third of patients will have evidence of tumor dissemination through the subarachnoid space either by imaging or cerebrospinal fluid (CSF) examination. Magnetic resonance imaging (MRI) of the craniospinal axis and CSF examination are complementary techniques for diagnosis of dissemination and both should be performed at diagnosis unless contraindicated. In that case lumbar puncture should be delayed for 2 weeks to avoid potential contamination of the specimen with surgical debris. Medulloblastomas rarely metastasize outside of the nervous system, and systemic staging is not required unless there are findings of bone metastases.

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© Springer Nature Switzerland AG 2019
G. Ozyigit, U. Selek (eds.), *Radiation Oncology*,
https://doi.org/10.1007/978-3-319-97145-2_1

Maximal safe resection is the first step in treatment of medulloblastoma, there is no role for a biopsy if the medulloblastoma diagnosis is supported by imaging studies. The differential diagnosis of a posterior fossa mass in a child includes pilocytic astrocytoma, ependymoma, and atypical teratoid/rhabdoid tumors (ATRT). Metastatic tumors should be kept in mind in an adult patient with a posterior fossa lesion.

Treatment includes a combination of surgery, radiation therapy (in patients >3 years old). Craniospinal irradiation (CSI) plays a critical role in providing long-term disease control. Patients >3 years old are stratified based on the volume of postoperative residual tumor, the presence or absence of metastases, and the presence or absence of diffuse anaplasia into "standard risk" and "high risk" categories. Recent trials treating standard-risk medulloblastoma using reduced-dose CSI and adjuvant chemotherapy have produced EFS rates of 81–86%. However the survival rates for high risk disease is 70%, respectively. Outcomes are inferior in infants and children younger than 3 years with exception of those patients with the MBEN histologic subtype. Treatment for medulloblastoma is associated with significant morbidity, especially in the youngest patients. Recent molecular subclassification of medulloblastoma has potential prognostic and therapeutic implications. Future incorporation of molecular subgroups into treatment protocols will hopefully improve both survival outcomes and post-treatment quality of life.

Key Words: Medulloblastoma; Radiotherapy

1.1.1 Case Presentation

Sixteen year old boy admitted to the hospital with complaints of headache and vomiting. His headache started a week prior to his admission. His physical examination revealed loss of motor strength in his left arm and leg (4/5). A cranial magnetic resonance imaging (MRI) was performed. The MRI showed a left heterogeneous contrast enhancing cerebellar lesion 5 × 4 cm in diameter (Fig. 1.1). There was cerebellar tonsillar herniation due to mass effect. Cranial MRI suggested that the lesion was highly suspicious of medulloblastoma so he underwent spinal MRI. The spinal MRI was normal with no signs of nodular seeding or leptomeningeal infiltration. The cerebrospinal fluid (CSF) examination was planned after surgery due to tonsillar herniation. A gross total resection was performed and in the postoperative MRI performed in the first 24 h there was no residual disease (Fig. 1.2). The pathological diagnosis was medulloblastoma. Histopathologically it was anaplastic large cell and genetically it was SHH active and p53 mutated. The CSF examination performed 2 weeks after the surgery was normal.

He had high risk disease so he underwent craniospinal irradiation to a total dose of 36 Gy with 1.8 Gy/fraction, and a posterior fossa boost of 18 Gy with 1.8 Gy/

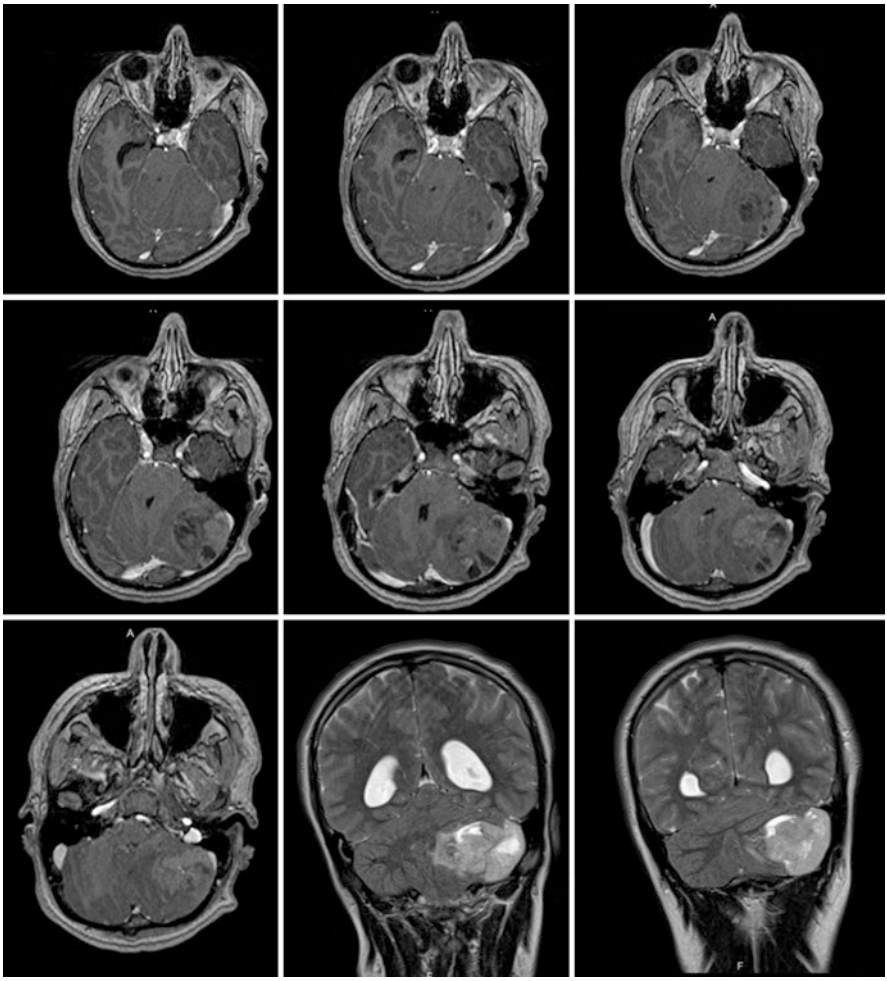

Fig. 1.1 Preoperative magnetic resonance images showing left cerebellar lesion

fraction. He received three cycles of cisplatin and etoposide after radiation, and consolidation chemotherapy consisting of vincristine and cyclophosphamide.

