Eric L. Chang · Paul D. Brown
Simon S. Lo · Arjun Sahgal
John H. Suh *Editors*

Adult CNS Radiation Oncology

Principles and Practice

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Adult Central Nervous System Radiation Oncology is dedicated to our parents, our families, and mentors who have greatly supported our careers.

We also dedicate this new textbook to countless patients who continue to motivate and inspire us. It is hoped that by disseminating and advancing knowledge through this new textbook, we will improve our collective capability to control disease, palliate patient suffering, and alleviate caregiver burden related to CNS disease.

—Eric L. Chang, Paul D. Brown, Simon S. Lo,
Arjun Sahgal, John H. Suh, the editors

Foreword

Thirty-one years ago, I became interested in adults patients with both benign and malignant brain tumors. I had to travel from the medical mecca of America (Boston) to do a mini-fellowship in San Francisco to work with Drs. Sheline, Liebel, Gutin, Larson, and Wilson—some of the most distinguished neuro-oncologists in the world—all in one institution (UCSF). In the first week of my time there, I saw more patients with benign and malignant brain tumors than I had in my entire residency in Boston. In San Francisco, I was exposed to research and clinical investigators, neuropathologists, and neuroradiologists who had dedicated their lives to improving the outcome for patients with these diseases. While the first comprehensive textbook on cancer had just been printed (*Cancer: Principles and Practice on Oncology*, Editors DeVita, Hellman, and Rosenberg), only a few chapters were dedicated to brain tumors. Fast-forward 31 years later and I am so excited to review this textbook completely dedicated to the role of radiation oncology in the treatment of these tumors.

Twenty years of studying the impact of treatment volume, fractionation schemes, dose, concurrent chemotherapy, and radiation sensitizers yielded little in the overall outcome for patients with malignant primary and metastatic disease. However, in the mid-1980s the introduction of MRI and internal and external stereotactic technologies allowed for better imaging definition of disease and the ability to deliver the most conformal treatments ever available. Intensity-modulated photons and protons soon followed to expand our armamentarium to increase dose and reduce late effects of radiation on normal brain tissue.

The editors and authors should be congratulated in putting together this fabulous new pedagogical addition to document where we are currently and where our dreams will take us in the future for the role of radiation in the treatment of our patients with brain tumors. I am particularly proud and humbled that I had a role in the training of two of the editors.

Boston, MA, USA — Jay S. Loeffler, MD, FACR, FASTRO

Preface

As active clinicians, educators, and researchers in the field of neuro-radiation oncology, the co-editors of this book identified a strong need to fill a gap in the medical textbook literature which until now lacked a modern comprehensive book dedicated to addressing the intersection of two important fields: radiation oncology and adult central nervous system (CNS) diseases.

The past two decades have witnessed remarkable developments and rapid advances in the field of neuro-radiation oncology, aided by image guidance, increasing sophistication of computers, software, radiation technology delivery, and ongoing development of molecular prognostic and predictive factors leading to improvements and refinement in the patient selection, and care of patients with CNS diseases.

Most recently, the World Health Organization classification of CNS tumors was updated in 2016 and now includes molecular subtypes in diagnoses as an important component. Therefore, indication for neuro-radiation oncology now requires an understanding of molecular diagnosis that will lead to appropriate utilization. Effective complication avoidance strategies employed when prescribing various forms of radiation therapy are more important than ever since patients with primary and secondary tumors of the CNS are now living longer than ever before.

This book is first organized into diseases afflicting the brain, skull base, and spine including benign tumors, vascular disorders and conditions, and malignant tumors. A chapter dealing with palliative radiation therapy of CNS tumors is also included. Then, radiation-related complications involving the brain, spinal cord, optic apparatus, neuroendocrine system, and neurocognition performance are covered. Finally, radiation treatment modalities including 3-D conformal therapy, intensity-modulated radiation therapy, LINAC-based radiosurgery, gamma knife, spine SBRT, proton beam therapy, and brachytherapy are addressed. Strategies to avoid CNS complications are covered across multiple chapters when appropriate, and radiation therapy is interwoven as a common theme in all chapters. Chapters include key learning objectives, and will frequently conclude with a highlighted case illustration, and self-assessment questions to help the reader consolidate their learning of the subject matter. It is hoped that this comprehensively organized book will help the reader achieve focused learning according to his/her own educational agenda and gain a thorough and nuanced understanding of specialty discipline of adult CNS radiation oncology.

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Part I

Brain Tumors: Benign

Meningioma

1

Timothy J. Harris, Samuel T. Chao, and C. Leland Rogers

Learning Objectives

- Epidemiology and natural history of meningiomas.
- The role of surgery in the management of meningiomas.
- Various radiation modalities used for meningiomas, specifically external beam radiation therapy and stereotactic radiosurgery.
- Guidelines for utilization of radiation for meningiomas, depending on extent of resection and grade.

Background

Meningiomas are typically characterized as benign tumors that ostensibly arise from arachnoid cap cells in the dura. However, 20–30% of meningiomas are WHO grade II or III and have aggressive features that result in a higher risk of recurrence, morbidity, and mortality [1]. Symptoms from meningioma may arise from local mass effect on the brain, cranial nerves, or vasculature which, depending upon tumor location and extent, may include motor and sensory deficits, vision loss, diplopia and other cranial nerve deficits, cerebellar dysfunction, headaches, and/or seizure. Surgery and radiation (including conventional and stereotactic radiosurgery) are the mainstays of treatment.

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Chemotherapy, hormonal therapy, immunotherapy, and targeted therapies are being investigated, but to date, none has been shown to have a frontline role. Some meningiomas persist or recur after multiple surgeries and radiation, and therapeutic advances are clearly needed to optimize management for these challenging patients. Leading the way, trials from the Radiation Therapy Oncology Group (RTOG 0539) and the European Organisation for Research and Treatment of Cancer (EORTC 22042-26042) have helped blaze the path by prospectively studying the role of radiation for meningioma, including patients with recurrence. This chapter will review the practical management of patients with meningioma.

Epidemiology

It is estimated that 27,000 new cases of meningioma will be diagnosed in the United States in 2017 [2, 3]. This represents 8 cases per 100,000 people, rendering meningioma the most prevalent primary intracranial neoplasm, accounting for approximately 37% of all primary brain tumors [3, 4]. These numbers are likely an underestimate of actual cases as meningioma has been discovered in as many as 2% of people in autopsy studies [5].

Meningiomas, much less common in the pediatric population, are most frequently diagnosed in the sixth and seventh decades of life; however, they remain the second most common CNS tumor in adolescents and young adults (ages 15–30) after tumors of the pituitary gland. With more frequent use of MRIs, particularly in evaluation of uncomplicated headaches, we may find the age at diagnosis, especially for subclinical meningiomas, to decrease [2, 6, 7]. Considering all WHO tumor grades, meningioma is more common in women than men. Nonmalignant meningiomas are identified two- to threefold more frequently in females than males [3, 8, 9]. This predilection is less apparent in childhood and with higher-grade histology. Males may be more likely to develop anaplastic (WHO Grade III) meningioma [3].

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Risk Factors

There are well-documented associations in the development of meningiomas with specific genetic, environmental, and hormonal risk factors; however, the majority is diagnosed without a known cause.

Genetic Syndromes

Type 2 neurofibromatosis is a rare genetic syndrome that most commonly occurs due to cytogenetic alteration in the NF2 (Merlin) gene found on chromosome 22q12 [10, 11]. Patients with NF2 are more prone to develop schwannomas and meningiomas [12, 13]. Development of meningiomas in patients with NF2 usually occurs at a younger age compared to patients without this germline mutation.

Multiple endocrine neoplasia type 1 (MEN1) is another rare genetic syndrome with a possible association of increased risk of meningioma [13, 14]. Patients usually have a mutation in the MEN1 gene on chromosome 11q13, which encodes the protein menin. Such patients may present with neoplasias of the pituitary, parathyroid, and pancreas, but meningioma were also found in this patient population at a higher frequency than that of the general population.

