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Toxicity of Cranial and Spinal Cord Irradiation

Jason Naziri and Steven J. DiBiase

Abstract

Along with surgery and chemotherapy, radiation therapy is an essential treatment option for metastatic and primary tumors of the central nervous system. Radiation toxicity may be compartmentalized into three subcategories including acute toxicities, early-delayed and late delayed effects. Radiation induced toxicity spans from self-limiting fatigue to more serious delayed side effects of radionecrosis. Stereotactic radiosurgery has recently emerged as a highly focused delivery method of tumoricidal irradiation with promising results compared to whole brain irradiation in many cases. Recognizing and understanding toxicity from cranial irradiation can help guide therapy as ever evolving new technologies develop within this integral component of cancer treatment.

Keywords: cranial irradiation, CNS toxicity, stereotactic radiosurgery, radionecrosis, radiation induced brain toxicity

1. Introduction

Treatment of central nervous system (CNS) tumors involves surgery, chemotherapy, radiation therapy, immunotherapy, or a combination of these modalities. Radiation therapy is a highly effect treatment that plays a role in the management of brain metastases, gliomas, primary central nervous system lymphomas, and meningiomas among other brain tumors.

Radiation toxicity can be divided into three subcategories including acute toxicities, usually arising within 6 weeks of treatment, early-delayed effects (up to 4 months post-irradiation) and late delayed starting 4 months after completion of radiation therapy to several years later.

Central nervous system toxicity can be better understood by compartmentalizing toxicities based on cell biology. Injury to brain parenchyma effected by radiation includes neuronal cells, glial cells, and vasculature. Surprisingly, side effects of radiation are likely not due to damage directly to neuronal cells [1]. This is in part due to the paucity of cell replication of most neurons. As such, radiation toxicity primarily effects glial oligodendrocytes which are the insulating myelin producing cells and glial astrocytes responsible for the essential blood brain barrier. Endothelial vasculature of post-capillary venules within brain parenchyma are also highly susceptible to damaging effects of ionizing radiation. Increased cranial pressure and edema caused by radiation is deemed to be related to damage to endothelial cells [2]. In addition to direct damage to the endothelia, the tight junctions of endothelial cells are another component of the blood-brain barrier. The saliency of

the blood brain barrier and the susceptibility to damage by irradiation, makes it a point of focus when discussing CNS toxicity.

Not all neuronal cells are uniformly resilient to ionizing radiation. Recent studies have shown extreme sensitivity to even low-dose irradiation to the hippocampus. This is due to damage to highly proliferative neuronal progenitor cells. Specifically, the subgranular zone (SGZ) of the dentate gyrus has been shown to be extremely susceptible to damage to progenitor cells. Research for why these phenomena exists is ongoing. In addition to direct damage to neural progenitor cells, recent studies have linked neuronal damage to endothelial vasculature within the SGZ. Loss of integrity of inter-endothelial tight junctions (and eventually the blood brain barrier) causes edema and an inflammatory response that prevents the proliferation of neuronal progenitor cells. Clinical manifestations of impairment within this very crucial part of the CNS (the dentate gyrus of the hippocampus which is responsible for transitioning short term memories into long term memories) is linked to the irreversible late delayed side effect of cognitive dysfunction [3–5]. It is worth mentioning that these sequelae of radiation to the hippocampus can manifest even with doses as low as 2 Gy or less [6, 7]. Strategies to preserve neurocognitive function in patients receiving whole brain radiation therapy now include hippocampal sparing techniques [8, 9]. Hippocampal avoidance is one of many creative strategies postulated by radiation oncologists to aid in minimizing toxicity. Modern radiation delivery techniques are beyond the scope of this chapter. Some of these modalities used to avoid sensitive anatomic regions and decrease healthy tissue exposure include IMRT, stereotactic radiosurgery, and proton therapy. These novel modalities of radiation therapy continue to be refined in hopes of decreasing brain injury and increasing local control.

Astrocytes also play an important role in support and function of neurons. The cell line responsible for proliferation and differentiation of astrocytes and oligodendrocytes is the oligodendrocyte type-2 astrocyte progenitor cell (O-2A) [2]. In addition to being a crucial component of the BBB, astrocytes have been shown to be homeostatic regulators providing multiple heterogeneous functions including protecting brain parenchyma from reactive oxygen species [10]. Neuroinflammation and reactive astrogliosis caused by irradiation to astrocytes and O-2A, disrupt the BBB and likely play a role in edema.

