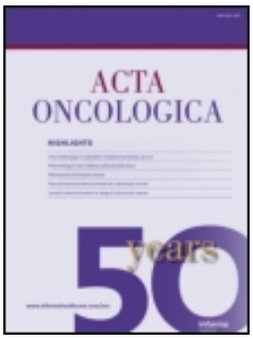

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Pathogenesis of Cognitive Decline Following Therapeutic Irradiation for Head and Neck Tumors

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Cognitive decline is a significant but largely unrecognized sequela following irradiation for several head and neck tumors, particularly cancer of the nasopharynx and paranasal sinuses. In this article the cellular mechanisms of radiation-induced vascular damage in the temporal lobe and its effects on the medial temporal lobe memory systems are described. Recognition of the mechanisms and site of the injury should permit the use of treatment planning systems, such as 3-dimensional (3-D) conformal and intensity-modulated radiotherapy (IMRT) techniques, to spare large volumes of the temporal lobe from receiving a high dose. Furthermore, the emerging concepts of vascular irradiation damage as an inflammatory fibroproliferative response to endothelial injury may permit the application of measures directed at inhibiting the expression of proinflammatory genes and thus mitigate the inflammatory response. Moreover, comorbid factors such as hypertension, diabetes, lipidemia, obesity and smoking are known to promote atherogenesis and therefore may exacerbate radiation-induced vascular damage. Control of these factors may also reduce the incidence and severity of this sequela.

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The problem of cognitive decline associated with irradiation for brain tumors and prophylaxis for leukemia has received much attention in children but less so in adults (1–3). Nevertheless, the problem of cognitive impairment associated with cranial irradiation is well recognized in adults (4–6). Although very little has been written about the neurocognitive sequela of therapeutic irradiation for extracranial head and neck tumors, there is increasing recognition of cognitive decline as a sequela of irradiation in the management of some head and neck tumors (7–10).

Cognitive impairment has been reported in patients irradiated for cancer of the nasopharynx and the paranasal sinuses, glomus tumors, tumors of the auditory canal and parotid gland and pituitary adenomas (7, 10–12). Most of the reported cases of cognitive decline following irradiation of extracranial head and neck malignancies have been among patients irradiated for cancer of the nasopharynx and paranasal sinuses. Because of the anatomic relationships, the temporal lobe is usually irradiated in the treatment of these tumors. Consequently, these patients are at an increased risk for temporal lobe injury (8, 13). A major manifestation of temporal lobe injury is the development of memory problems and learning difficulties (14, 15). There are no reports on the pathogenetic mechanisms of these sequelae following irradiation for cancer of the nasopharynx and paranasal sinuses.

The purpose of this review is to describe the cellular mechanisms of temporal lobe injury and the pathogenesis of radiation-induced cognitive decline in patients treated for head and neck tumors, particularly cancer of the nasopharynx and paranasal sinuses. Possible preventive measures will be discussed in the light of emerging concepts of the mechanisms of irradiation damage to the temporal lobe.

POST RADIATION TEMPORAL LOBE INJURY

Clinical findings

Numerous reports have been published on cognitive decline in patients following cranial irradiation for primary brain tumors or metastases and following prophylaxis for leukemia and small cell carcinoma of the lung (16–18). However, there are only a few reports on brain injury following irradiation for extracranial neoplasms of the head and neck (10, 19, 20). These patients typically present with memory impairment, headache, seizure or dysphasia and on further evaluation are found to have radiological changes compatible with brain injury. A significant proportion of these patients are asymptomatic and only manifest evidence of injury incidentally on follow-up CT or MRI (8, 13).

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Lee et al. reported on the largest series of patients developing temporal lobe injury following irradiation for cancer of the nasopharynx (20). Most of their patients presented with dizziness, impairment of memory, headache and confusion. CT findings in these patients included areas of decreased attenuation in the temporoparietal region and most of the patients showed contrast enhancement, predominantly in the medial temporal region within the target volume. CT and histological confirmation of injury was obtained in 12 patients who had undergone a biopsy or had gone to autopsy. Temporal lobe necrosis represented the extreme of a range of injuries that had been sustained by the temporal lobe following irradiation in these patients. The development of late temporal lobe necrosis was correlated with treatment using a large fraction size. This was confirmed in a later study showing that the fraction size and the volume of temporal lobe receiving a high dose were predictive of temporal lobe injury (21).