Radiation

Exposure to ionizing radiation is an accepted risk factor for meningioma. Data supporting radiation-induced meningioma largely comes from children treated with scalp irradiation for maladies such as tinea capitis, as well as from atomic bomb survivors [15–19]. In one study of children who immigrated to Israel following World War II treated with scalp irradiation for tinea capitis, there was a sevenfold increase in neoplasms of the central nervous system, diagnosed an average of 18 years following radiotherapy. Out of 11,000 patients treated with scalp irradiation, there were 19 incidences of meningioma and 7 of glioma [18]. Another study estimated the risk of developing a radiation-induced meningioma at 0.53% and 8.18% at 5- and 25-year postradiation, respectively [19].

Staging/Diagnosis

Staging is not used for meningiomas, but diagnosis and pathology are critical to treatment decision-making. The preponderance of data regarding the clinical presentation of meningioma comes from surgical series. This results in a bias toward symptomatic tumors. Symptoms depend largely on the location and size of the tumor and can further be influenced by the presence of cerebral edema. Whereas sphenoid wing meningiomas may present with seizures, skull base meningiomas can present with cranial nerve deficits [20, 21]. With the increasing use of contrast-enhanced CT and MRI for the evaluation of head trauma and headache, the number of incidentally diagnosed meningiomas has risen.

Meningiomas are typically diagnosed or suspected following contrast-enhanced neuroimaging, classically appearing on MRI as an enhancing extra-axial mass with a dural tail [22–25]. Calcifications, which may be present and best visualized on unenhanced CT, have occurred more commonly in lower-grade lesions [26]. Either benign or higher-grade meningiomas can invade the bone. Necrosis or brain invasion may also be noted on MRI and portend higher grade.

Meningiomas can generally be identified by imaging with relatively high reliability. Differential diagnoses include, among other entities, dural-based metastases, schwannoma, and hemangiopericytoma. The majority of cases of dural-based metastases occur in patients with known metastatic cancer. Thus in a patient with no personal history of malignancy, and with no evidence of an extracranial primary lesion or metastatic disease, an isolated dural-based metastasis is rare. Although a consideration, hemangiopericytoma is rare, accounting for less than 1% of CNS tumors. While the common imaging characteristics of meningioma are largely diagnostically predictive, there is far less certainty determining tumor grade by imaging. Appreciating this, WHO Grade I meningiomas, associated with slower growth, more often exhibit homogeneous enhancement, calcifications, iso- or hypo-intense T2 signal, and smooth surface contour [22–25]. Advanced imaging may ultimately predict aggressive features with greater certainty, but to date, multiple studies of MR spectroscopy, diffusion-weighted MR, MR perfusion, and positron-emission tomography have not identified definitive correlations between imaging findings and pathologic grade [27–34].

Prognostic/Predictive Factors Including Pathology

Meningiomas likely derive from arachnoid cap cells, the epithelioid cells on the outer surface of arachnoid villi. Arachnoid cap cells are cytologically similar to meningioma. Arachnoid cap cells are as well found in greater number at sites where meningioma more commonly occurs, and increase with age in keeping with the age-related incidence of meningioma [1].

The WHO recently published new meningioma grading criteria in 2016. Building upon the prior criteria of 2000 and 2007, the new grading parameters solidify brain invasion as an independent criterion for WHO Grade II, and as with the prior two iterations incorporate mitotic activity, sheet-like

growth, hypercellularity, nucleolar prominence, nuclear-to-cytoplasmic ratio, spontaneous necrosis, and certain meningioma variants into the assignment of grade. Strong associations between grade, recurrence-free survival, and overall survival have now been independently validated [35–37].

Before adoption of the 2000 WHO criteria, Grade II histology was identified in approximately 5% of meningiomas. However, with incorporation of the recent criteria, 20–35% of meningiomas are identified as Grade II. Based upon the most recent 2016 definitions, a WHO Grade II (atypical) meningioma has 4–19 mitoses per 10 high-power field (hpf), brain invasion, or exhibits three of five atypical features (sheeting architecture, hypercellularity, prominent nucleoli, high nuclear/cytoplasmic ratio, necrosis). Choroidal and clear cell meningiomas are also defined as WHO Grade II. WHO Grade III, also referred to as malignant or anaplastic, is defined by 20 or greater mitoses per 10 hpf, frank anaplasia, or papillary or rhabdoid meningioma variants. These are aggressive tumors, but with modern grading, only about 1–3% of meningiomas are WHO Grade III. Atypical or malignant histology carries a higher risk of recurrence, morbidity, and mortality and, thus, influences management [1]. Extent of resection may influence risk of recurrence and survival, which will be discussed later in this chapter as part of management.

Table 1.1 Simpson grade

Simpson grade	Definition of resection extent	Clinically apparent recurrence risk
I	Gross total resection of tumor, dural attachments, and abnormal bone	9%
II	Gross total resection of tumor, coagulation of dural attachments	19%
III	Gross total resection of tumor without resection or coagulation of dural attachments or extradural extensions (e.g., invaded or hyperostotic bone)	29%
IV	Partial resection of tumor	44%
V	Simple decompression (biopsy)	N/A

Definition of Simpson resection grade according to Donald Simpson's initial publication [38]. All recurrences were clinically apparent. Some were confirmed at reoperation or necropsy

Table 1.2 Local recurrence risk following gross total resection

First author	Year	*n*	5-year (%)	10-year (%)	15-year
Mirimanoff	1985	145	7	20	32%
Taylor	1988	90	13[a]	25[a]	33%[a]
Condra	1997	175	7	20	24%
Stafford	1998	465	12	25	–
Soyuer	2004	48	23	39	60%[a]
McGovern	2010	124	27	53[a]	68%[a]
Gousias	2016	901	12	18	21%[a]
	Total	1976	7–27	18–53	21–68%

Reported risks of local recurrence at 5, 10, and 15 years from several studies with long-term follow-up after gross total resection of a known or presumed Grade I meningioma. Many of these patients were treated predating modern WHO grading criteria
[a]Actuarial data taken from graph

Multimodality Management

WHO Grade I Meningiomas

Surgery

Surgery remains the primary therapy for meningiomas, and numerous publications have demonstrated relationship between resection extent and recurrence. Simpson, in 1957, reported on 265 patients managed with surgery and carefully described resection extent [38]. Based on this data, Simpson resection grades, still in common usage, were defined [38]. Table 1.1 summarizes the Simpson resection grades, along with the rate of clinical recurrence he reported for each grade. Contemporary surgical series have generally confirmed the association between the degree of resection of the meningioma, adjacent dura and any involved bone, and local recurrence.

There have been some contemporary surgical series that challenge the Simpson grading scheme. In one study, there was no significant difference in 5-year progression-free survival when comparing Simpson Grades I through IV [39]. Others have reported no significant difference in local progression risk with Simpson Grades I–III, although typically with improved progression-free survival comparing Grades I–III with Grade IV surgery [40, 41]. However, in support of findings from earlier series, a recent, large report by Hasseleid analyzed 391 patients and found a significant difference in progression-free survival comparing outcomes with Simpson Grade I, Grades II and III, and Grades IV and V [42]. Together the majority of reports support the use of Simpson's grading system and suggest that, similar to gliomas, the surgical goal should be maximal safe removal of tumor, which for many convexity meningiomas would be gross total and correspond to Simpson Grades I–III. Indeed, Simpson Grades I–III resection is achieved in up to 95% of convexity tumors and about two-thirds of all meningiomas treated surgically [43]. For WHO Grade I meningioma, a gross total resection is considered definitive therapy; however, with long follow-up, local recurrence after gross total resection is not infrequent. As shown in Table 1.2, single-institution reports with long-term follow-up have identified local recurrence in 7–27% at 5 years, 18–53% at 10 years, and 21–68% at 15 years [37, 40, 44, 45].

