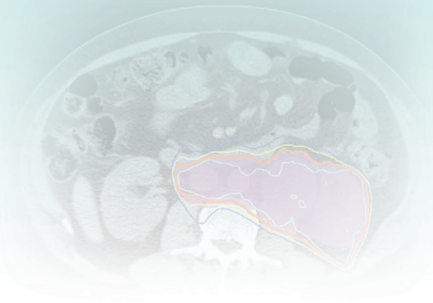
Overview



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Since the last edition of this book, significant advances in neurooncology have been made that have changed the standard of care for several central nervous system (CNS) neoplasms, and these are reviewed in detail in the following chapters. The purpose of this overview is to present the "headlines" relative to these major practice events, which will then set the stage for the reader to delve into greater detail in the ensuing chapters.

SPECIFIC TUMORS: GLIOMAS AND LYMPHOMA

For *glioblastoma*, despite a name change from the prior glioblastoma multiforme (GBM), few true advances in survival prolongation have been identified. Two major efforts, focused at dose-intensifying temozolomide and incorporating antiangiogenic strategies, have failed to prolong survival. However, for recurrent glioblastoma, antiangiogenic agents have become well-established in practice, and newer technologies such as alternating electric field devices are emerging as options. More importantly, an explosion of molecularly driven knowledge has opened up several avenues, for example, the recognition that the benefit of temozolomide in methyl-guanine methyl transferase (MGMT)-unmethylated tumors might in fact be a reflection of undetected methylated tumors; that some subsets of GBM might actually benefit from antiangiogenic strategies (based on preliminary analysis); and the rapidly emerging investigation of immune checkpoint inhibitors and vaccine-based strategies. Management of elderly patients with GBM, always a major challenge, is also being rapidly refined, with the understanding that as far as single agent therapy alone is being contemplated, temozolomide might be superior to radiotherapy for methylated tumors, with the converse being true for the unmethylated tumors.

For *anaplastic gliomas*, the role of combined modality chemoradiation has now become truly established with the recognition of a major benefit in overall survival with procarbazine/CCNU/vincristine (PCV) plus radiotherapy especially in the 1p19q co-deleted tumors. Further, it appears that the survival benefit seen with concurrent chemoradiation in the 1p19q non codeleted anaplastic oligodendroglioma might in fact be limited to the cohort of patients with mutated isocitrate dehydrogenase (IDH), and in fact IDH mutations might supplant 1p19q analysis in this context. In practice, this has posed a major conundrum, because of practitioner preference for temozolomide, which is currently being compared to PCV in a randomized trial, with only limited prospective data supporting the use of temozolomide in this context. More importantly, even though there are no categorical data to support such an approach, there is an emerging trend to withhold radiotherapy from some of these patients, driven in large measure because the long-term survival of these patients raises the specter of delayed radiotherapy toxicities. However, advances in the realm of intensity-modulated radiotherapy (IMRT) have now convincingly demonstrated improved cognitive sparing and such techniques are rapidly being adapted in practice. The significant increase in the number of proton centers is also allowing greater access to this technology, which is also associated with clear dosimetric advantages, the clinical benefits of which remain to be categorically demonstrated.

For *low-grade gliomas*, chemotherapy historically had no role; recent results from seminal trials conducted by the Radiation Therapy Oncology Group (RTOG) and other North American cooperative groups with long-term follow-up now provide convincing evidence of major survival benefit from combined chemoradiation, compared to radiotherapy alone for all patients older than the age of 40, and for patients who are subtotally resected, irrespective of age. This survival benefit also comes from PCV chemotherapy, and limited data supporting similar possible outcomes are beginning to emerge when PCV is replaced with temozolomide. Whether radiotherapy could be withheld or not remains an investigational question and data from a recently completed prospective randomized European Organisation for Research and Treatment of Cancer (EORTC) trial will likely provide the answer in the near future. The role of molecular fingerprints determining the extent of benefit and identifying appropriate subsets is being unraveled, and as would be expected, MGMT, 1p19q, IDH, and several others are being intensively interrogated. Clearly, for most gliomas, therefore, the landscape appears to be shifting in favor of combined chemoradiation, and especially in the context of molecular subtyping to identify tumors most likely to benefit.