1.1.2 Evidence Based Treatment Recommendations

1.1.2.1 Risk Stratification

Chang et al. proposed an operative staging system for medulloblastomas in 1969 [1]. The Chang Staging system for medulloblastoma is given in Table 1.1.

T stage of the Chang system, relating to tumor size and extent of local invasion at surgery, does not seem to demonstrate prognostic significance and is no longer used. Instead of the initial T stage the presence of residual tumour >1.5 cm^2 confer an increased risk for local recurrence.

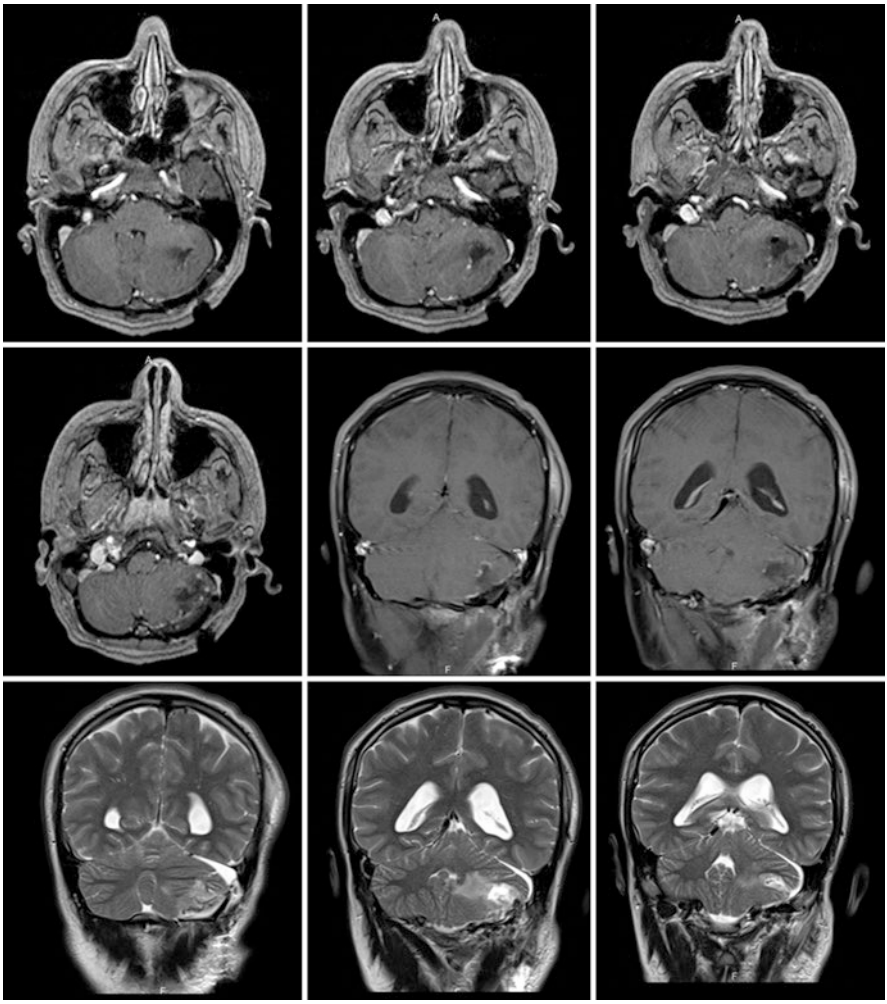

Fig. 1.2 Postoperative magnetic resonance images showing gross total excision of the left cerebellar lesion

The most important factors affecting outcome have been the extent of disease, the residual tumour volume and the age of the patient at diagnosis. There is a non-linear relationship between age and prognosis in patients with medulloblastoma. Those younger than 3 years old and adults do worse.

Historically the treatment decisions were based on these three factors. CSI causes severe neurologic impairment if performed in patients younger than 3 years of age. In this specific group aim is not just to improve disease control but also to prevent progressively worse neurologic outcome.

Children ≥3 years of age are stratified to average-risk disease and high-risk disease groups.

Table 1.1 Chang staging system for medulloblastoma

T stage	
T1	Tumor <3 cm in diameter and limited to the classic midline position in the vermis, the roof of the fourth ventricle, and less frequently to the cerebellar hemispheres
T2	Tumor more than 3 cm in diameter, further invading one adjacent structure or partially filling the fourth ventricle
T3	T3a: Tumor further invading two adjacent structures or completely filling the fourth ventricle with extension into the aqueduct of Sylvius, foramen of Magendie, or foramen of Luschka, thus producing marked internal hydrocephalus T3b: Tumor arising from the floor of the fourth ventricle or brain stem and filling the fourth ventricle.
T4	Tumor further spreading through the aqueduct of Sylvius to involve the third ventricle or midbrain, or tumor extending to the upper cervical cord
M stage	
M0	No evidence of gross subarachnoid or hematogenous metastasis
M1	Microscopic tumor cells found in cerebrospinal fluid
M2	Gross nodular seedings demonstrated in the cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles
M3	Gross nodular seeding in spinal subarachnoid space
M4	Extraneuroaxial metastasis

Standard risk disease was defined as total or near-total resection (<1.5 cm^2 residual disease) at the time of surgery and no evidence of disseminated disease by brain and spine magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis [2].