As one might expect, subtotal resection (Simpson Grades IV and V) has resulted in considerably higher rates of progression in most studies. As reviewed in Table 1.3,

Table 1.3 Local recurrence risk following subtotal resection

Author	Year	*n*	5-year (%)	10-year (%)	15-year
Wara (UCSF)	1975	58	47	62	–
Mirimanoff (MGH)	1985	80	37	55	91%
Barbaro (UCSF)[a]	1987	30	40	100[a]	–
Miralbell (MGH)[a]	1992	79	40	52	–
Condra (U Florida)	1997	55	47	60	70%
Stafford (Mayo)	1998	116	39	61	–
Soyuer (MDA)	2004	32	62	82[a]	87%[a]
McGovern (MDA)	2010	69	63	75[a]	87%[a]
	Total	519	37–63	52–100	70–91%

Reported progression risks at 5, 10, and 15 years from several studies with long-term follow-up after subtotal resection of a known or presumed Grade I meningioma. Many of these patients were treated predating modern WHO grading criteria

[a]Actuarial data taken from graph

single-institution reports have identified local progression following subtotal resection of benign meningioma in 37–63% of patients at 5 years, 52–100% at 10 years, and 70–91% at 15 years [9, 40, 44–46]. Furthermore, in one study cause-specific survival was significantly decreased in patients receiving subtotal compared to gross total resection, with 15-year cause-specific survival 51% versus 88%, respectively [40].

Radiotherapy

For WHO Grade I meningioma, gross total resection is considered definitive treatment. However, as detailed in Table 1.2, with extended follow-up, even following gross total resection of a WHO Grade I meningioma, there remains considerable local recurrence risk. In a contemporary study, recurrence following gross total resection was 23% at 5 years, 39% at 10 years, and 60% at 15 years [46]. A more recent report confirmed a high recurrence risk, approximately 65% at 15 years [37]. It can be postulated that the higher rates of recurrence in recent series are the result of improved surveillance imaging. For patients with subtotal resection, the risk of long-term progression is, as expected, greater, 70% or more at 15 years [40, 45, 46].

For a WHO Grade I tumor that either recurs following gross total resection or is not gross totally resected, radiotherapy is the only validated nonsurgical intervention. Radiotherapy is commonly delivered with conventionally fractionated (1.8–2.0 Gy per fraction) external beam approaches or via stereotactic radiosurgery, whether single fraction or hypofractionation.

External Beam Radiotherapy

Numerous retrospective studies have demonstrated improvement in progression-free survival with conventionally fractionated external beam radiotherapy as a definitive therapy for unresected tumors, as an adjuvant to subtotal resection, and as salvage for recurrence or progression. External beam radiotherapy may also be employed as definitive therapy for tumors diagnosed radiographically or via biopsy. Imaging alone is the appropriate method of diagnosis for optic nerve sheath meningioma, and the diagnosis is commonly reached in this fashion for patients who either refuse biopsy or surgery, or are not appropriate candidates. Imaging has also been used in many series as the sole method of diagnosis preceding radiosurgery. In contemporary studies, 5- to 10-year rates of progression-free survival and local control rates following primary external beam radiation therapy (EBRT) or stereotactic radiosurgery (SRS) have been approximately 90%, readily comparable with local control rates after gross total resection [47–54].

Optic nerve sheath meningiomas are an illustrative subgroup. They arise from the meningeal lining of the optic nerve. Growth rates are typically slow, but eventually the optic nerve and/or its vascular supply may become compromised. Surgical resection is technically possible but is associated with a high risk of vision loss from disruption of blood supply to the optic nerve. The standard therapy for optic nerve sheath meningioma is radiotherapy without biopsy or resection. From multiple clinical experiences, local control with conventionally fractionated radiotherapy is approximately 95%, which is readily comparable to local control of meningioma at other intracranial sites with fractionated EBRT, with radiosurgery, or with gross total resection. Moreover, vision often improves with EBRT [55–58].

Dose and Toxicities

Recommended doses for external beam radiotherapy for WHO Grade I meningiomas generally range from 45 to 54 Gy in 1.8–2.0 Gy fractions. Goldsmith and colleagues suggested improved 10-year local control with doses greater than 52 Gy; however, in further analysis, this was not established unequivocally [59]. In one study, there was no correlation between the local control and dose ranging from approximately 36 Gy to as high as 79.5 Gy in 1.5–2.0 Gy fractions [60]. In general WHO Grade I meningiomas are treated to approximately 54 Gy in 1.8–2.0 Gy fractions, but this may be reduced (e.g., 50 Gy) when the optic pathway is involved or abuts the gross disease. A total dose in the range of 45–54 Gy has been effective for optic nerve sheath meningioma, appreciating that meningiomas at this site tend to be smaller when diagnosed and treated [55, 57, 58, 61].

Peritumoral edema occurs frequently with intracranial meningioma, whether at diagnosis or following radiation therapy, particularly radiosurgery. The reported rates of edema preceding treatment vary depending upon how it is defined, for instance, by imaging findings alone or by signs or symptoms. A wide range of rates between 11 and 92% have been reported [62–64].

As a sequela of treatment, intracranial edema occurs less frequently following fractionated external beam irradiation than single-fraction radiosurgery [65].

Edema, and in particular symptomatic edema, has been rarely reported following conventionally fractionated external beam radiotherapy and appears to occur in approximately 1% of patients so treated [65]. Selch and colleagues serially evaluated patients for post-external beam radiotherapy edema, and in 45 patients none had developed post treatment edema, with median follow-up of 3 years [66]. In a separate study by Tanzler and colleagues, 2 of 146 patients—or 1.4%—developed edema following external beam radiotherapy [67].

Cranial neuropathies are rare when radiation doses are kept to 54 Gy or less and dose per fraction is 2 Gy or less. One report, evaluating 140 patients, found only five complications related to external beam radiotherapy including retinopathy, optic neuropathy, and brain necrosis [59]. Another found no optic pathway complications when median the dose was 50.4 Gy in 2 Gy fractions or less [68]. Regarding the cavernous sinus, Selch et al. found no cases of cranial neuropathies with doses of 50.4 Gy [66].

Stereotactic Radiosurgery

Stereotactic radiosurgery is a newer technique than conventionally fractionated radiotherapy but has been utilized extensively in the treatment of meningioma over the past three decades. The reported rates of 5- and 10-year local control have been excellent, commonly 90% or greater [69–71].

Given the excellent local control and limited edema and other side-effect risks with conventionally fractionated external beam radiotherapy, patient selection for stereotactic radiosurgery is crucial. In general, smaller lesions (10 cc and less) with well-defined borders located at a suitable distance (approximately 5 mm or more) from critical structures are good candidates for stereotactic radiosurgery. Parasagittal meningiomas are at higher risk of peritumoral edema, especially those with preexisting edema, so this needs to be considered when deciding on radiation approach [72].

Marginal doses of 12–16 Gy have been found to confer local control of 90% or greater at 5 years and over 80% at 10 years. Ganz and colleagues reported that marginal doses of 10 Gy or less resulted in greater local failure risk than 12 Gy or higher [73, 74]. Stafford and colleagues found no improvement in local control with dose in excess of 16 Gy [7]. Likewise, Kondziolka and colleagues found no benefit in doses above 15 Gy [75].

Regarding tumor size, there does appear to be inferior local control with larger lesions. DiBiase and colleagues reported 92% 5-year local control with lesions ≤10 cc, compared with 68% exceeding 10 cc[76]. Additionally, Pollock et al. found less treatment-related toxicity with smaller lesions (<9.6 cc) [77].

Traditionally stereotactic radiosurgery has been delivered in a single session, but there are now many reports of hypofractionated stereotactic radiotherapy, a common fractionation scheme being 25 Gy in 5 fractions. In multiple studies this appears to have local control similar to single-fraction radiosurgery, potentially with fewer side effects, particularly edema [78, 79].