For *lymphomas* of the CNS, major survival gains have been made with high-dose methotrexate-based regimens, and biological agents such as rituximab in conjunction with chemotherapy are rapidly being incorporated into practice based on the results of two recent clinical trials.

IMAGING

Despite the superb detail provided by today's high-resolution high-field magnets, a major limitation of magnetic resonance imaging, especially for infiltrative neoplasms, is definition of the true extent and range of spread, something that no established imaging technique comes even close to estimating with precision. The unusual phenomena of pseudo-progression, and more recently, pseudo-response, rarely seen outside the

CNS continue to pose a further diagnostic conundrum, and new and more sophisticated biologically based imaging is being developed for this purpose.

The success of local therapies such as surgery and radiotherapy is comprehensively dependent on accurate estimation of tumor extent. As several studies have now demonstrated, current imaging is simply inadequate for this, especially for detecting microscopic infiltration, which in CNS neoplasms can assume extremely complicated patterns, such as along fiber tracts, along subependymal planes, through the cerebrospinal fluid, by exhibiting "skipping" and "multifocality," and more recently the presumed phenomenon of "cooption."

PRIMARY THERAPY: SURGERY AND IRRADIATION

The surgical challenges in the CNS remain immense. Unlike other anatomic sites, the concept of "redundant" tissue simply does not exist in the brain and spinal cord, and therefore, every surgical procedure is technically risky, and en bloc oncologically complete resections with wide margins are almost impossible. Before the advent of pre- and intraoperative neuronavigation with three-dimensional (3D) navigating capabilities, intraoperative microscopes, the availability of brilliant illumination, improved instrumentation and techniques for hemostatsis, as well as neuroanesthetic advances, aggressive resections with an intent to remove all visible tumors were infrequently undertaken. The consequences of this were multiple. Many tumors remained "imaging and clinical diagnosis," for example, skull-base meningiomas, vestibular schwannomas, brainstem gliomas, and presumed pineal germ cell tumors. Inclusion of these tumors, with uncertain diagnosis, as well as uncertain clinical behavior, makes interpretation of generalized treatment results inaccurate. Further, a tendency toward "small" biopsies was common, adding to diagnostic uncertainty. And most importantly, although level 1 evidence is sparse, an increasing body of literature suggests that more complete resections are important for almost all CNS neoplasms, a trend that has clearly increased in practice in the last decade. Agents to guide complete resection through tumor-specific visualization have already been approved in Europe and remain under investigation in the United States; their advent could be practice changing.

Advances in radiotherapeutic techniques over the last two decades have had a major impact in neurooncology. Because the majority of cell populations within the CNS have a low mitotic index, and proliferate slowly, they are the prototypical "late-responding tissues" of conventional radiobiologic literature. Consequently, the effects of CNS radiation are sometimes not apparent for years, and even then, the historic approach has assumed that "all brain is equally sensitive," with a nascent appreciation of compartment and cell-type specific radiosensitivity. This, too, is changing rapidly, and the advent of 3D conformal, stereotactic, IMRT, image-guided radiotherapy (IGRT), and proton solutions now offers unique opportunities for altering the therapeutic index in CNS tumors. Some elegant and practical examples include the avoidance of the optic apparatus during stereotactic radiosurgery (SRS) to prevent blindness, cochlear sparing with IMRT in children with medulloblastoma to spare hearing, minimizing the dose to the hypothalamic-pituitary axis to avoid endocrinopathies, the emerging hypothesis of compartmental stem cell sparing to retain neurogenesis and hence memory, etc. The recent QUAntitative estimates of Normal Tissue Effects in the Clinic (QUANTEC) analysis provides a new dataset for normal tissue tolerance, and although still limited in scope, it is substantially improved over what was available just 3 years ago for the treating physician. This should help standardize dose-selection practices.

SUMMARY

In the series of detailed chapters that follow, a team of internationally acclaimed authors, infused with this newfound enthusiasm in neurooncology, review the issues I have highlighted in considerable detail. This will provide the treating physician with an up-to-date resource that is practical, comprehensive, and thoroughly referenced, which we hope will ultimately serve our patients' needs.