Radiation therapy for gliomas

Abstract Radiotherapy remains one of the cornerstones of treatment of patients with gliomas. Radiation-induced damage to DNA can result in the loss of proliferative capacity of neoplastic cells. In addition to mitotic cell death, it has recently been found that other cellular events can lead to reproductive failure. Apoptosis, or programmed cell death, has been described as a response to radiation in many cell types. Gradually, radiation has been found to cause a great variety of other changes in both normal and neoplastic tissue, ranging from necrosis due to changes in the vasculature to alterations in gene expression. As radiosurgery becomes more common and the patients have longer survival, investigators are working to understand the responses of brain tissue to radiation. We present several studies related to the effects of radiation on normal brain and gliomas. One paper suggests a mechanism of radiation-induced reproductive failure that is separate from mitotic cell death and apoptosis. Others describe changes in cytokine regulation and receptor density. After irradiation, necrosis of normal tissue can be indistinguishable from recurrence of the tumor with conventional studies. However, functional imaging can differentiate between neoplasm and functional alterations in tissue due to radiation. While much more work must be done in this field, these papers indicate that radiation therapy results in a variety of cellular and molecular alterations. As a result of these changes, they suggest that irradiated brain tissue is functionally and clinically different from untreated brain.

Key words Radiation · Gliomas · Radiosurgery · Glioblastoma · Apoptosis

Introduction

Cerebral radiation has long been a key component of therapy for brain tumors. Longer patient survival, increased use of aggressive schemes of irradiation, and improvements in noninvasive imaging underscore the importance of understanding the effects of radiation on both normal and neoplastic brain tissue.

The use of radiotherapy to treat malignant tumors is based on the ability of ionizing radiation to produce cell death, defined as the loss of reproductive capacity. At the atomic level, ionizing radiation has both direct and indirect effects on biologic tissues. The major direct effect of electromagnetic radiation (such as x-rays and gamma-rays) is Compton scattering, in which a photon interacts with electrons, deflecting off its
course, and gradually loses energy. Most biologic damage, however, is caused by the indirect effects of ionizing radiation. These indirect effects are due to the formation of reactive free radicals formed when the radiation interacts with water, which is abundant in tissues. These free radicals can react with other molecules, such as oxygen, to form other radicals. This underlies the correlation between tissue oxygenation and radiosensitivity. Ultimately, the free radicals formed react with and damage cellular constituents such as proteins, lipids, and ribonucleic acids. All organelles are subject to damage, but probably the most important biologic effect of radiation is damage to DNA. Radiation damage can be lethal, sublethal, or potentially lethal, depending on the extent of DNA damage and the cell’s ability to repair it. The effects of DNA damage are expressed when cells undergo mitosis. This explains why radiosensitivity of cells is cell-cycle dependent, and why in the central nervous system (CNS) neoplasms and benign proliferating tissues such as the endothelial cells and glia are more vulnerable than the post-mitotic neurons.

In addition to mitotic cell death, irradiated cells can undergo apoptosis, a form of programmed cell death. Importantly, radiotherapy does not rely only on its effects on the malignant cells themselves. Ischemia and coagulative necrosis of the tumor can result from vascular damage within and around the tumor.

Ionizing radiation is not specific for malignant cells. Normal cells around the tumor and in the path of the radiation beam are also affected. The clinical sequelae of radiation therapy largely result from damage to normal tissue. Clinically there is variety in the types of injury caused by cerebral radiation. Acute, early delayed, and late-delayed injury are classified according to how long after therapy symptoms appear. Acute injury occurs within days of irradiation and presents with transient, focal symptoms localized to the area treated. Bright signal on T2-weighted images is consistent with edema found on pathologic examination in animal studies of early radiation injury [Cicciarello et al. (1996) Neurosurgery 38:772].

Like acute injury, early delayed injury also presents with transient exacerbation of focal symptoms and appears from weeks to months after irradiation. Computed tomography (CT) shows low density in the area treated, with bright signal on T2-weighted magnetic resonance imaging (MRI). Few pathologic studies on humans have been done, but studies in animals have found edema, gliosis, demyelination, and changes in the blood-brain barrier (BBB) [Chiang et al. (1991) Brain Res 566:265; Rubin et al. (1994) Radiother Oncol 31:51]. These changes may be mediated by radiation-induced cytokines such as tumor necrosis factor (TNF) and interleukin 1 (IL-1), which may play a role in astrocyte proliferation, oligodendrocyte damage, and alterations in vascular permeability [Hong (1995) Int J Radiat Oncol Biol Phys 33:619].

In contrast to the other two types of injury, late-delayed damage is not transient, presents from months to years after treatment, and can be progressive. Presentations range from headache to focal neurologic symptoms to cognitive or neuropsychiatric alterations. Lesions typically have decreased density on T1-weighted images and CT, with ring enhancement of contrast. Biopsy specimens of patients with late-delayed damage typically show abnormalities in the vasculature such as hyalinization, fibrinoid necrosis, capillary dilatation, thrombosis, and endothelial hyperplasia, accompanied by coagulative necrosis, gliosis, and calcification [Asai et al. (1989) Cancer 63:1962]. Evidence from animal studies indicates that these vascular abnormalities are the primary pathogenetic cause of delayed radiation injury [Tiller-Borich et al. (1987) Radiat Res 110:161; Calvo et al. (1988) Br J Radiol 61:1043]. Dilatation and thrombosis might lead to ischemia and eventually necrosis. Some authors have proposed an important role for glial injury in the demyelination and necrosis seen in late-delayed damage [van der Kogel (1983) In: Gutin et al. (eds) Radiation injury to the nervous system. Raven Press, New York].

While most research on radiation-related cerebral injury has been done on normal brain tissue, the same may also apply to brain tumors. Histologic studies of glioma specimens after radiosurgery show central coagulative necrosis with fibrosis and vascular changes in the periphery. Similar to studies in normal brain after irradiation, these vascular changes include fibrous thickening of vessel walls, thrombosis, and proliferation of endothelial cells and pericytes [Hirato et al. (1995) Stereotact Funct Neurosurg 66 (Suppl 1):4]. Analogous to experiments in benign tissue, medial thickening leads to occlusion and ischemic necrosis in the tumor.

Inevitably, benign tissue as well as tumor is included in the field of radiation. Irradiating a mass of neoplastic and normal cells causes profound effects on a cellular, morphologic, and functional level. The findings discussed above, as well as the studies reviewed here, explore the intriguing possibilities of changes in normal and malignant brain tissue after radiotherapy.