There remains considerable controversy regarding the management of patients with WHO Grade I meningioma. There is a broad consensus that gross total resection of a newly diagnosed WHO Grade I meningioma is definitive but little consensus regarding the optimal approach to patients following subtotal resection or following recurrence of a benign tumor. Figure 1.1 shows a bar and whiskers plot comparing results from gross total resection (GTR), subtotal resection (STR), STR with fractionated external beam radiation therapy (EBRT), EBRT alone, and stereotactic radiosurgery (SRS). The studies evaluated are those using modern WHO grading parameters.

WHO Grade II (Atypical) Meningioma

Surgery

Prior to the year 2000, WHO Grade II meningioma was diagnosed in only approximately 5% of cases; however, with the updated 2000, 2007, and now 2016 WHO criteria, atypical meningioma is now identified in 20–35% of cases. It cannot be overstated that when reviewing the literature for management of atypical meningioma, care must be given to identify what grading system was used to distinguish atypical meningioma and, even if WHO standards were used, whether the criteria predated WHO 2000.

There is a general consensus that postoperative radiotherapy is of benefit following subtotal resection of WHO Grade II meningioma, but this is by no means uniform and is amenable to discussion given the lack of prospective data. In a recent publication from McGill University, only 4 of 30 patients with a subtotally resected WHO Grade II meningioma received postoperative radiation [80]. Goyal and colleagues reported on 22 patients with atypical meningioma, 8 of whom received radiotherapy. Ten-year local control was only 17%, and they found no significant improvement with radiotherapy [81]. However, several recent studies using modern WHO grading parameters have found improvements in progression-free survival with postoperative RT following GTR or STR [42, 80, 82–87].

With respect to adjuvant RT following Simpson Grade I GTR of a WHO Grade II meningioma, Aghi et al. used modern grading criteria and with mean follow-up of 39 months found a 5-year local recurrence risk of 50% in 100 patients after GTR alone [87]. A small cohort ($n = 8$) received adjuvant radiotherapy following GTR, with no recurrences. In a

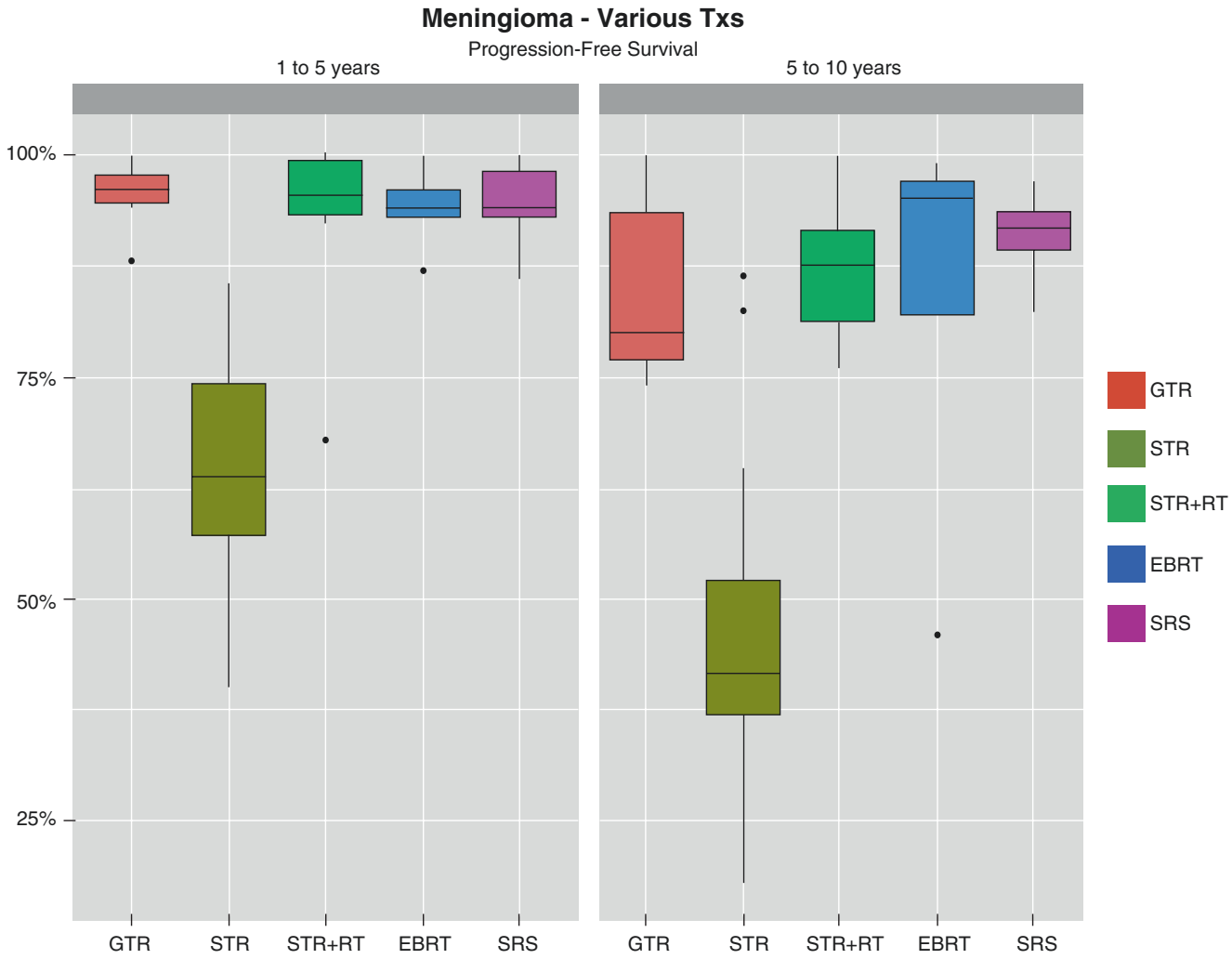

Fig. 1.1 Progression-free survival (PFS) rates in patients with meningioma in the era of modern microsurgery and/or fractionated radiation therapy (RT) or radiosurgery (RS). The outcomes are grouped by median duration of clinical and radiographic follow-up (1–5 years [left panel] and 5–10 years [right panel]) and mode of treatment (gross total resection [GTR], subtotal resection [STR], STR + RT, RT, and RS). [Courtesy of Igor Barani, Barrow Neurological Institute 2017]

separate contemporary study, GTR alone (Simpson Grades I–II) resulted in 42% recurrence rate at 5 years versus 20% with the addition of adjuvant radiotherapy [85]. In patients with recurrent WHO Grade II meningioma, neither repeat surgery nor salvage radiotherapy reliably provide durable tumor control. Aghi and colleagues noted that following first recurrence, 10-year disease-specific survival was reduced to 69%, even with active treatment interventions [87]. Additionally, Komotar and colleagues concluded that recurrence of a WHO Grade II meningioma resulted in worsened overall survival [85]. Talacchi et al. have shown that, for atypical meningioma, both the disease-free interval and the pattern of progression change with successive recurrence [88]. The mean interval declines from about 33 months with first recurrence down to 5–10 months with fourth or fifth recurrence. This occurs even when histologic grade remains unchanged. Stable histology grade at recurrence is seen on about 80% of cases [89]. A large retrospective study by Kessel and colleagues found no survivors at 15 years following recurrence of a WHO Grade II meningioma, compared with 64% in patients without recurrence [90]. There is thus compelling justification in a management strategy that decreases recurrence risk if this can be safely achieved.