High-risk disease was defined as the presence of ≥1.5 cm^2 of residual tumor after surgery and/or evidence of metastatic disease.

However there is an evolving understanding other prognostic factors such as molecular markers and histopathology in determining prognosis.

The 2007 WHO classification system recognizes classic medulloblastoma, desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity (MBEN), anaplastic medulloblastoma, and large cell medulloblastoma as histopathologic variants of medulloblastoma, and all are categorized as grade IV neoplasms. The desmoplastic/nodular and MBEN variants are associated with an improved prognosis, and large cell and anaplastic medulloblastomas have a distinctly poor prognosis when compared to the classic variant [3]. Large cell and anaplastic variants are differentiated by the degree of anaplasia, Significantly inferior outcomes have been observed in patients with increasing degrees of anaplasia [3].

Current risk stratification includes the presence of diffuse anaplasia as high risk (Table 1.2).

In 2010, in Boston, a consensus on the molecular subgrouping was developed between experts of medulloblastoma. Four distinct subgroups were identified [4]. Wingless (Wnt), sonic hedgehog (Shh), Group 3, and Group 4 subgroups were characterized which have divergent cell histology, genetics, clinical behavior. These subgroups predict outcome more accurately than the histopathological or clinical staging. Tumors that show activation of the Wingless (WNT) pathway have

Table 1.2 Medulloblastoma risk stratification in patients older than 3 years of age

Risk group	Characteristics
Standard risk	Total or near-total resection with <1.5 cm^2 residual disease and M0 disease and No diffuse anaplasia
High risk	Residual disease more than 1.5 cm^2 or M+ disease or Diffuse anaplasia

Table 1.3 2016 WHO classification of medulloblastoma based on genetics

2016 WHO classification of medulloblastoma
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated
TP53-mutant
TP53-wildtype
Medulloblastoma, non-WNT/non-SHH
Medulloblastoma, Group 3
Medulloblastoma, Group 4

excellent prognosis with the standard therapeutic approaches. Whereas, tumors with amplification of the MYC proto-oncogene ("group 3") have the worst prognosis. The sonic hedgehog (SHH) pathway activated group and those in group 4 have an intermediate prognosis, with the exception of SHH tumors containing TP53 mutations, which are associated with a particularly poor prognosis.

In the last update of WHO classification (2016) besides the histopathological features the molecular characteristics are used in the classification of medulloblastoma. The molecular classification is based on the transcriptome or methylome profiling (Table 1.3).

These subgroups are being integrated into clinical trial designs. In 2015, a consensus conference was held in Heidelberg and the risk stratification based on molecular subgroups was defined in childhood medulloblastoma [5]. The consortium reached a consensus on the following risk groups: low risk (>90% survival), average (standard) risk (75–90% survival), high risk (50–75% survival) and very high risk (<50% survival) disease (Table 1.4).

1.1.2.2 Treatment Recommendations for Standard Risk Patients Older than 3 Years of Age

The term "medulloblastoma" was first introduced by Harvey Cushing and Percival Bailey in 1925. In this era no children with this diagnosis survived until craniospinal irradiation was used potoperativelly. Paterson and Farr, in 1953, reported a 65% of

Table 1.4 Proposed risk stratification for non-infant childhood medulloblastoma

Risk group	Characteristics
Low risk	Non-metastatic WNT patients under the age of 16 Non-metastatic Group 4 patients with chromosome 11 loss
Standard risk	SHH: Non-metastatic, TP53-wild type, no MYCN amplification Group 3: Non metastatic, no MYC amplification Group 4: Non-metastatic, no chromosome 11 loss
High risk	SHH: Metastatic or MYCN amplification Group 4: Metastatic
Very high risk	SHH: TP53 mutation Group 3: Metastatic
Indeterminate groups, unanswered questions	Non-metastatic MYC amplified group 3 patients Cut-off for MYC or MYCN amplification Melanotic medulloblastoma and medullomyoblastoma Anaplastic and/or large cell histology in Group 3 and Group 4 Isochromosome 17q in Group 3 Metastatic WNT patients

3 year survival rate with 35 Gy craniospinal irradiation and a 15 Gy posterior fossa boost [6]. In the subsequent multicenter randomized trials chemotherapy was integrated to surgical resection and RT with the purpose of increasing the overall survival and decreasing the long term toxicity related to high dose craniospinal irradiation.

In standard risk patients several strategies were used to decrease the craniospinal radiation (CSI) dose and to increase overall survival. Deutsch *et al.* decreased the CSI dose to 23.4 Gy but in their early report they observed an increased rate of CNS failure compared to 36 Gy [7, 8]. With longer follow-up there were no differences between the two groups [8]. Packer et al. combined chemotherapy with 23.4 Gy CSI and reported a 5 year event free survival rate of 90% [9]. Studies conducted by the International Society of Pediatric Oncology (SIOP) and the Children's Oncology Group supported the use of 23.4–24 Gy CSI with adjuvant chemotherapy [10, 11].

In Children's Oncology Group (COG) phase III study, published in 2006 and updated in 2012, 379 patients with M0 medulloblastoma between the ages of 3 and 21 years were treated with 2340 cGy of craniospinal and 5580 cGy of posterior fossa irradiation and concomitant weekly vincristine [2, 9]. Patients were randomized between postradiation cisplatin and vincristine plus either CCNU or cyclophosphamide. Five- and 10-year event-free survivals were 81% and 76%; overall survivals were 87% and 81%. Event-free survival was not impacted by the chemotherapeutic regimen.