Therapeutic techniques investigating the loss of neurogenesis are also underway. Inflammation is primarily instigated by microglial cells. Decreasing the inflammatory load within the SGZ by using a nonsteroidal anti-inflammatory, namely indomethacin in this case, helped preserve neuronal progenitor cells [6]. Reducing the inflammatory load caused by radiation may decrease CNS toxicity which in this study was cognitive decline. Prophylactic nonsteroidal anti-inflammatory drugs are not currently standard of care in preventing radiation side effects.

As mentioned earlier, glial cells are by far the most abundant types of cells within the CNS and responsible for neuronal support and protection. Glial progenitor cells which gives rise to oligodendrocytes and astrocytes are vulnerable targets of damage induced by radiation. In addition to glial progenitors, fully differentiated oligodendrocytes are also known to be sensitive to radiation. Enough damage to the DNA of oligodendrocytes can induce a P53 dependent apoptosis [2, 11]. Taking these two cell lines into consideration, damage to myelin producing oligodendrocytes in addition glial progenitor cells responsible for generating new oligodendrocytes and astrocytes leads to CNS toxicity [2]. Treatment strategies to ameliorate CNS toxicity focused on re-establishing the efficacy of glial progenitor cells are ongoing. To date, optimal treatment for CNS toxicity is still unknown and strategies for managing side effects have yet to be delineated.

When considering the source of CNS toxicities, it is important to take into consideration the timeframe of manifestations, the specific presentation of symptoms,

as well as whether the volume treated and dose deliver are compatible with side effects to the CNS. Other modalities of treatment including chemotherapy and immunotherapy as well as tumor progression can also have adverse effects on brain parenchyma on a cell biologic level. Deciphering the cause of CNS injury is not completely understood but should be taken into consideration in guiding treatment options.

2. Acute and early-delayed toxicities of cranial irradiation

Early side effects of radiation treatment are considered to manifest during or within 6 weeks of completion of radiation therapy. Acute side effects are usually transient and self-limiting, due to transient demyelination [3]. Symptoms are rare but may include fatigue, nausea, vomiting, headache, and focal neurologic deficits. These reported side effects were historically common with patients receiving doses >2 Gy per fraction. Reflected in current NCCN guidelines, most clinicians do not deliver conventional doses that exceed 2 Gy in one fraction as to avoid side effects. Acute radiation toxicities are rare with modern techniques with reports of grade 3 and 4 acute toxicities occurring in <5% of patients and are usually self-limiting [12].

Side effects occurring within 4 months of radiation treatment are considered early delayed effects and most commonly involve transient demyelination and somnolence. Similar to acute toxicities, early to late side effects are usually reversible and resolve spontaneously.

2.1 Fatigue

One of the most common side effect of radiation therapy to the central nervous system is fatigue and lethargy. Similar to patterns of irradiation outside of the CNS, side effects are cumulative and initially start to present 2 weeks into therapy [13, 14]. Fatigue usually starts around 2 weeks of therapy, peaks at or around completion of therapy, and resolves within several months. A severe form of fatigue, lethargy, and lack of concentration is known as somnolence syndrome (SS). SS typical occurs as an early delayed toxicity approximately 5–6 weeks after completion of radiation therapy. In one study, patients receiving a hypofractionated treatment plan compared to conventional fractionation experienced more severe fatigue [15].

2.2 Alopecia and radiation dermatitis

Another common side effect of acute radiation toxicity is hair loss. Alopecia from radiation only occurs in areas where hair follicles are exposed to radiation and therefore can be sparse depending on scalp exposure. Alopecia can be permanent or temporary with higher doses to the scalp signifying permanent hair loss [16]. Radiation dermatitis is a desquamating rash that can occur to areas of the scalp exposed to radiation. Most cases are mild and are treated with moisturizing ointments. In severe rare cases of moist desquamation, topical antibiotic ointment may be used.

3. Late-delayed toxicities of cranial irradiation

Late-delayed side effects are of the most concern when discussing radiation toxicity. These effects occur starting after 4 months of treatment up to decades later. Unlike acute and early-delayed side effects, late-delayed side effects are largely irreversible and progressive.

