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Radiation-Induced Glioma

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<http://dx.doi.org/10.5772/59047>

1. Introduction

Radiation therapy is widely used for patients with intracranial tumors. However, there are many complications, including cerebral atrophy, calcifying microangiopathy, radiation necrosis, leukoencephalopathy and development of radiation-induced tumors [1-5]. Radiation-induced central nervous system (CNS) neoplasms are recognized in patients who have had therapeutic radiotherapy to the head or face [6]. Radiation-induced CNS neoplasms are rare, but the cumulative risk of brain tumor after therapeutic cranial irradiation is reported as 0.5-2.7% at 15 years [7]. Among radiation-induced CNS neoplasms, meningiomas are about 70%, gliomas about 20% and sarcomas less than 10% [4,6,8]. In children, high-grade gliomas are the most common radiation-induced tumor [9]. Type of post-radiation gliomas are glioblastoma (GBM) in 75% and anaplastic astrocytoma in 25% [7]. Brada et al. [6] described a relative risk of secondary glioma of 7.92 times higher than that of the normal non-irradiated population, with an average latency period to glioma diagnosis of 7 years, in 334 patients with pituitary lesions, irradiated to a median dose of 45 Gy for the sellar region. Cahan et al. [10] established criteria to diagnose a radiotherapy induced brain tumor. These criteria were modified in 1972 by Schrantz and Araoz [11] as follows: (1) the tumor must appear within the irradiated field; (2) the tumor was not present prior to the radiotherapy; (3) a sufficient latency period must elapse between irradiation and appearance of the tumor (usually >5 years); (4) the radiation induced tumor must be histologically proven and a different histological type from the original neoplasm treated by the radiation therapy.

2. Radiation-induced gliomas in the literature

In a review of the literature, 191 cases of radiation-induced glioma that analyzed in detail were identified in the period 1960-2014 [9,12-120]. The latency period from the irradiation to the

onset of the secondary glioma ranged from 6 months to 50 years, with an average of 11.1 years. More than 40 Gy irradiation was delivered in 50% of cases, with an average of 37.2 Gy. As shown in Table 1, 29 grade II, 37 grade III and 97 grade IV gliomas had been reported, and no specific grade had been shown in other 28 cases. Grade II gliomas developed after 10.7 years, and grade IV gliomas developed after 10.6 years from the time of irradiation. The radiation dose of grade II gliomas for primary lesion is 29.7 Gy, grade III 37.4 Gy and grade IV 37.3 Gy, respectively. There was a significant difference of radiation dose between grade II and grade IV glioma ($p<0.05$). In Table 2 and 3, the relation of primary lesion and radiation dose, latency to radiation induced glioma occurrence, glioma grade are shown. The latency in acute lymphoblastic leukemia (ALL) / acute myeloblastic leukemia (AML), Hodgkin/non-Hodgkin lymphoma and cancer patients is short compared to that of intracranial and scalp lesion. And, the irradiated dose in ALL/AML patients is rather small compared to that of intracranial lesion. Patients with ALL/AML and Hodgkin/non-Hodgkin lymphoma are usually intensively treated with anticancer agents with carcinogenic effects, so the patients may suffer from glioma by the synergistic effects of prophylactic irradiation and chemotherapy.

WHO grade	Number of cases	Irradiated dose (Gy)	Latency (years)
Grade II	29	29.7±18.4	10.7±7.7
Grade III	37	37.4±15.9	12.6±8.6
Grade IV	97	37.3±17.5	10.7±6.6

Table 1. Radiation induced glioma

	Number of cases	Irradiated dose (Gy)	Latency (years)	Radiation induced glioma
Pituitary adenoma	20	52.2±12.7	13.5±7.5	Grade III/IV 16, II 3
Craniopharyngioma	15	63.9±7.0	11.7±7.0	Grade III/IV 13, II 1
Medulloblastoma	16	44.9±9.5	15.8±12.2	Grade III/IV 12, II 4
Germ cell tumor	10	44.9±8.5	15.2±13.4	Grade III/IV 9, II 1
Optic glioma/ Retinoblastoma	6	46.5±10.9	7.2±2.4	Grade IV 6
Meningioma/Neurinoma	6	38.4±14.2	10±5.7	Grade III/IV 5, II 1
Low grade glioma	12	47.0±7.8	13.5±10.1	Grade III/IV 11, II 1