A COG (ACNS0331) study investigated further CSI dose-reduction to 18 Gy in young children (aged 3–7 years) with standard risk disease [12]. However the preliminary results showed worse outcomes with the reduced (18 Gy) dose of CSI, and therefore 23.4 Gy CSI remains the standard of care in this group.

A retrospective study analyzing pattern of recurrence in patients treated with a CSI and a posterior fossa boost showed that isolated failures in the PF but outside the tumor bed is rare (1 out of 27 pts) [13]. Other studies also confirmed that posterior fossa failures are primarily in the tumor bed and are often associated with leptomeningeal failure [14]. Current protocols use a tumour bed boost instead of a posterior fossa boost to further decrease the neurological side effects of radiotherapy by decreasing the total dose to the temporal lobes [10].

In a study analyzing the impact of neoadjuvant approach on survival as compared to maintenance chemotherapy after completion of radiotherapy, delays in the initiation of radiation therapy was associated with inferior outcomes [15–17].

1.1.2.3 High–Risk Disease in Children Older than 3 Years

The optimal treatment for children with high risk disease is unknown. There is an increased risk for recurrence and death even with intensified treatments.

In a Pediatric Oncology Group Randomized Trial (POG 9031) 224 patients with high-risk medulloblastoma were randomly assigned to receive either chemotherapy entailing three cycles of cisplatin and etoposide before radiation or the same chemotherapy regimen after radiation; both groups received consolidation chemotherapy consisting of vincristine and cyclophosphamide [18]. CSI dose for patients with M0-1 disease was 35.2 Gy. Patients with M2-3 disease received 40.0 Gy CSI. Five-year EFS and OS rates for initial chemotherapy arm were 66.0% and 73%, in the radiotherapy first arm these values were 70.0% and 76% respectively.

In a phase II COG study, 161 children ≥3 years of age with high-risk medulloblastoma were treated with postoperative craniospinal RT with concurrent carboplatin and vincristine, followed by six maintenance cycles of cyclophosphamide and vincristine with or without cisplatin. The five-year progression-free and overall survival rates for patients treated with the cisplatin-containing regimen were 59% and 68%; for those not treated with cisplatin, progression-free and overall survival rates were similar (71 and 82%) [19].

Treatment modifications to improve outcomes in high risk medulloblastoma patients are being studied. High-dose chemotherapy and autologous hematopoietic cell transplantation (HCT) following RT or hyperfractionated accelerated RT with increased dose have been shown to be feasible but long term results are needed [11, 20].

1.1.2.4 Infants and Children Younger than 3 Years of Age

Children younger than 3 years of age are at high risk of severe neurologic impairment if treated with craniospinal RT. The studies focused on intensifying chemotherapy at the postoperative setting to delay or omit CSI. However survival outcomes have been poor with 1 and 2 year progression free survival rates of 42% and 34% [21, 22].

Studies using intensive five-drug chemotherapy regimen and intraventricular methotrexate reported five-year overall survival and progression-free survival rates were 66% and 58%, respectively [23]. In patients without postoperative residual tumor or evidence of metastatic disease, five-year progression-free survival and overall survival rates were up to 82% and 92%, respectively. Unfortunately, the use intraventricular methotrexate was shown to be associated with significantly lower age-matched IQ scores, but the impairment was less severe than in children in who received RT.

Totally resected M0 desmoplastic nodular medulloblastoma or medulloblastoma with extensive nodularity (MBEN) histological subtypes are an exception. The HIT-SKK'92 trial showed five-year progression-free and overall survival of 85% and 95% in this group [22]. Outcomes were significantly inferior in patients with other histologic variants.

1.1.3 Target Delineation and Treatment

Craniospinal radiotherapy is a critical component in the management of medulloblastoma. The goal is to treat the entire intracranial volume and the subarachnoid space throughout the spinal axis.

During target delineation attention should be paid to the cribriform plate, inferior border of the theca sac, lateral sacral nerve roots, and the subdural space extending alone the nerve roots. An example of target delineation for craniospinal irradiation is given in Fig. 1.3.

When the posterior fossa volume is considered as boost CTV, one should cover the tentorium superiorly and C1 inferiorly. Laterally the posterior fossa volume includes the entire cerebellum and anteriorly it includes the brainstem and lower midbrain. The involved field volume GTV should include the tumor bed (anything in contact with the initial tumor before surgery) and any residual gross disease. Care should be taken to account for anatomical shifts following surgery. An expansion of 1–1.5 cm is typically used to form the CTV for the involved field boost. An example of target delineation for posterior fossa boost and involved field boost are given in Figs. 1.4 and 1.5.

Most CSI treatments are delivered with the patient in the prone position, and most techniques involve field matching with fields matched anterior to the spinal cord, which creates a small area of underdosing in the cord but avoids any areas of overlap (Fig. 1.6). The use of IMRT and scanning proton techniques allow for treatment without matching of fields (Figs. 1.7 and 1.8). Protons have a theoretical advantage because of the lack of exit dose which avoids dose to the thyroid, heart, lungs, abdominal organs and ovaries. However in a recent report no difference in patterns of failure, recurrence free survival, or overall survival was found according to radiotherapy modality.

