A Bump in the Road More than the Tip of the Iceberg

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Radiation-induced malignant glioma (RIMG) is uncommon. RIMG after radiotherapy (RT) for childhood cancer is a well-described but rare complication. RIMG was described mainly after RT for acute lymphoblastic leukemia (ALL) and medulloblastoma (9). With RT and radiosurgery becoming more widely used, a greater number of patients receive different forms of ionizing radiation, and their survival has improved as a result of advances in resection, radiation, and adjuvant therapy. More than a decade ago, Loeffler et al. (6) called attention to the potentially emerging problem of radiosurgery-induced secondary tumors, describing 2 patients and raising the question whether this is “the tip of the iceberg or a bump in the road?” The treatment of patients with RIMG is problematic as well because physicians consider past treatment dosages when choosing treatment regimens and modalities. These past treatment dosages vary widely: Patients with ALL usually receive prophylactic cranial radiation on the order of 18–24 Gy, whereas patients with medulloblastoma receive a dosage of 55–60 Gy. In addition, RIMGs may not respond well to repeat irradiation, and they are believed to be more aggressive tumors (9).

We commend Elsamadicy et al. for their article, which sheds light on this complex phenomenon and underlying pathogenesis. They included 172 cases from a literature review and 4 cases occurring at their institution in their analysis. The median radiation dosage administered was 35.6 Gy. The minimum and maximum radiation thresholds for RIMG were found to be 13.6 Gy and 110 Gy, respectively. The median latency period was 9 years until diagnosis of RIMG, and diagnosis of RIMG occurred within 15 years for 82% of the patient cohort. The median latency period for ALL was 8 years. The median latency periods for medulloblastoma and pituitary adenoma were significantly different at 9.5 years (P = 0.0012) and 10.5 years (P = 0.0010), respectively. These differences in latency times have been described previously, with ALL characteristically having a shorter latency to radiation-induced neoplasia. Various theories explaining the shorter latency with ALL exist, such as the focus on the large RT fields for patients with ALL and the potentially accompanying carcinogenic therapies (9). The authors report estimated mean, median, minimum, and maximum radiation thresholds for RIMG as 63.3 Gy, 66.7 Gy, 13.6 Gy, and 110 Gy. The 5 most frequent original lesions for which patients underwent ionizing radiation were ALL (31.8%; n = 56), medulloblastoma (13%; n = 23), pituitary adenoma (10.8%; n = 18), craniopharyngioma (8%; n = 14), and tinea capitis (4%; n = 7).

In 1948, Cahan et al. (3) defined the parameters for radiation-induced neoplasia. The radiation-induced tumor must develop in the same region where RT was delivered. Also, an adequately long latency period must be observed between RT and diagnosis of the tumor. The radiation-induced tumor must have a different histology than the original pathology. Finally, the patient should not have a underlying tendency for tumor formation (e.g., von Recklinghausen disease, Li-Fraumeni syndrome, tuberous sclerosis, xeroderma pigmentosum, retinoblastoma, immunosuppression states) (3, 10). With the growing body of knowledge including newer genetic markers and immunophenotyping rendering the old tumor terminology obsolete, this fourth stipulation seems vague. For example, medulloblastoma is no longer viewed as a single entity in terms of treatment and prognosis. The previous numerous histologic subtypes have been revised in

Key words
- Anaplastic astrocytoma
- Glioblastoma
- Malignant gliomas
- Radiation-induced malignant gliomas
- Radiotherapy
- Reirradiation

Abbreviations and Acronyms
- ALL: Acute lymphoblastic leukemia
- RIMG: Radiation-induced malignant gliomas
- RT: Radiotherapy
- SRS: Stereotactic radiosurgery
current views to 4 core subgroups—WNT, SHH, Group 3, and Group 4—differing widely in their radiosensitivity and prognosis (16). The classification of ALL also has been reformed in recent years to accommodate for the effect that different genetically guided therapies have on prognosis (13).