3.1 Cumulative effects

Decline in neurocognitive function in patients with brain tumors is a multifactorial phenomenon. The connection between radiation toxicity and cognitive decline has been well documented. Nevertheless, it is important, however, to consider other factors as well as cumulative effects contributing to cognitive decline. Many patients treated with radiation are also treated in combination with chemotherapy. Multiple new targeted therapies have also been approved for use. Given that each of these individually may cause CNS side effects, it is of utmost importance for healthcare providers to be able to recognize toxicity and delineate whether symptoms are indeed being caused by treatments (either in combination or individually). Furthermore, there are multiple other reasons for why patients may have CNS complications, including tumor progression and advancement of pathologies unrelated to malignancy (dementia, depression, polypharmacy, anxiety, etc.).

3.2 Long term delayed effects

There exist patients who have undergone radiation treatment with an overall survival of multiple years and even decades. For many, cognitive deficits have not arisen even after 6 years of follow-up [6, 13]. Most patients even after 6 years have maintained a stable neurocognitive status. Differences in cognitive deficits were seen, however, in patients with low-grade gliomas who received radiation compared to patients who were radiation naïve after a 12 year follow up [6]. It is worth mentioning however that patients who do receive adjuvant radiation in low grade gliomas are more likely to have local control, better progression free survival and overall survival [14]. Multiple considerations should be taken into account when deciding the correct treatment plan for each individual patient. In the case of low grade gliomas, radiation and chemotherapy with procarbazine, CCNU, and vincristine is recommended by current NCCN guidelines. Given that neurocognitive effects are being reported over a decade after radiation treatment and less so at 6 years, additional long term delayed effects are of more trepidation now compared to years prior.

4. Stereotactic radiosurgery

Advances in the technique and technology of radiation treatment to the brain has given rise to stereotactic radiosurgery. The use of localized radiosurgery in the setting of metastatic disease compared to whole-brain radiotherapy is an ongoing and complex discussion. In general, brain metastases arise from hematologic dissemination and have a poor overall prognosis [17]. Whole brain radiation has been utilized given the assumed likelihood of "seeding" or micrometasis to areas of the brain outside of visible metastasis seen on imaging. As mentioned earlier however, whole brain radiation therapy has high rates of toxicity, the most serious being cognitive impairment without the added benefit of overall survival [18–20]. It is worth mentioning that the concept of oligometastases has arisen among oncologists whereby disease may in fact be truly limited and treated as such. SRS alone, or in combination with whole brain radiation therapy, has thus become a viable option in single lesions or oligometastases. Being a localized modality of treatment, SRS alone has a higher likelihood of intracranial progression when compared with SRS in combination with WBRT. There has not been shown an increase in overall survival nor a better side effect profile with the addition WBRT to SRS vs. SRS

alone [19, 20]. Researchers have also concluded that the addition of WBRT results in excess morbidity and a decreased quality-of-life resulting in a 35% increase in neurocognitive deficit compared to SRS alone at 12 months. In one study, there was also a non-statistically significant survival benefit with SRS alone compared to SRS with WBRT [20]. Even with the better distant control of the addition of WBRT to SRS, the increase in morbidity does not outweigh the benefits and thus SRS alone is preferred.

Another viable option for limited brain metastases is surgical resection. Given similar outcomes in overall survival with surgical resection, decreased cost and, most importantly, less invasive nature of treatment compared to neurosurgery, SRS treatment of metastasis is being widely used [19, 21, 22].

The most common long term side effect of SRS is radionecrosis. While in certain cases radionecrosis can cause serious neurocognitive deficits requiring steroids or even surgical resection, certain patients remain asymptomatic and are diagnosed on imaging studies. Only about one third of patients with radionecrosis present with symptomatic neurologic deficits [23, 24]. Image based diagnoses can be difficult to distinguish from other phenomena including self-limiting inflammation [25]. There is a wide range of reported data on the rate of actuarial radionecrosis. In recent studies with adequate follow-up, rates vary from as low as 1.5% [26] to as high 34% [19, 25, 27] The main risk factor of radionecrosis are total dose, maximum tumor diameter and treated volume [25, 27, 28].

Given the variability in data and to help gain a better understanding of risk factors for radionecrosis, it may be salient to delineate the setting in which SRS is being administered. Prevalence of radionecrosis can be divided based on single fraction treatments, hypo fractionated treatments (usually three fractions), and adjuvant SRS after resection.

In patients receiving single fractionation SRS, the risk of radionecrosis are reported to be higher compared to hypofractionated [24]. Additionally, local control in hypofractionated regimens have had similar outcomes. Current NCCN guidelines recommend either single fraction or multi-fractionated SRS for the treatment of brain metastases, with multiple fractions utilized more commonly in patients with larger lesions [25, 29].