Most patients remain asymptomatic despite the appearance of evidence of late radiation damage in the temporal lobe. Leung et al. (8) studied a cohort of 60 patients irradiated for nasopharyngeal cancer and followed prospectively for 1–3.5 years. Nine of the patients developed temporal lobe necrosis during the study period. Five were asymptomatic for temporal lobe injury. The authors drew attention to the high incidence of temporal lobe necrosis within 3.5 years after treatment in these patients followed prospectively and suggested that the incidence was likely to be higher with a longer follow-up. A significantly higher incidence of temporal lobe injury was found among patients treated without eye shields in the anterior field. The omission of the eye shields resulted in the inclusion of larger volumes of the temporal lobe within the target volume. Moreover, patients treated with hyperfractionation schemes delivering 67.2 Gy in 42 fractions in 6 weeks were also at higher risk for temporal lobe injury, and the incidence of temporal lobe injury was 35% in this group. The incidence of temporal lobe injury in the group with omitted eye shields was 56%. Patients with less severe injury to the temporal lobe may present with cognitive decline as the only manifestation of injury.

Lee et al. (7) performed a battery of neuropsychological tests on 16 patients treated with radiation therapy for nasopharyngeal cancer and followed for a median period of 5.5 years. For comparison, the authors tested a comparable group of patients with newly diagnosed nasopharyngeal cancer, awaiting treatment. The tests consisted of information, comprehension, similarities, coding and block design subtests of the Wechsler Adult Intelligence Scale (WAIS). The irradiated group had significantly lower scores on tests of general recall of information from memory, non-verbal concept formation and analytic capabilities when compared with the unirradiated group. The authors concluded that patients irradiated for nasopharyngeal cancer are at increased risk for the development of cognitive decline.

Two other studies of neurocognitive sequelae of irradiation in the treatment of skull base lesions have been reported (10, 22). One series comprised patients with chordomas and low-grade chondrosarcoma of the skull base (22), and the other comprised patients with carcinoma of the paranasal sinuses (10). Those with chordomas and low-grade chondrosarcoma were treated with a CT-based, 3-D planning system. Target volumes in the brain stem, pyramidal tracts, substantia nigra, hippocampi and temporal lobes were outlined. The patients received 80% of the dose from the 160 MSV beam of the cyclotron and 20% from 4–10 MV photons. Dose-volume histograms (DVHs) were developed for each delineated structure. The median dose was 68.4 CGE (cobalt Gy equivalent) (proton Gy x RBE x 1.1) The patients with cancer of the paranasal sinuses were treated with a 2-dimensional (2-D) planning system using cobalt or 6 MV photons with three fields, an anterior and opposed lateral fields. The mean dose was somewhere between 60 and 70 Gy. Both groups received post-treatment neuropsychological testing. The group treated for base of skull chordomas and chondrosarcoma was prospectively studied, while the group treated for cancer of the paranasal sinuses was retrospectively studied. On assessment for effects of cranial irradiation on neuropsychological functioning with full scale IQ assessments using the Wechsler Adult intelligence Scale-Revised (WAIS-R), tests of language, memory and higher attentional functions, the group treated for chordomas and chondrosarcoma manifested no significant changes in post-treatment scores when compared with baseline scores obtained prior to treatment (22). In contrast, when neuropsychological function was evaluated using a battery of tests in the group treated for cancer of the paranasal sinuses, patient performance was significantly below that expected with tests of memory function. Over 50% of the patients experienced difficulty learning new information. Eighty percent of the patients manifested accelerated loss of memory over time, and one-third of the patients had difficulty with motor speed and executive functions (10).