Table 2. Radiation induced glioma of intracranial primary lesion

	Number of cases	Irradiated dose (Gy)	Latency (years)	Radiation induced glioma
ALL/AML	64	23.6±7.6	8.6±3.9	Grade III/IV 52, II 10
Hodgkin/non-Hodgkin Lymphoma	6	35.6±10.7	8±5.7	Grade III/IV 6
Cancer	6	60.5±15.4	8±3.2	Grade III/IV 6
Scalp lesion (non-cancer)	14	12.2±12.1	15.5±9.2	Grade III/IV 9, II 5

ALL: acute lymphoblastic leukemia, AML: acute myeloblastic leukemia

Table 3. Radiation induced glioma of extracranial primary lesion

3. Genetic characteristics of radiation-induced glioma

In a patient reported by Gessi [36], the genetic alterations were p53 mutation (C to G transition at codon 176 of Exon 5), loss of heterozygosity (LOH) of 17p and 19q, O(6)-methylguanine DNA methyltransferase (MGMT) promoter methylation, and no amplification of epidermal growth factor receptor (EGFR). In Yang's case [115], p53 mutation (deletion at codon 233 of Exon 7 and a C to G transition at codon 278 of Exon 8) and no amplification of EGFR were reported. In Tada's case [104], 3-bp homozygous deletion in exon 7 of the p53 gene was described. In Kon's case [58], although LOH and amplification of EGFR, phosphatase and tensin analog (PTEN) was not observed, LOH of 1p, K-ras, p16, p53 were observed. In Alexous's two cases, LOH of 1p was found in both cases [15]. Nine radiation-induced high-grade gliomas were studied for possible molecular alterations in p53, PTEN, K-ras, EGFR, and p16 by Brat [121]. Exon 8 of p53 gene mutation (G to A substitution in codon 285) is detected in one case, EGFR amplification in 2 cases and p16/ methylthioadenosine phosphorylase (MTAP) gene deletion in 2 cases [121]. However, genetic alterations similar to those described in spontaneous, sporadic primary GBM, except the absence of PTEN mutations in the radiation-induced group were found. Radiation-induced GBMs have a lower percent of EGFR and p16 alterations than primary GBM [121]. Donson et al. [122] demonstrated by gene expression analysis genetic homogeneity relative to de-novo gliomas, suggesting a common precursor cell for radiation-induced gliomas. It is not well known about the molecular alteration of radiation-induced gliomas, due to the limited number of cases and limited genes were analyzed.

4. Therapeutic implications

Radiation-induced glioma is difficult to treat; radiotherapy is not always a therapeutic option because the patient has already been exposed to radiation. However there are several patients

reported who had a sustained remission following chemotherapy alone or radiochemotherapy. About the reports of treatment of radiation-induced glioma, a dramatic response and prolonged survival by carmustine, nimustine hydrochloride and temozolomide were reported [52, 58, 71, 75]. These tumors have a poor prognosis due to their intrinsic resistance to treatment and the difficulty using aggressive therapies in previously irradiated patients. However, vigorous chemotherapeutic approaches may yield prolonged disease control in some patients with radiation-induced glioma. The relationship of 1p LOH and chemosensitivity in oligodendroglial tumors is well known [123]. 1p LOH may account for the marked response to chemotherapy [52,58], although the reason of the chemosensitivity is not discussed in other case. In Fukui's case [32], 40 Gy of local radiotherapy and chemotherapy with nimustine hydrochloride and Interferone- β yielded dramatic response. The patient received 15 Gy of whole brain radiotherapy 7 years prior to the onset of radiation-induced glioma. Although the tolerable radiation dose is not well known after initial radiation therapy, additional radiotherapeutic approaches may yield prolonged disease control in some patients with radiation-induced glioma. The marked chemo and radiosensitivity should be further investigated for the development of glioma therapy.

5. Conclusion

In case that intracranial and extracranial lesions are treated by standard fractionated radiation or stereotatic radiosurgery, radiation-induced gliomas should be considered as possible long-term side effect. And the patients should be followed for a long term, even long after the period of risk for relapse of the primary site has passed.

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