Radiotherapy

External Beam Radiotherapy

Based on the above data demonstrating detriment in survival following recurrence of WHO Grade II meningioma, many clinicians recommend postoperative radiotherapy for atypical meningioma regardless of the extent of resection. However, others, including Goyal [81], Hardesty [91], and

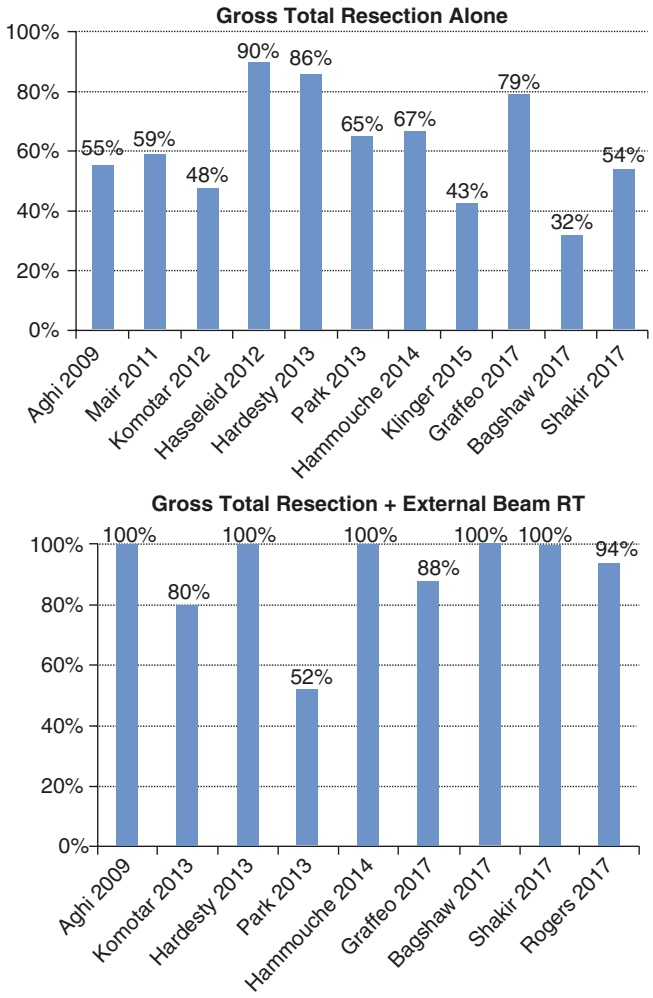

Fig. 1.2 Five-year progression-free survival for gross total resection (GTR) versus GTR and external beam irradiation. Note: in the Park 2013 study the majority of patients (67%) were treated prior to three-dimensional techniques

Jenkinson [92], have found no clear improvement in disease control with postoperative radiotherapy and have concluded that it should not be routinely recommended, especially following GTR. Figure 1.2 compiles recent data with modern grading and compares 5-year PFS following GTR alone or GTR and external beam RT. This suggests a benefit to adjuvant RT, but with the cited data to the contrary, randomized trials are required in order to resolve this important controversy. Two phase III cooperative group studies are currently addressing adjuvant RT following complete resection: the ROAM trial and NRG BN-003.

Based on a completed phase II clinical trial, NRG/RTOG 0539, and the current NRG BN-003 phase III trial, the dose recommendations for patients following GTR are 54–59.4 Gy in 1.8 Gy fractions. Following STR or recurrence, 59.4–60 Gy with standard fractionation (1.8–2.0 Gy) is conventional [93]. More data will be required to better establish optimal dosing for patients with gross residuum. The phase II EORTC 22042-26042 trial employed a boost to 70 Gy after subtotal surgery.

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) has generally been employed in the setting of residual/recurrent disease. Stafford and colleagues reported on 13 patients (12% of their patient cohort) with atypical meningioma treated with radiosurgery. The median marginal dose was 16 Gy and resulted in 5-year local control of 68% compared to 93% for patients with WHO Grade I histology [7]. Harris and colleagues reported on 30 patients with non-benign meningiomas treated with SRS, of which 18 were WHO grade II. Five-year progression-free survival (PFS) was 83% [94]. Huffman and colleagues treated 15 patients with atypical meningioma, median 16 Gy; local control was 60% [95]. Kano et al. reviewed 12 patients with non-benign meningioma (10 WHO Grade II) with SRS, mean margin dose 18 Gy. Five-year PFS was 48%; they found improved PFS with 20 Gy or higher [96].

Attia and colleagues evaluated dose and conformality index, defined as the prescription dose volume divided by the tumor volume. Local recurrence was described as progression within 2 cm of the original tumor margin. With radiosurgery at a median 14 Gy, 5-year local control was 44%. Lower conformality index associated with in-field and marginal failure, but when conformality index was considered, margin dose was not predictive of local control [97]. This raises interesting questions, such as whether higher doses employed for WHO Grade II meningioma in some radiosurgery studies might, in part, be a proxy for a larger conformality index and whether the appropriate target for higher-grade meningiomas exceeds new or residual enhancing tumor alone [98].

Several studies have suggested that atypical meningioma often progresses outside the SRS target yet inside the initial tumor and resection bed. Huffmann reported 15 patients treated with single-fraction radiosurgery to a median 16 Gy. At 18–36 months, 9 were progression-free, for a crude local control rate of 60%. Six (40%) progressed, one (17%) in field, but all within the surgical approach or resection bed [95]. Similarly, Choi reported 25 WHO Grade II patients treated to a median dose of 22 Gy in 1–4 fractions; 9 developed recurrence, 3 (33%) within the targeted region, 5 (56%) elsewhere in the resection bed, and 1 (11%) in both regions [99]. Recently Zhang [100] reported 5-year locoregional control of 36% after SRS for atypical meningioma and Valery [101] a 3-year PFS of 23%. In both these analyses, many of the recurrences were regional. These findings imply that a volume beyond residual or recurrent enhancement is at risk, including the entire tumor and resection bed. Hypofractionated SRS or standard fractionation external beam approaches may safely and effectively address this important issue.

WHO Grade III (Anaplastic/Malignant) Meningioma

WHO Grade III meningiomas account for about 1–2% of newly diagnosed meningiomas. As a result there are fewer than 500 newly diagnosed malignant meningiomas annually in the United States. There thus is far less data to guide management than for patients with WHO Grade I or II meningioma. However, anaplastic meningiomas behave aggressively, with significantly poorer local control and overall survival than lower-grade meningiomas. In some studies, median overall survival has been less than 3 years. Given the poor prognosis of these tumors, there is a general consensus toward aggressive upfront therapy, including surgery and postoperative radiotherapy regardless of the extent of resection. Moreover, effective systemic therapies are needed and remain a challenge for future investigation.

Surgery

Surgery is the first-line therapy and indeed is necessary to assign tumor grade. Similar to lower-grade meningiomas, the extent of resection impacts recurrence; however, surgery as a sole modality is insufficient. Jaaskelainen observed a 5-year recurrence rate of 78% following GTR in patients with malignant meningiomas managed with surgery alone. Similarly, Dziuk and colleagues reported a 5-year progression-free survival of 28% following gross total resection and 0% following subtotal resection [102]. Most clinicians recommend adjuvant radiotherapy after initial surgery for a WHO Grade III meningioma, irrespective of resection extent.

Regarding extent of resection, Sughrue and colleagues noted that heroic surgery did not improve survival, rather near total resection (defined as >90% tumor removal) resulted in superior overall survival and neurologic outcomes than gross total resection, provided that adjuvant radiotherapy was given [103]. They also reported that salvage surgery was beneficial with median survival of 53 months with salvage surgery compared to 25 months without [103].

Radiotherapy

There are yet no published prospective studies regarding multimodality therapy with surgery and adjuvant radiotherapy (RT) in the management of WHO Grade III meningiomas. We await publication of the RTOG-0539 high-risk cohort which includes WHO grade III patients. However, multiple retrospective series, although varying in treatment approach, dose, and definition of malignant meningioma, do strongly suggest benefit with adjuvant RT.