Not all patients radiologically diagnosed with radionecrosis are symptomatic. For patients that are symptomatic common manifestations include headache, seizures, motor deficits, sensory deficits, ataxia, and speech deficits [25].

In the past decade, SRS has more frequently been utilized in the post-resection adjuvant setting of brain metastases rather than WBRT. In hopes of optimizing local control and overall survival, SRS is administered to the tumor bed with the goal of covering subtotal resections and unrevealed disease that may have been left behind. In this setting, the prevalence of radionecrosis is varied with trends towards decreased toxicity with hypofractionated schedules compared to single fraction SRS [23, 26, 30]. The region of the brain being irradiated may have implications of morbidity as well. Infratentorial metastases are particularly problematic in that they portend worse outcomes and have a higher rate of radionecrosis [30]. Patients with higher risk of radionecrosis, including large tumors >3 cm, should be considered for hypofractionated treatment.

Another method of predicting radionecrosis in patients being treated with SRS is looking at volumes of brain parenchyma receiving a specific dose. Specifically, volumes receiving 10 Gy (V10) and 12 Gy (V12) have demonstrated strong predictive value in single fraction SRS [24, 25, 31]. The risk of radionecrosis can be predicted using specific volumes that receive certain doses. For example, risk of radionecrosis for V12 of less than 10 cm^3 is 22% compared to more than 10 cm^3

which more than doubles the risk to 55% [32]. Novel studies have proposed using V12 as the standard method of reporting dose to assess toxicity [25]. For patients receiving V12 of <8.5 cm^3, the risk of radionecrosis increase to >10% and patients should be considered for hypofractionated rather than single fraction SRS [25].

Options in the treatment of radionecrosis includes steroids, hyperbaric oxygen, and surgery. There exist novel therapies such as bevacizumab and focused interstitial laser thermal therapy with variable efficacy in treatment [33].

Stereotactic radiosurgery (SRS) is usually well-tolerated and risks of high grade toxicity are low. The most important sequelae of SRS is radiation necrosis. Risks and benefits must be weighed out on an individualized basis using an evidence based and patient centered approach.

5. Hypopituitarism induced by radiation

Endocrine deficiencies have also been reported in lesions irradiated near the hypothalamic-pituitary axis or pituitary gland. The prevalence of endocrinopathies are higher with nasopharyngeal cancers compared to intracerebral tumors, yet there were no differences in the rate of endocrine dysfunction based on underlying tumor type [34]. Endocrinopathies may include panhypopituitarism, hypothalamic hypothyroidism, and hypothalamic hypogonadism among others. A significant portion of the pediatric population treated with radiation therapy are vulnerable to pituitary dysfunction, most commonly growth hormone deficiency revealing short stature and retarded growth [35].

Patients with the pituitary adenomas are commonly treated with either single fraction SRS or hypofractionated SRS with similar rates of efficacy in tumor control and prevalence in new-onset hypopituitarism. Rates of hypopituitarism vary but are reported to be as high as 66% in conventional radiotherapy and significantly lower with stereotactic radiosurgery 5–37% [35–39].

Endocrine dysfunction is considered a late-delay side effect, but current literature is lacking in predicting a timeline for when hypopituitarism can occur. Follow up with dynamic serum hormonal values is of paramount importance given higher likelihood of developing endocrinopathies with longer follow up [35, 37].

6. Radiation induced optic neuropathy and stereotactic radiosurgery

Certain tumor types treated with SRS expose the optic nerves to high doses of radiation that may induce a decrease in visual acuity and blindness. Deterioration of vision may be reversible in an acute setting and is more likely to be permanent >6 months after treatment. Optic neuropathy from radiation is usually painless and can be monocular or biocular depending on whether optic nerves or the optic chiasm are exposed to radiation. Doses of radiation to optic nerves are closely monitored and circumvented as best as possible for patients receiving treatment for meningiomas, pituitary adenomas, and craniopharyngiomas.

Significant risk factors for radiation-induced optic neuropathy include prior radiation re-exposure to the optic chiasm. Prior EBRT and SRS are both risk factors for radiation induced optic neuropathy. Although multiple centers consider <8 Gy to be the upper limit of acceptable tolerability, single fractions of <12 Gy have been validated by recent literature [40–42]. A large recent analysis of pooled data consider the risk of radiation induced optic neuropathy to be 0–2% in patients with no prior irradiation to the optic apparatus and a single fraction <12 Gy [42] and even lower (<1%) for patients with a single fraction of <10 Gy [43].

