Curr Probl Cancer 39 (2015) 70–88

Contents lists available at ScienceDirect

Curr Probl Cancer

journal homepage: www.elsevier.com/locate/cpcancer

A new paradigm in treatment of brain metastases

Mark W. McDonald, MD, Kevin P. McMullen, MD

History of radiotherapy in management of brain metastases

Anectodal reports of clinical improvement in patients with brain metastases following "well-placed, moderate x-ray therapy" were reported as early as 1931, supporting the role of even primitive radiation techniques in palliation of patients with brain metastases.[1] In this era before the introduction of computed tomography (CT) and magnetic resonance imaging (MRI), patients with brain metastases presented with significant clinical symptoms. "Hemiplegia and incontinence are usually present by the time the patient is referred to the radiotherapist, and many have fits and papilledema" reported the first critical assessment of whole-brain radiation therapy (WBRT) in 1954.[2] Symptomatic improvement in most patients justified application of palliative whole-brain radiation in patients judged to have more than a few weeks of life expectancy.

Current scope of the problem of brain metastases

Although patients still present with seizures and motor and sensory deficits from metastatic brain disease, the increased use of MRI means more patients may be diagnosed with minimally symptomatic or asymptomatic metastatic brain disease. The subsequent result is a more heterogeneous population than in historical series with varied performance status and prognosis. There appears to have been an overall increase in the number of patients diagnosed with brain metastases, perhaps related to increased MRI utilization, increasing cancer incidence, or increasing cancer survivorship.[3] As cancer therapies improve and patients survive longer, they are at risk for development of brain metastases over a longer duration. Although the US incidence is not tracked, an estimated 170,000 patients are diagnosed with brain metastases in the US each year[4]; some estimates are as high as 300,000 cases per year.[5]

Whether at presentation or in the event of future progression, brain metastases have potentially devastating sequelae including severe headaches, seizures, and both focal and global neurologic and neurocognitive deficits. Treatment-related side effects include morbidity and mortality associated with steroid use, surgical intervention, radiotherapy, and a significant financial burden for patients, families, and payers. The overall cost of management for patients

http://dx.doi.org/10.1016/j.currproblcancer.2015.03.001

with brain metastases will potentially continue to increase with the development of more sophisticated local and systemic therapies, and prolonged survival in a subset of patients who may require multiple central nervous system (CNS)–directed therapies.

The blood-brain barrier creates a sanctuary site for metastatic disease, which is relevant in the development and evaluation of new drugs and creates challenges with increasing cancer survivorship. One example is the development of trastuzumab, an effective monoclonal antibody for systemic treatment of human epidermal growth factor receptor-2–positive breast cancer. Effectively treating systemic disease and prolonging survival in these patients, trastuzumab uncovered the brain as a sanctuary site for distant metastases, resulting in an apparent increased incidence of brain metastases in these patients who would not previously have survived long enough to clinically manifest brain metastases.[3] More effective systemic therapies have created a population of patients with stable or slowly smoldering extracranial disease, which may seed the CNS potentially multiple times during the course of their disease.[4-6] Clinical trials of new drugs often require CNS imaging before and during enrollment, particularly when the CNS bioavailability and effect of the study drug is uncertain, which can preclude trial enrollment[7] and increase the detection of asymptomatic brain metastases.[8]

Radiation therapy continues to play a role in the management of many patients with brain metastases. Technological advances in delivery of radiotherapy and an increased appreciation of the potential neurocognitive toxicities of cranial radiation have led to an ever-increasing body of evidence for new approaches, which are rapidly changing the management of brain metastases to an increasingly tailored approach. The new paradigm in the management of brain metastases revolves around the simultaneous goals of improving local control of index lesions and preserving or protecting neurocognitive function. Several strategies in this new paradigm are reviewed here, including upfront stereotactic radiosurgery (SRS) to delay or defer whole-brain radiation,[9-12] repeat salvage SRS in lieu of whole-brain radiation,[13,14] surgical resection coupled with SRS to the resection cavity,[15] hippocampal-sparing WBRT,[16] and WBRT with pharmacologic neurocognitive protectors like memantine.[17]

Origins and patterns of spread

Parenchymal brain metastases develop from hematogenous (primarily arterial) spread of disease. The precipitating event is often a “shower” of tumor emboli, which, like other emboli, typically lodge in the terminal arterial capillary beds at the gray-white matter junction of the brain.[18,19] Other sites of CNS involvement from metastatic disease include the leptomeninges via cerebrospinal fluid (CSF) spread, pachymeningeal spread from direct extension of skull metastases or by perineural or hematogenous spread,[20] and epidural usually from direct extension.[21] Some primary brain tumors such as medulloblastoma, ependymoblastoma, pineoblastoma, and other primitive neuroectodermal brain tumors have a high occurrence of CSF dissemination and leptopmeningeal spread; specific histologies of leukemia and lymphoma also have a high risk of CSF dissemination.[22] For the purpose of this review, we are concerned primarily with parenchymal brain metastases.

Lung cancer, breast cancer, melanoma, and gastrointestinal malignancies represent the most common source of brain metastases. Most brain metastases are supratentorial (~80%), with the remainder arising in the cerebellum (~15%) or brainstem (~5%), proportional to the distribution of CNS blood flow.[23] Brain metastases from pelvic and retroperitoneal malignancies occur at a higher frequency in the posterior fossa, which is theorized to be due to retrograde spread along Batson (paravertebral) venous plexus.[24]

Presentation, workup, and initial management

Using pooled data from 2 series totaling 392 patients with brain metastases, Klos and O'Neill[5] reported that approximately one-third of patients were asymptomatic at diagnosis. Increased