External Beam Radiotherapy

Milosevic and Dziuk both demonstrated benefit with the addition of RT as a surgical adjuvant, rather than reserving radiotherapy for salvage [102, 104]. This is now, in general, the standard approach for managing malignant meningioma. Milosevic demonstrated that radiation doses of less than 50 Gy were insufficient and associated with poor cause-specific survival [104]. Dziuk reported that adjuvant external beam RT improved 5-year PFS from 28% to 80% for gross totally resection lesions [102]. Regarding salvage radiotherapy, some studies have demonstrated a modest advantage, whereas others have found little to no benefit. Dziuk et al. reported that external beam radiotherapy for recurrent malignant meningioma improved the 2-year progression-free survival from 50% to 89% but had no such impact at 5 years [102]. This corroborates other studies showing poor tumor control even with salvage therapy for non-benign meningioma [82].

Radiation dose appears to correlate with disease control for WHO Grade III meningioma. Milosevic demonstrated improvement with a 5-year cause-specific survival of 42% with 50 Gy or greater and 0% with less than 50 Gy [104]. Likewise, Goldsmith reported that 5-year PFS improved from 17% to 63% with radiation doses exceeding 53 Gy [59]. With protons, DeVries and Hug noted improvement in local control and survival with doses above 60 Gy [16, 105]. Specifically, Hug demonstrated improved overall survival at 5 and 8 years to 87% with at least 60 CGE, compared to 15% with less than 60 CGE [16].

Recurrent Meningioma

Despite appropriate therapy including surgery and radiotherapy, meningiomas can recur. Tumor volume, grade, location, and other factors have been correlated with recurrence risk following upfront therapy. For a meningioma that recurs following initial therapy, repeat resection should be considered [39]. If radiation has not been given initially, it should be considered after resection of a recurrent meningioma, irrespective of resection extent. Ultimate control of a meningioma is compromised by recurrence [82, 88, 106]. Onodera compared patients with newly diagnosed benign meningioma to those with recurrence. With median 90-month follow-up, they found better overall survival, progression-free survival, and local control in patients who received radiation therapy, 48–54 Gy in 2 Gy fractions with or without surgery as initial compared to salvage therapy. OS, PFS, and LC were 100%, 91.7%, and 100%, respectively, with initial EBRT, versus 90.9%, 68.2%, and 68.2% if radiation was given after relapse. The difference in local control was statistically significant with $p = 0.01$ [106].

For progression outside of previous fields, RT may clearly be considered. Re-irradiation, either external beam RT or SRS, may also be applied judiciously for in-field or marginal failure, particularly if there has been a long disease-free interval.

Systemic Therapy

Multiple systemic therapy regimens have been evaluated for meningioma, primarily in phase I and II studies. To date

there has only been one published phase III clinical trial. The ribonucleotide reductase inhibitor, hydroxyurea, demonstrated 6-month progression-free survival of only 3–10% in nonrandomized studies [107]. Somatostatin analogues (e.g., Sandostatin LAR, octreotide) have demonstrated 29–44% in nonrandomized trials [108, 109]. Tyrosine kinase inhibitors, also in nonrandomized trials, have demonstrated 6-month progression-free survival of 28–61.9% [110, 111]. Bevacizumab in nonrandomized studies demonstrated 6-month progression-free survival of 43.8–85.7% [112].

Yong Ji and colleagues published data from the SWOG S9005 phase III study of mifepristone, the anti-progesterone. To date, this is the only drug with published randomized data in meningioma. In this trial 164 patients with unresectable meningiomas were randomized to receive mifepristone versus placebo. Only one-quarter of the patients had previously received radiotherapy. At 2 years failure-free survival was approximately 30% in both arms [113]. Pharmacological approaches have thus met with limited results, and considerable opportunity exists for the development of systemic or targeted agents for the treatment of recurrent or high-grade meningioma. A current phase II Alliance trial is evaluating SMO, AKT, and NF2 inhibitors for patients with progressive meningioma.

Contemporary Clinical Trials

EORTC 22042-26042

This EORTC phase II trial evaluated progression-free survival with WHO Grades II and III meningioma. Patients were stratified by extent of resection and pathologic grade. Patients with gross total resection, defined by Simpson Grades I–III, received postoperative radiotherapy to 60 Gy in 2 Gy fractions, whereas patients with gross residual disease received an additional 5-fraction boost to a total dose of 70 Gy. This study is closed to accrual and data analysis is pending.

RTOG 0539

The RTOG 0539 clinical trial utilized a risk stratification approach to postoperative management of meningiomas. Low-risk was defined as a gross totally resected or subtotally resected WHO Grade I meningioma, and patients were observed. Intermediate-risk included recurrent/progressive WHO Grade I and gross totally resected WHO Grade II patients. Intermediate-risk patients received radiotherapy, 54 Gy in 1.8 Gy fractions. High-risk was defined as subtotally resected or recurrent WHO Grade II or new or recurrent WHO Grade III regardless of extent of resection. These patients received 60 Gy in 2 Gy fractions. This study has closed to accrual and initial analysis or some of the risk groups is pending. An informative report of pathology concordance from this trial has been published [93].

The results of the intermediate risk arm of RTOG 0539 are in press [114]. The primary endpoint was 3-year PFS, with both progression and death considered as events. With 48 fully evaluable patients 3-year PFS was 93.8%, and 3-year OS was 96%. Only two patients developed local recurrence within 3 years, resulting in 3-year actuarial local failure rate 4.1%. Treatment was well tolerated, with CTCAE adverse events related to protocol therapy limited to Grade 1 or 2.

NRG Oncology BN003 and ROAM/EORTC1308

Presently, one of the most controversial subjects in meningioma management is the appropriate therapy for a grossly resected WHO Grade II meningioma. This phase III trial, opened in the summer of 2017, will randomize patients with a grossly resected WHO Grade II meningioma to either observation or radiotherapy (59.4 Gy in 33 fractions). Created in concert, a very similar trial ROAM/EORTC1308, is also open internationally. These studies will address one of the most clinically relevant topics in meningioma management and will include, in addition to tumor control outcomes, neurocognitive and quality of life endpoints.

Treatment Field Design/Target Delineation

External Beam Radiotherapy

For WHO Grade I meningioma, external beam radiotherapy is generally applicable only for gross residual disease either following subtotal resection or recurrence. Patients are commonly immobilized with a thermoplastic mask, typically with the head in neutral position. A contrast-enhanced T1 sequence MRI is used for delineation of gross tumor volume (GTV). Overlying hyperostotic bone should be included in the GTV as this generally represents tumor invasion; however, the dural tail does not need to be included in the GTV [115]. Clinical tumor volume (CTV) expansion from GTV for WHO Grade I meningioma can range from 0 to 1 cm primarily along dural surface and the hyperostotic bone, with margin restrictions to spare uninvolved normal tissues such as the adjacent brain and respecting natural barriers to tumor growth such as uninvolved falx and bone. The planning target volume (PTV) is a geometric expansion of the CTV and is institutionally defined to account for setup and treatment delivery uncertainties and is usually at least 3 mm. Radiation dose generally ranges from 50.4 to 54 Gy in 1.8–2.0 Gy fractions.