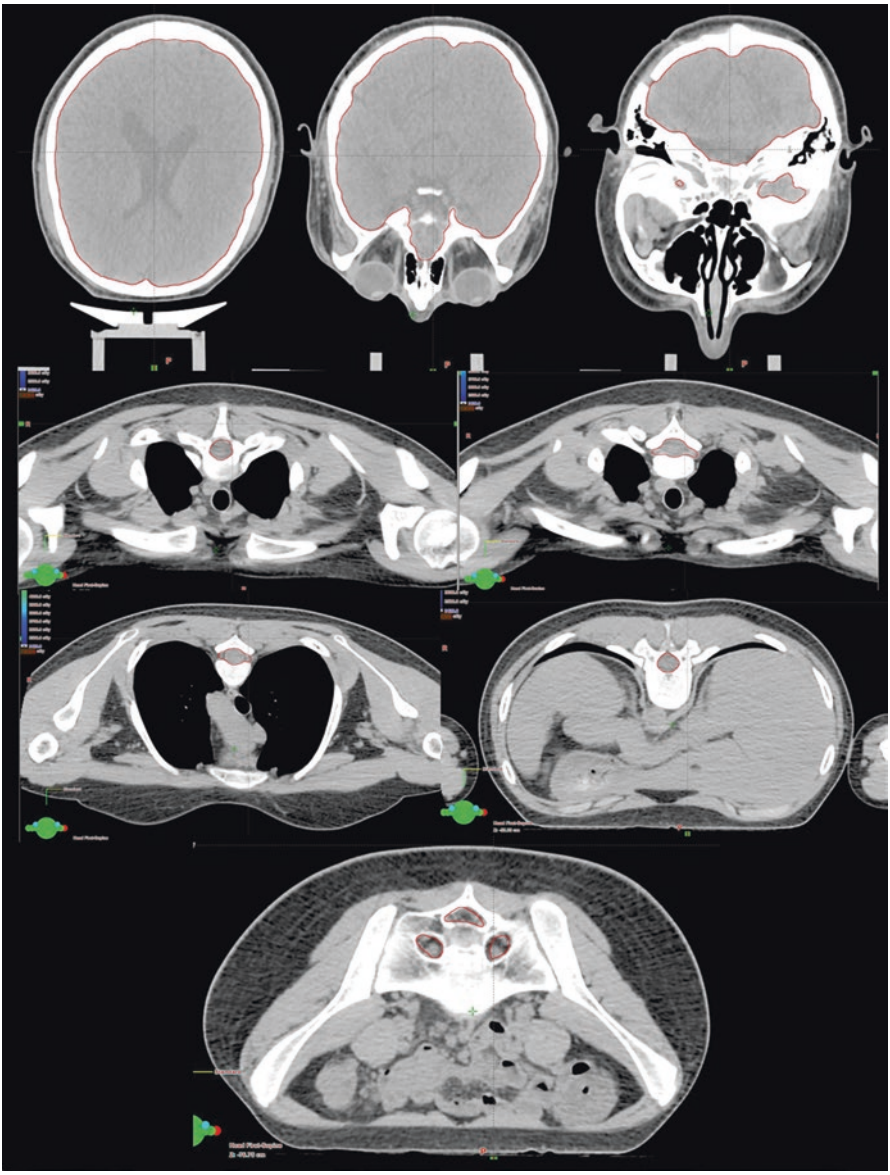

Fig. 1.3 Target delineation for cranispinal irradiation

1.1.4 Follow-Up

Patients should be followed at regular intervals to monitor for treatment complications and disease recurrence. The recommended follow-up periods are every 3 months for the first 1–2 years, then every 6–12 months thereafter. Recurrence after

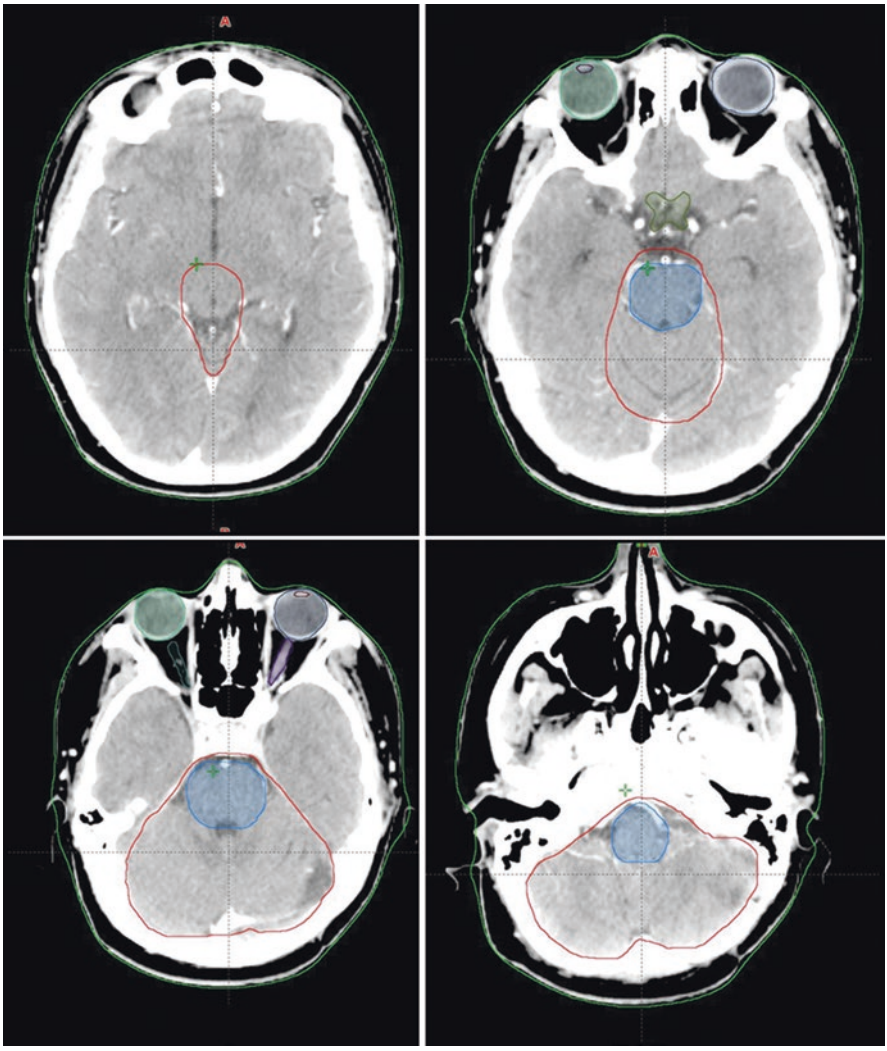

Fig. 1.4 Target delineation for posterior fossa boost

7 years is uncommon but the follow-up should continue to evaluate treatment related complications.