Thus, two studies of patients irradiated for base of skull tumors showed conflicting results on tests for neuropsychologic sequelae. The likely explanation for this finding is the difference in the volumes of the medial temporal lobe receiving full-dose irradiation in the two groups. The group with chordoma and chondrosarcoma was treated using CT-based, 3-D treatment planning techniques and mixed proton:photon beams. This resulted in the inclusion of a smaller volume of the infero-medial portion of the temporal lobe (hippocampus) in the high-dose region. Review of the DVHs in these patients revealed that the mean of maximum dose (to 5% of the volume) to the hippocampi was between 34 and 44 Gy (22). In the group treated for cancer of the paranasal sinuses using 2-dimensional techniques, the medial temporal lobe received a

mean dose > 60 Gy (10). Thus, these studies show that the volume of medial temporal lobe (hippocampus) exposed to a high dose of irradiation is an important factor in the development of neuropsychologic sequelae following irradiation.

Imaging studies

Patients with nasopharyngeal cancer who develop clinical signs of temporal lobe injury following treatment usually demonstrate abnormalities of white matter in the inferior portions of the temporal lobes (13). These areas manifest on MRI as high-signal intensities on the T2-weighted spin echo sequence. CT was found to be less sensitive, but those patients with positive CT manifested characteristic signs of finger-like hypodense areas and cyst-like shadows in the region of the temporal lobe. On the basis of histopathologic studies in these patients, Lee et al. (20) suggested that the finger-like hypodense areas represented reactive white matter edema, while the cyst-like changes represented liquefactive necrosis with surrounding gliosis. In their study of a cohort of 60 patients treated for carcinoma of the nasopharynx, Leung et al. (8) found a correlation between the volume of temporal lobe included in the high-dose region, the fractionation schemes employed, and the risk of temporal lobe injury.

Pathologic findings

Histopathological confirmation of temporal lobe damage following irradiation for nasopharyngeal carcinoma was reported in 12 patients, 3 cases revealed by biopsy and 9 found at autopsy (20). All showed the characteristic findings of radiation damage: varying degrees of coagulative necrosis of the brain parenchyma and fibrohyaline changes in the blood vessels (23). These findings are similar to those found in patients with frank dementia and diffuse white matter hypodensity on CT (24).

THE NATURE OF VASCULAR IRRADIATION DAMAGE

The effects of irradiation are most prominent in the microvasculature (25). The typical features of these changes have been extensively studied. These consist of endothelial damage, hyaline thickening and fibrinoid necrosis of the vessel wall, presence of thrombosed vessels, and infiltration of abnormal multinucleated macrophage cells, loaded with fat (11, 19, 20, 23). Similar changes have been found in vessels damaged by hypertension. Indeed, histologically, atherosclerosis caused by hypertension is identical to atherosclerosis caused by irradiation (26–28). Thus, it has been suggested that blood vessels are damaged by irradiation and hypertension through similar mechanisms (29, 30).

Pathophysiologic studies of atherosclerosis in humans and animals have led to the formulation of a hypothesis that atherogenesis is a fibroproliferative response to injury. Based on these studies, atherosclerosis is now defined as an inflammatory disease, rather than a degenerative disease. The underlying cellular mechanisms have been described (31–36). The process involves interactions among endothelial cells, monocytes, T-lymphocytes, and smooth muscle cells and represents a form of protective response to various types of insults to the artery wall. Thus, irradiation of blood vessels results in the formation of free radicals, which can cause vascular endothelial damage. Endothelial dysfunction results in increased permeability, increased leukocyte migration and adhesion, and formation of vasoactive molecules, cytokines and growth factors. Peripheral blood monocytes and T-lymphocytes invade the artery walls and localize subendothelially, while monocytes are converted to macrophages. These monocyte-derived macrophages become scavenger cells capable of secreting cytokines, chemokines and growth-regulating molecules. Platelet-derived growth factor (PDGF), fibroblast growth factor 2 (FGF2) and transforming growth factor β (TGF_β) stimulate smooth muscle cell migration and proliferation in the wall of the artery. T cells become activated and secrete cytokines, interferon γ, and tumor necrosis factors α and β, which in turn amplify the inflammatory response. Macrophages scavenge oxidized low-density lipoprotein (LDL) to form foam cells (37). The foam cells, together with T-lymphocytes and smooth muscle cells, form the first lesion of atherosclerosis, the fatty streak. The fatty streak can progress through further inflammatory responses to an intermediate fibrofatty lesion and ultimately a fibrous plaque (38). These events can lead to thickening of the arterial wall, plaque formation and thrombosis, disturbance of flow or occlusion of the artery and hemorrhage (32).