7. Toxicities of spinal cord irradiation

Radiation myelopathy is the term commonly used for side effects of radiation toxicity to the spinal cord. Late effects of radiation myelopathy are a serious concern for radiation oncologists during treatment planning of CNS as well as extra-neural tumors within the treatment field. This is, in part, due to higher doses of radiation required for certain tumors (lung, certain head and neck, mediastinal tumors). Moreover, metastatic disease to the spine often requires radiation therapy and is becoming more common thanks to the advent of immunotherapy [44]. Long term effects may cause life limiting sequelae and are of paramount concern to radiation planning and treatment.

Adverse facts of spinal cord irradiation are largely determined by the radiation treatment field and can affect both the central and peripheral nervous system. Just as side effects can be subdivided by timeframe in radiation toxicity to the brain, toxicities of spinal cord irradiation are classified as early toxicity, early-delayed effects, and long term effects. Accordingly, the durations are during treatment and up to a couple weeks after treatment, within 3 months of treatment, and more than 3 months after treatment. Although acute central nervous system damage has been reported following acute brain irradiation, there is no clinical or experimental evidence that radiation induces acute spinal cord toxicity. Single doses of up to 100 Gy have been given without acute effects [32].

Significant advances have been made in the treatment of spinal malignancies extrapolating progress made from cranial stereotactic techniques of within millimeter precision high dose focal treatment plans. Recently, SRS has also been utilized for metastasis to the spinal cord. It is important to note that metastasis to the spinal bone, although extremely painful at times, does not carry the risk of neurologic compromise posed by spinal cord tumors or spinal impingement.

Side effects using SRS are extremely rare for spinal tumors. Short-term toxicity although more common, are still at low rates and are usually self-limiting [45]. One study showed no long term side effects with SRS patients with spinal metastasis.

It seems as if long-term toxicity from radiation using SRS and dose sparing techniques to organs at risk is extremely rare with modern treatment techniques and attention to dose volume parameters. The complication of vertebral compression fracture (VCF) is multifactorial including older age portending to higher incidences osteoporosis but may be attributed to, in part, radiation therapy [46]. Doses above 20 Gy in a single fraction have been implicated as a risk factor. The risk of VCF tends to occur in the acute period of toxicity [47].

The main factors associated with risk of neurologic deficit relate to total dose, length of spinal cord irradiated, fractionation scheme and total duration of treatment. An absolute threshold for development of myelopathy cannot be stated. There has not been an established threshold; however the risk of myelopathy varies from 0.2 to 5% at 5 years [39]. Another side effects or radiation to the spine is characterized by acute paralysis presumably secondary to ischemia. Brown-Séquard syndrome is another rare syndrome that has been documented and is characterized by paralysis and loss of proprioception to the ipsilateral side and loss of pain and temperature to the contralateral side. Similar to irradiation to the brain, the greatest concern is delayed-onset radionecrosis of the spinal cord.

Common types of side effects for single dose SRS with 10–16 Gy include: neurologic signs of motor weakness and sensory changes of the extremities [48]. There was no detectable acute or subacute radiation toxicity in this series noted clinically during the maximum follow-up time of 24 months. Other more disabling manifestations of radiation injury, including acute paralysis secondary to ischemia, hemorrhage within the spinal cord, and a lower motor neuron syndrome, are much less

common, with only a few case reports in the literature. The treatment of radiation myelopathy has not been well studied. High dose corticosteroids are considered first line therapy.

8. Conclusions

Radiation therapy is highly effective in CNS malignancies. Nevertheless, the rate limiting step in treatment is associated with adverse side effects to healthy tissue. As the treatment of CNS malignancies advance with novel therapies and ever evolving therapeutic combinations, the goal of minimizing treatment side effects remains the same. Significant progress has been made in attempting to understand the dynamic mechanisms of brain injury caused by irradiation to healthy tissue. As patients continue to live longer, central nervous system side effects are of utmost importance to recognize and treat. Radiation oncologists among other cancer specialists are putting keen focus and effort towards increasing and optimizing quality-of-life in addition to overall survival in cancer patients.

Conflict of interest

Authors do not have conflicts of interest to declare.

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