Isolated spinal relapse are less frequent than brain or combined brain and spine relapses. The imaging of the brain should be performed in all patients. However spinal imaging can be restricted to patients with M+ disease at diagnosis.

Endocrinopathies such as GH, adrenocorticotrophic hormone (ACTH), and thyroid-stimulation hormone (TSH) deficiencies, neurocognitive and neurosensory impairment, primary hypothyroidism and cerebrovascular disease can be observed in survivors of medulloblastoma. We should be aware of these side effects during the follow up.

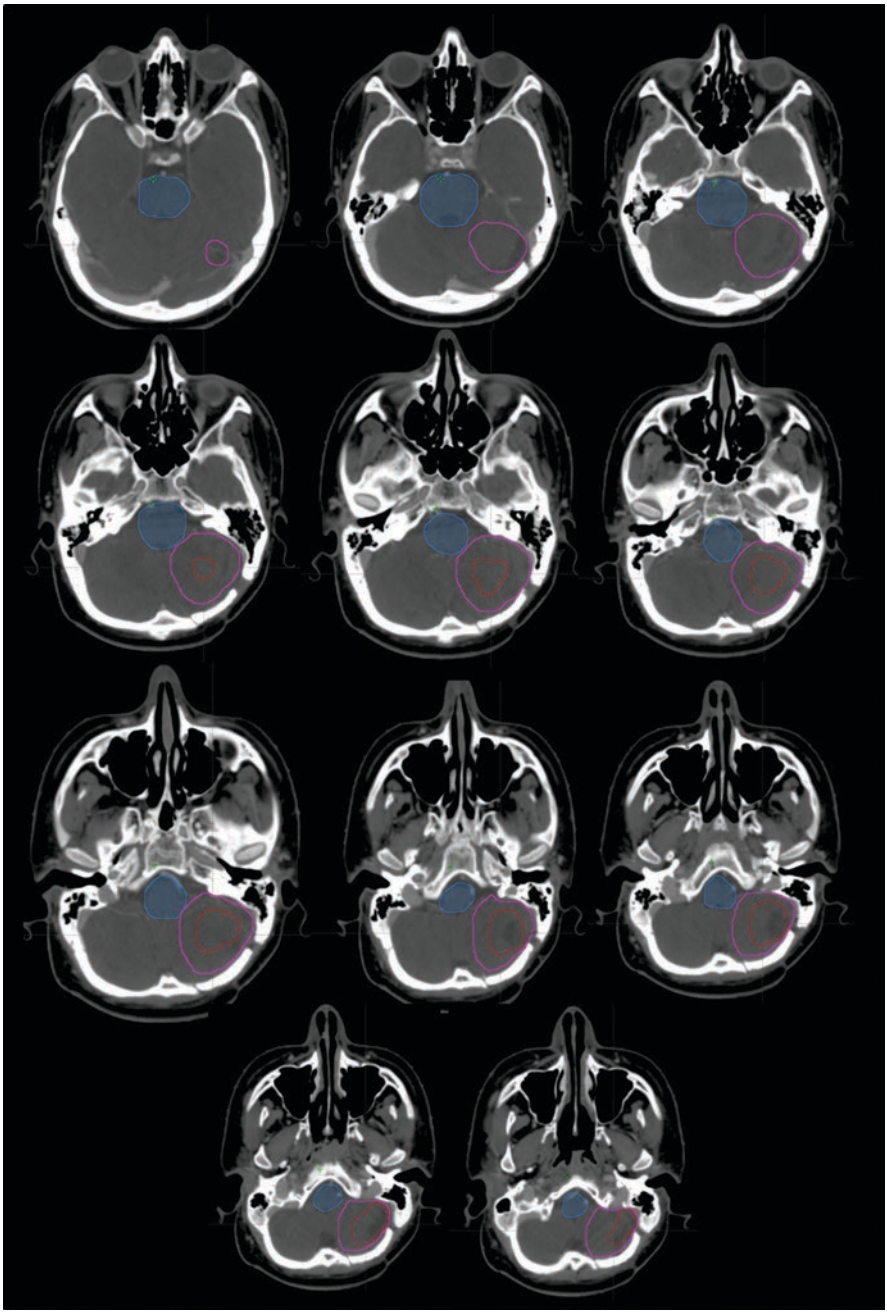

Fig. 1.5 Target delineation for tumor bed boost. Gross tumor volume (GTV) is delineated as red, and clinical target volume (CTV) is formed by defining 1 cm margin around GTV. Gross tumor volume (GTV) is delineated as magenda