In addition, incidence results for stereotactic radiosurgery (SRS)—induced malignancies in patients with phakomatoses do not fulfill the fourth stipulation of Cahan et al. (3). These patients, postulated to be at greater risk for radiation-induced malignancies, based on the “two-hit” hypothesis, when treated with SRS for vestibular schwannomas, did not show an increased risk for secondary malignancies (8).

Reviewing the genetics of RIMG also reveals some unique features. Radiation-induced glioblastoma multiforme has a much lower incidence of mutations of the tumor suppressor genes PTEN and p53, which are usually observed in “spontaneous” gliomas with a high degree of malignancy (2). Radiation-induced glioblastomas appear to have a more aggressive clinical course and are more treatment-refractory than de novo cases (4). Gene amplification of tumor cells shows a homogeneous pattern among RIMG cases compared with the great heterogeneity of de novo glioblastoma multiforme tumor cells. The gene amplification patterns in RIMG have a significant overlap with pilocytic astrocytomas (37%), suggesting a common clonal origin (4).

An absolutely safe dose of radiation delivered to the cranial may not exist. It is likely that secondary tumor formation does not just occur in high-dose regions but can occur in low-dose regions too (9). Also, the treatment volume (i.e., the volume of irradiated tissue in the target and the immediately surrounding region) likely affects the risk of radiation-induced neoplasia. Nevertheless, RT has helped patients much more than harming them. In the case of ALL, approximately 6000 new patients receive a diagnosis of ALL each year, with most receiving some sort of RT (5). The authors report an incidence from 1960–2010 that approached 0.0176% (53 per 300,000). It seems that a steep dose gradient and small irradiated volume may reduce the risk of neoplasia, which may explain the difference in radiation-induced tumors seen between conventional RT and radiosurgery (1, 7, 12, 14, 15).

In more than 500,000 patients who have been treated with radiosurgery worldwide, a recent review of the literature yielded 36 cases of SRS-induced central nervous system neoplasms (8). Reviewing these cases, a few comments can be made: Secondary tumors were found inside and outside of the original target, in high-dose and low-dose regions, respectively. In addition, the size of the original tumor tended to be >2 cm in diameter, supporting previous reports. The most common secondary neoplasms were malignant gliomas (36%) and malignant peripheral nerve sheath tumors (36%), followed by sarcomas (17%), meningiomas (8%), and vestibular schwannomas (3%). The mean latency to development of a SRS-induced neoplasm is 7.9 years (range 0.7–19 years). Malignant SRS-induced neoplasms have a shorter mean latency (7.1 years; range 0.7–19 years) than benign SRS-induced neoplasms (14.25 years; range 10–19 years). Based on the literature, the risk of development of radiation-induced neoplasms with radiosurgery seems to be less than the risk associated with conventional RT and is estimated to be 0.04% at 15 years (8). We recently reported 3 cases of radiation-induced tumors after Gamma Knife radiosurgery for intracranial arteriovenous malformations (11); 1 patient had RIMG glioblastoma multiforme. We found a cumulative rate of radiosurgically induced tumors in patients with a minimum of 10-year follow-up to be 3 in 4692 person-years, or 64 in 100,000 person-years. Patients were calculated to have a 0.64% chance of developing a radiation-induced tumor in ≥10 years after Gamma Knife radiosurgery.

Although radiosurgery is generally considered to be a safe modality in the treatment of intracranial pathologies, radiosurgery-induced neoplasia very rarely develops. The possibility of radiosurgery-induced tumors underscores the necessity of long-term follow-up in patients receiving treatment. With the proposed American Association of Neurological Surgeons and American Society for Radiation Oncology national SRS registry, we will have a better understanding of the specific incidence of this rare event, and we finally may be able to answer whether it is “the tip of the iceberg or a bump in the road” in the world of radiosurgery. The work by Elsamadicy et al. is a major step forward in deepening our understanding of this unintended clinical phenomenon.

REFERENCES


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