Thus, in a manner similar to hypertension and other promoters of atherogenesis, irradiation causes endothelial dysfunction, followed by a fibroinflammatory response that is mediated by cytokines and growth factors and results in vascular changes that may lead to vascular insufficiency and hypoxia. Furthermore, there is evidence that radiation-induced arterial occlusive disease can be exacerbated by hyperlipidemia and hypertension (30, 39).

VASCULAR DAMAGE AND THE MEDIAL TEMPORAL LOBE MEMORY SYSTEM

The medial temporal region is particularly susceptible to the effects of vascular injury. The principal components of the medial temporal lobe memory system have been described. They are the hippocampus, the entorhinal cortex, the perirhinal cortex, and the parahippocampal cortex (40, 41). These areas have extensive connections to the neocortex. Studies in humans and animal models of human amnesia have provided information on the functioning of the memory system (40, 42). Information is perceived in

the neocortex and then transmitted to the perirhinal cortex or the parahippocampal formation, from where it passes through the entorhinal cortex to the dentate gyrus and the CA3 and CA1 subregions of the hippocampus. The information is processed in the hippocampus and exits through the subiculum and entorhinal cortex, returning through efferent projections to the neocortex, for storage (40). The hippocampus and the adjacent cortex integrate and process the perceived information into a single memorable experience that can be recalled. Thus, the medial temporal lobe memory system is crucial for the acquisition of new information as well as its storage and retrieval. Declarative memory, the conscious recollection of facts and events, depends on the integrity of the hippocampus (40, 41). Consequently, damage to the hippocampus and the surrounding cortex results in memory impairment or dementia (40, 43).

The neuropathologic basis of cognitive decline has been studied in humans and animals (44, 45). These studies have shown that disturbances of cerebral blood flow are associated with a decline in cognitive function. Furthermore, there is a strong correlation between the extent of hypoperfusion and the severity of cognitive decline. The CA1 subregion of the hippocampus is crucial for memory formation. Moreover, this subregion is especially sensitive to an impaired microcirculation and hypoxia (45, 46). Thus, microvascular damage from temporal lobe irradiation can result in hypoxic injury that is most severe in the CA1 subregion of the hippocampus, resulting in cognitive decline (45, 47).

PREVENTION

Recognition of the medial temporal lobe as the site of injury, coupled with an understanding of the cellular mechanisms of vascular radiation damage and the potentiating effects of comorbid factors on cognitive sequelae following irradiation for head and neck tumors should provide new avenues for preventive measures.

Studies of patients irradiated for carcinoma of the nasopharynx and chordomas and low-grade chondrosarcoma of the base of the skull provide evidence that limiting the volume of the temporal lobe receiving a high dose lowers the risk of cognitive sequelae (22, 48, 49). A comparison of conventional 2-D radiotherapy planning and 3-D planning for cancer of the nasopharynx revealed significant deficiencies in conventional 2-D techniques. The median volume of gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) covered by the 95% isodose line in the 2-D plan was 60%. When 3-D beam eye views (BEV) customization of the treatment portals was used, there was a significant improvement in the median volume of target covered by the 95% isodose (50). Moreover, with the introduction of a hypothalamico-pituitary shield, 50% of the volume of the optic chiasmata and temporal lobe received 19.3 Gy and 4.5 Gy, respectively, out of a total possible dose of 66 Gy. Thus, by using CT-based 3-D planning, it is possible to deliver the desired tumoricidal dose to the nasopharynx while reducing the total dose and dose per fraction to the temporal lobes. Optimization of treatment by CT-based 3-D conformal techniques and intensity-modulated radiotherapy (IMRT) can permit the exclusion of large volumes of the medial temporal lobe from the high-dose region as well as a reduction in the dose per fraction to the temporal lobes, thereby reducing the risk for cognitive sequelae.