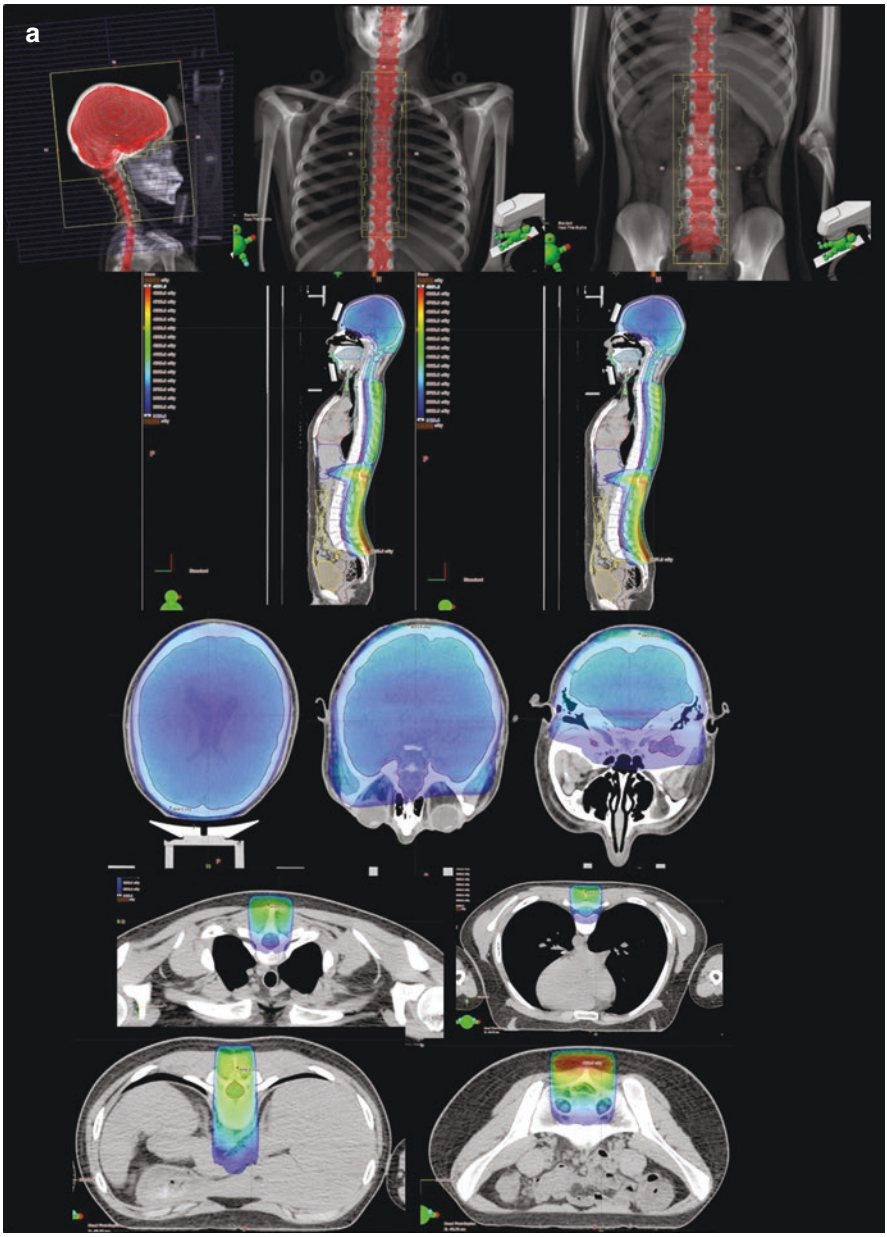

Fig. 1.6 (**a**) 3D conformal plan of craniospinal irradiation with coach angle. Notice the overdose is in abdomen. (**b**) 3D conformal plan of craniospinal irradiation with asymetric collimation. Notice the overdose is in heart

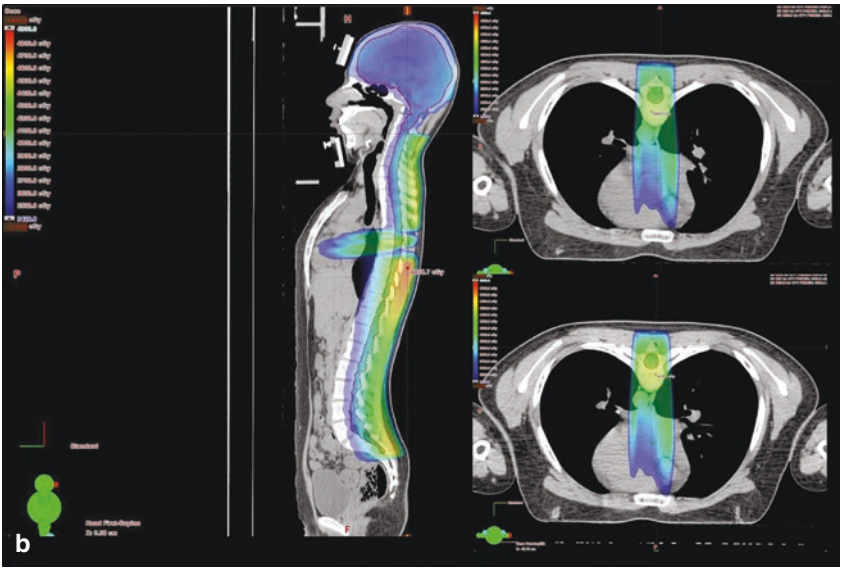

Fig. 1.6 (continued)