For WHO Grade II meningiomas, as discussed in detail above, radiation is commonly recommended with gross residual but is also an appropriate strategy following a gross total resection (GTR). After GTR, the GTV is defined as the tumor bed. The CTV is the GTV plus an approximately 0.5 cm anatomically constrained expansion. Known or suspected brain invasion with a WHO Grade II meningioma must be addressed, and it is thus reasonable to include a rim

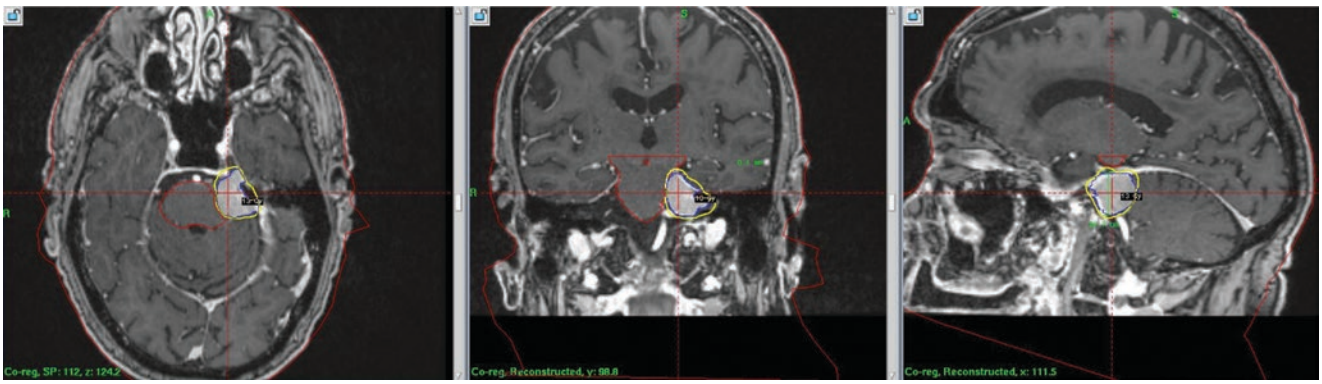

Fig. 1.3 Petrous apex meningioma stereotactic radiosurgery plan, 13 Gy in 1 fraction

of the adjacent brain in such cases. The PTV expansion is similar to that previously discussed for WHO Grade I meningiomas. Recommended dosing for atypical meningioma following GTR is at least 54 Gy in 1.8–2.0 Gy fractions, some clinicians advocating for 59.4–60 Gy. The NRG Oncology/RTOG 0539 trial employed 54 Gy in 30 fractions following GTR of a WHO Grade II meningioma; however, supported by several intervening studies, the upcoming second-generation randomized trial stipulates 59.4 Gy in 33 fractions in the same setting [93]. Following subtotal resection (STR) or recurrence, at least 60 Gy in fractions of 1.8–2.0 Gy is recommended, and higher doses in the range of 66 Gy may be considered when organs at risk permit. The EORTC trial (22042, 26042) uses a final 70 Gy for gross residual disease in these settings. Total doses of this extent should be used vigilantly until their utility is confirmed.

For WHO Grade III meningioma, radiation is recommended regardless of resection extent. GTV is defined as T1 post-contrast-enhancing tumor bed and any remaining nodular enhancement and hyperostosis. Based upon NRG Oncology/RTOG 0539, two CTVs may be defined for a simultaneous integrated boost. CTV54Gy is the GTV plus a 2 cm expansion and CTV60Gy is GTV plus a 1 cm expansion. The standard institutional PTV, typically 3–5 mm, is used to expand each of these volumes to define a PTV54Gy and a PTV60Gy. Dose escalation beyond 60, up to 70 Gy—see the separately referenced EORTC trial—have been reported but should be used cautiously, with careful attention to normal tissue (organ at risk) constraints [116].

Stereotactic Radiosurgery

Stereotactic radiosurgery is an appropriate option with gross residual WHO Grade I and possibly WHO Grade II tumors. Immobilization, or another form of stereotaxis, is required generally resulting in setup uncertainties on the order of a single millimeter. The GTV is defined by the T1 post-contrast MRI. There is commonly no CTV margin, and the PTV is routinely defined as GTV plus 0–2 mm. For a WHO Grade I meningioma, a marginal dose of 12–15 Gy is recommended. Figure 1.3 shows a stereotactic radiosurgery plan for a patient with a left petrous meningioma. For WHO Grade II meningioma, recommended marginal doses from varying reports are 14–20 Gy. This is an important arena additional research to help define optimal dosing for higher-grade meningioma based upon factors such as location, volume, and perhaps even molecular characteristics. For larger (>10 mL) WHO Grade I meningioma, fractionated stereotactic radiotherapy, such as 5 Gy times 5 (total dose 25 Gy), may be considered, and for a WHO Grade II or III tumor 5.5–6 Gy times 5 (27.5–30 Gy).

Normal Critical Structure Constraints

Restriction of dose to critical structures reduces the risk of toxicities. Table 1.4 summarizes the normal critical structure constraints used in RTOG 0539 and in NRG-BN003. With these considerations, radiation is well tolerated with 5% or less long-term toxicity rate when modern techniques are used [114].

Table 1.4 Organ-at-risk point dose constraints (point defined as 0.03 cc volume)

Critical structure	RTOG-0539 group 2 (Gy)	RTOG-0539 group 3 (Gy)	NRG-BN003 (acceptable variation) (Gy)
Lenses	5	7	≤7 (>7 to 10)
Retinae	45	50	≤45 (>45 to 50)
Optic nerves	50	55	≤54 (>54 to 58)
Optic chiasm	54	56	≤54 (>54 to 58)
Brainstem	55	60	≤54 (>54 to 58)

RTOG-0539 included two groups. Group 2 was defined as intermediate-risk meningioma treated with IMRT, 54 Gy in 30 fractions. Group 3 was high risk, treated to 60 Gy in 30 fractions, with differing organ-at-risk constraints. NRG-BN003 includes patients with a gross totally resected WHO Grade II meningioma, treated to 59.4 Gy in 33 fractions. Note that desirable organ-at-risk doses in patients with WHO Grade I meningioma may indeed be less than those with WHO Grade II or III

Debus et al. reviewed 189 patients treated to a mean 56.8 Gy with fractions of 1.8 Gy and reported that 2.2% developed clinically significant toxicity [48]. In patients without a preexisting neurological deficit, this was even lower (1.7%). Reduced vision, visual field cut, and trigeminal neuropathy were noted as the most common toxicities. Goldsmith et al. reported a 3.6% toxicity rate for subtotally resected meningioma patients who received EBRT. Of the five patients with side effects, retinopathy developed in two, optic neuropathy in one, and radiation necrosis in two [59].

A more recent study by Farzin et al. focused on optic toxicity in 213 treated with radiation for meningiomas [117]. Dry eye developed in 7% and cataracts developed in 11.2%. Two patients developed visual issues due to radiation. They received a maximum and median dose to their neuro-optic structures of 57.3 Gy and 54.6 Gy, respectively.

Selch et al. looked at 45 cavernous sinus meningioma patients who received a total dose of 50.4 Gy at 1.7–1.8 Gy per fraction and found no patients with treatment-related cranial neuropathies [66]. Pituitary dysfunction, cerebrovascular effects, secondary malignancy, orbital fibrosis, and edema have been described but are rare as well.

Cognitive morbidity may occur following radiation. Steinvorth et al. prospectively evaluated patients treated with fractionated radiation for meningioma [118]. By using a comprehensive neurocognitive battery, they found a decline in memory with an increase in attention after the first fraction. There was no cognitive loss with further follow-up. On the other hand, Meyers et al. assessed patients treated to the paranasal sinuses and demonstrated memory impairment in 80% of the patients [119]. This study did use older techniques however.

For stereotactic radiosurgery, optic nerve constraints range from 8 to 12 Gy in the literature. Tishler et al. reported a 24% risk of optic neuropathy with doses greater than 8 Gy to the optic pathways [120]. Other studies have suggested that slightly higher doses than 8 Gy are perhaps safe. Leber et al. looked at 50 patients and did not see radiation optic neuropathy in patients who received less than 10 Gy [121]. Optic neuropathy, however, developed in 26.7% of patient receiving 10 to less than 15 Gy and 77.8% for those receiving 15 Gy or more. According to a series of patients treated at the Mayo Clinic, only 1.1% of the patients developed optic neuropathy at 12 Gy or less to the optic nerves and chiasm [122]. As long as doses are kept reasonably low to the optic nerve and chiasm, risk of vision loss is also low.