Other risk factors associated with the development of vascular damage and consequent cognitive decline in these patients include coexisting hypertension, hyperlipidemia, diabetes and cigarette smoking (30, 51, 52). Hypertension, diabetes, hyperlipidemia, cigarette smoking and irradiation cause vascular damage by similar mechanisms (28, 30, 51, 52). Studies have shown that hyperlipidemia, hypertension, diabetes and smoking can cause vascular damage and cerebral hypoperfusion. Moreover, there is experimental evidence that hypertension and hyperlipidemia accelerate vascular radiation damage and reduce the threshold dose of irradiation (30, 39). Thus, irradiation-induced vascular damage and the resulting hypoperfusion and cognitive decline can be exacerbated by coexisting hypertension, diabetes, smoking and hyperlipidemia. However, there is evidence for reversibility of the pathophysiological alterations linked to cigarette smoking, hypertension, diabetes, and hyperlipidemia (53–55). Cross-sectional studies of cerebral blood flow have shown that cerebral perfusion levels improve following cessation of smoking (54).

Other studies have demonstrated similar improvements in cerebral blood flow following more effective control of systolic blood pressure (52, 55). Moreover, a randomized clinical trial on patients with dementia receiving daily aspirin therapy showed significant improvement in cerebral perfusion and cognitive performance scores in these patients (56). Similarly, measures such as smoking cessation, exercise, effective management of diabetes, control of hyperlipidemia and obesity, antihypertensive therapy and aspirin have the potential to reduce the severity and incidence of cognitive decline resulting from vascular damage following irradiation for head and neck tumors.

Furthermore, recognition of atherosclerosis as a chronic inflammatory process in the artery presents other modes for limiting the process. Antioxidants can be used to inhibit lipid peroxidation of low-density lipoprotein (LDL) and thereby limit atherosclerosis and its clinical manifestations (57). Antioxidants act by reducing vascular cell oxidation of LDL and the cellular responses to oxidized LDL. Epidemiologic studies have demonstrated that antioxidant intake and a vitamin E supplement in particular reduce the incidence of atherosclerosis (58). Moreover, since endothelial dysfunction is the first step in the process of vascular damage, the endothelium may be a target for therapeutic intervention. Therefore, therapies directed at

inhibiting the expression of proinflammatory genes may be effective in mitigating this process. It may also be possible to inhibit atherogenesis and neuronal damage by targeting inflammation mediators and immune response (adhesion molecules, cytokines and chemokines) (59–61).

Thus, the severity and incidence of cognitive decline in patients receiving head and neck irradiation can be reduced not only by changes in treatment techniques to limit the volume of the medial temporal lobe exposed to a high radiation dose, but by counseling patients about changes in lifestyle such as smoking cessation, control of hypertension, and diabetic preventions such as diet and exercise, and by modification of cellular responses to inflammation. Recognition of the effectiveness of these measures may bring about modification of treatment techniques as well as a more vigorous promotion of these lifestyle changes in patients, following treatment.

CONCLUSION

The problem of cognitive decline following irradiation for head and neck neoplasms is receiving increasing attention. Because temporal lobes receive a significant dose of irradiation in the treatment of cancer of the nasopharynx and paranasal sinuses, patients with neoplasms of these sites are at an increased risk for cognitive decline. This sequela is mediated through microvascular damage and the resulting hypoxia in the medial temporal lobe. The application of 3-D, CT-based conformal treatment planning and IMRT techniques in the treatment of these tumors should make it possible to limit the volume of high-dose irradiation received by the temporal lobes, thereby decreasing the incidence of this sequela.

Furthermore, a new understanding of the cellular mechanisms of radiation-induced vascular damage and its effect on the medial temporal lobe memory system provides new avenues for reducing the incidence and severity of this sequela. This can be achieved by modification of immune response, appropriate management of comorbid conditions such as hypertension, diabetes and hyperlipidemia and by behavior modification measures such as control of obesity, exercise and smoking cessation.

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