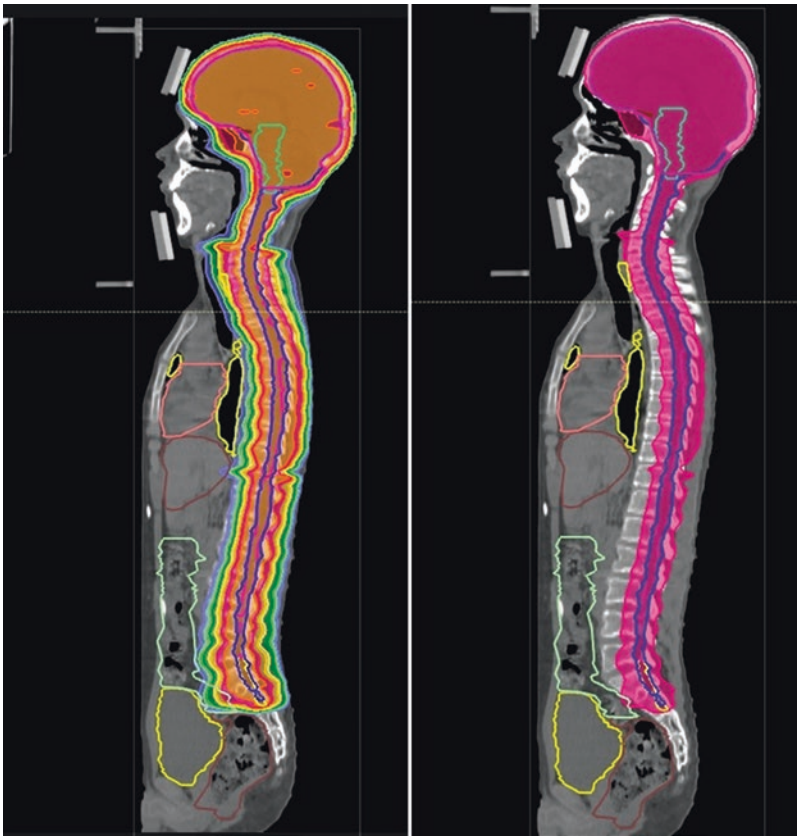

Fig. 1.7 VMAT plan for the cranispinal radiotherapy

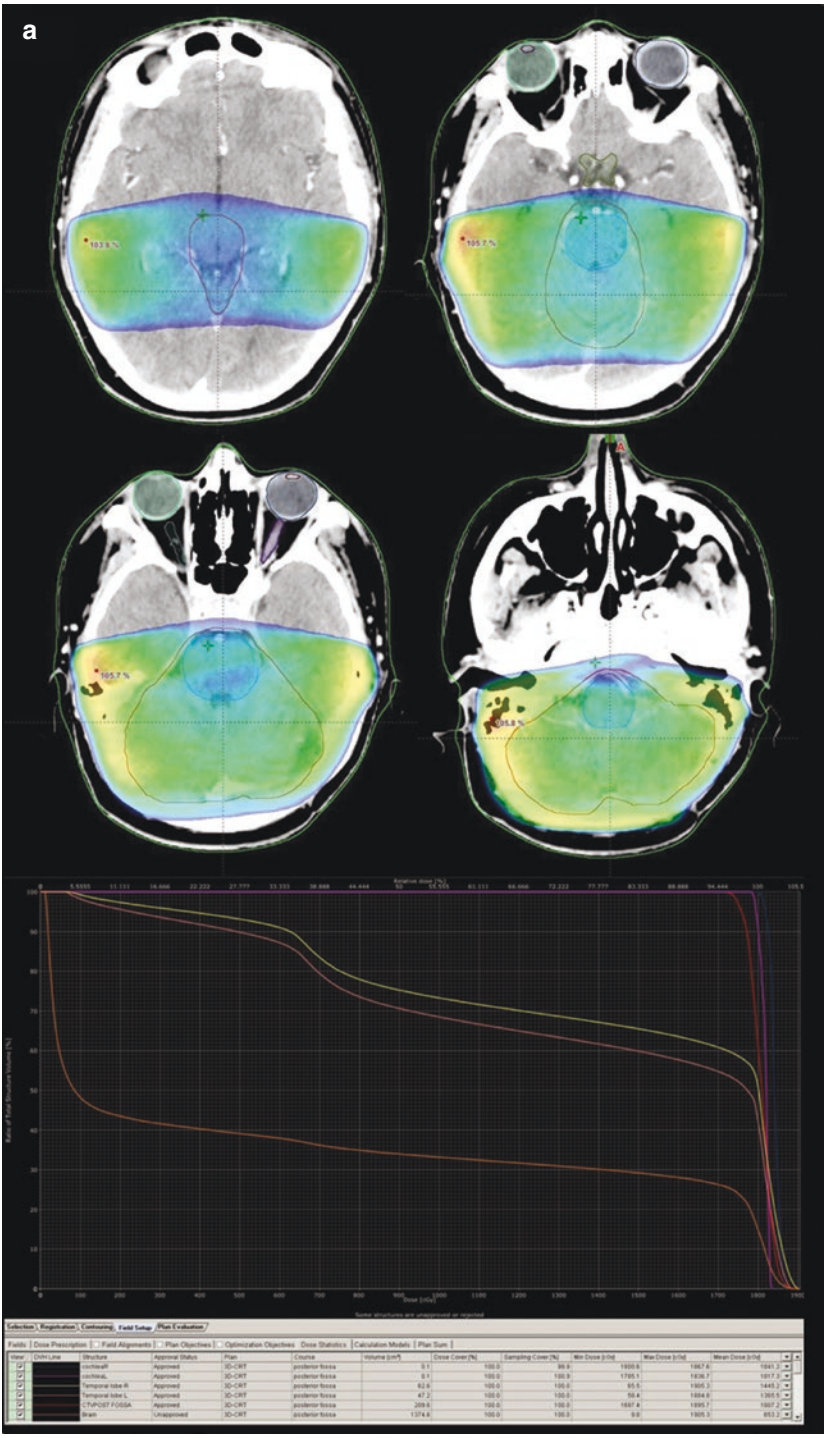

Fig. 1.8 (**a**) 3D plan for the posterior fossa boost, (**b**) IMRT plan for the posterior fossa boost, (**c**) IMRT plan for the tumor bed boost