Conclusion

The main management options for meningioma are surgery and radiation. The evidence supporting radiation, up until recently, had relied upon retrospective studies, which made it difficult—especially in an era with considerable revisions in grading criteria—to establish widely acceptable treatment guidelines. Controversy remains over the use and timing of radiation particularly for Grade II atypical meningiomas. With the completion of EORTC 22042-26042 and RTOG 0539, the role of radiation will be better defined. The NRG BN003 and ROAM/EORTC1308 trials, once completed, will further eliminate controversy for patients with gross totally resected atypical meningiomas. While the role of radiosurgery for Grade I meningioma is well supported by retrospective data with long-term follow-up, its use for atypical and anaplastic meningioma is less clear. There remain important questions regarding the optimal target volume. Beyond radiation therapy, more studies are needed for targeted therapies and immunotherapy, especially for patients who fail surgery and radiation therapy.

Case Study

A 60-year-old woman presented with increasing difficulty with balance. Her past medical and family history were noncontributory. Given her symptoms, her neurologist ordered an MRI of the brain without and with contrast. She was found to have two separate parasagittal masses and a left posterior fossa dural-based mass consistent with multiple meningiomas (Fig. 1.4a). Given the size of her parasagittal meningiomas, she underwent a Simpson Grade II resection of these masses (Fig. 1.4a). Pathology was consistent with WHO Grade II (atypical) meningiomas. After discussion of options which included observation, she elected to proceed with radiation to the resection bed to decrease risk of local recurrence, with plans to watch the posterior fossa meningioma. She received a total dose of 54 Gy (Fig. 1.4b). Given the histologic grade, a CTV margin was included, but given the extent of resection (GTR), the CTV margin was limited to 0.5 cm.

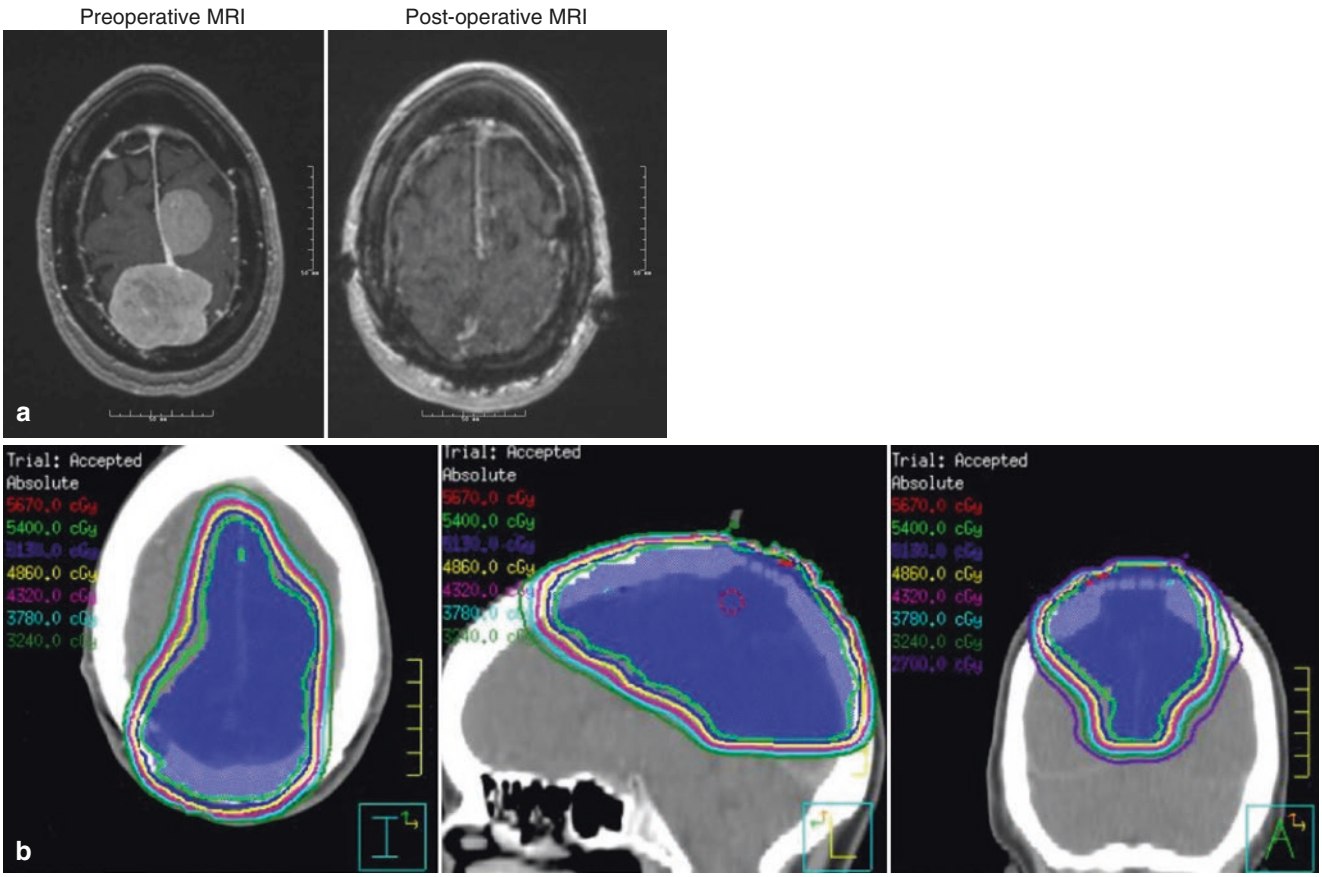

Fig. 1.4 (**a**) Gross totally resected multifocal parasagittal WHO Grade II meningioma. (**b**) Isodoses in axial, sagittal, and coronal planes for post-operative radiation therapy, 54 Gy in 30 fractions

Self-Assessment Questions

1. Which of the following statements is true regarding surgical resection of a meningioma?
   A. The extent of surgery is classically defined according to the "Cushing Grade" of resection.
   B. In modern surgical series, gross total resection is accomplished at initial surgery in over three-fourths of patients.
   C. Gross total resection alone results in excellent local control, exceeding 90% at 15 years.
   D. The intracranial primary site with the greatest likelihood of achieving gross total resection is the sphenoid wing.

2. Which of the following is *not* true regarding meningioma cooperative group trials?
   A. Two cooperative group trials evaluating gross total resection (GTR) alone versus GTR and adjuvant fractionated external beam RT for WHO Grade II meningioma are underway.
   B. Targeted systemic interventions are being evaluated in an Alliance trial.
   C. Mifepristone improved failure-free survival for patients with recurrent or progressive meningioma in a phase III SWOG trial.
   D. The EORTC phase II trial (22042-26042) will report on final RT doses of 70 Gy for patients with subtotally resected high-grade meningioma.

3. Which of the following statements regarding the incidence of meningiomas is *false*?
   A. Historically, the incidence increased following radiation therapy for tinea capitis.
   B. Meningiomas often occur with type 2 neurofibromatosis.
   C. Nonmalignant meningiomas are more common in males than females.
   D. Meningiomas are the second most common primary intracranial tumor, following gliomas.

4. Meningiomas are graded histopathologically by the World Health Organization (WHO) criteria. Which of the following is *false* regarding various WHO grades?
   A. Approximately 70% of meningiomas are benign (WHO Grade I).

B. According to WHO 2007–2016 criteria, approximately 25% of meningiomas are atypical (WHO Grade II).
C. Atypical meningiomas treated with surgery alone have 10-year progression-free survival rates exceeding 75%, similar to WHO Grade I.
D. Anaplastic meningiomas (WHO Grade III) carry a median overall survival of less than 3 years.

5. Which of the following is *not* true concerning the use of radiation therapy (RT) in the management of meningioma?
   A. There is a large body of retrospective literature indicating that (RT) improves local control following subtotal resection.
   B. Progression-free survivals following either fractionated RT or stereotactic radiosurgery (SRS) for a known or supposed WHO Grade I meningioma are very similar.
   C. With fractionated RT or SRS, it is necessary to include the "dural tail" within the target volume.
   D. Fractionated RT or SRS may be employed in selected patients diagnosed by imaging criteria, without histopathologic confirmation.

Answers

1. B
2. C
3. D
4. C
5. C

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