8. **Radiosurgical Pathology of Brain Tumors: Metastases, Schwannomas, Meningiomas, Astrocytomas, Hemangioblastomas**

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*Abstract*

Systematic human pathological background to brain tumor radiosurgery explaining biological and pathophysiological effects of focused irradiation barely exists. The goal of this study was to explore histopathological changes evoked by single high-dose irradiation in a set of different brain tumors following Gamma Knife radiosurgery (GKRS). Light microscopy revealed that GKRS evokes degenerative and proliferative pathological changes in the parenchyma, stroma and vessels of the irradiated tumors. Three main histological types of gamma radiolesions, that is acute, subacute and chronic variants of tissue reactions were recognized in different neoplasms irrespective of their ontogenetic nature. Acute type gamma radiolesions were characterized mainly with necrotic changes and appeared either early or in a delayed time interval. Subacute type gamma radiolesions expressed resorative activity also with early or delayed chronology. Chronic type lesions showed a reparative tendency but presented only at the delayed stage. These changes seem to follow each other consecutively. There was no significant relation between morphological characteristics of the generated tissue reaction and the time interval elapsed after GKRS. This relative time and environment autonomy of the developed pathological lesions with similar histological picture in different neoplasms suggests either a vascular mechanism or/and a genetically directed origin presumably induced by the ionizing energy of high-dose irradiation.
During the past 4 decades, radiosurgery has become an effective and widespread treatment modality in the neurosurgical realm [1–4] for the management of intracranial neoplasms with a variety of histological types, including traditionally radioresistant ones as well [5–14]. The first pituitary adenoma was treated by Leksell on January 27, 1968 in the Sophiahemmet Hospital, Stockholm, Sweden, with the prototype Gamma Knife (GK), a dedicated neurosurgical tool to perform stereotactic radiosurgery for predetermined intracranial targets [2, 15–17]. The first vestibular schwannoma was treated also by Leksell in June 1968 and the first meningioma by Backlund in 1971 [17, 18]. Since then, it has been widely accepted either as a primary alternative intervention, or as a supplementary tool to microsurgery especially for high-risk cases with difficult surgical access in critical locations [19–34]. Complications related to GK radiosurgery (GKRS), which are usually temporary, are rare and the risk for permanent neurological deficit following irradiation is low [35–39].

Although radiosurgical treatment methods have become quite straightforward and well elaborated for brain tumors [40–48], the radiobiological effect of focused single high-dose gamma irradiation on neoplastic tissue is still not fully understood [49, 50]. More than 200,000 patients with benign and malignant intracranial neoplasms have already been treated worldwide with the GK, but the pathophysiological mechanism by which radiosurgery can control or stop tumor progression has not been elucidated completely. Apart from sporadic neuropathological reports [51–55], systematic comprehensive pathological background to brain tumor radiosurgery basically does not exist. Therefore the purpose of this study was to analyze histopathological changes in cases where a GK treatment had been performed as a first step and then the patient underwent an open conventional craniotomy-related surgery for some reason.

**Patients and Methods**

Out of a series of 7,500 patients who had Leksell GKRS at two centers (Université Libre de Bruxelles, n = 1,000, and University of Pittsburgh, n = 6,500), 5,776 patients harbored cerebral tumors with a variety of histological types. We selected 38 patients who underwent later craniotomy for lesion resection (n = 47) after radiosurgery because of radiological and clinical progression. Histopathological review revealed 26 metastases, 5 astrocytomas grade III, 1 astrocytoma grade II, 5 meningiomas, 3 atypical meningiomas, 3 sporadic vestibular schwannomas, 2 NF-2 vestibular schwannomas, 1 jugular bulb schwannoma and 1 hemangioblastoma among the resected tumors. Radiosurgery was carried out using the Leksell GK Models U, B or C (Elekta Instruments AB, Stockholm, Sweden). Dose planning was based on MR and CT imaging. Treated volumes ranged between 266 and 25,600 mm$^3$ (median 4,700 mm$^3$). Tumors received 12–20 Gy as a marginal dose (median 16 Gy) at 30–60% isodose line (median 50%), with 24–40 Gy maximal dose (median 32 Gy).
Histopathological investigations were performed on surgical pathology materials. Resected specimens were fixed in 10% neutral buffered formaldehyde, processed routinely, and embedded in paraffin. Besides routine hematoxylin-eosin and Masson’s trichrome staining, immunohistochemical reactions were carried out for GFAP, vimentin, S100, neurofilament, synaptophysin, EMA, pankeratin, CK7, CK20, CAM5.2, CD3, CD20, CD31 and CD68 (PGM1) antigens to characterize phenotypic nature of tumor cells and the reactive cell population around/or infiltrating neoplastic tissues. Ki67 and p53 reactions were used to assess proliferative activity of tumor cells. Biotin-streptavidin-peroxidase complex methods were performed according to standard protocols on 5-μm paraffin sections.

**Results**

The morphological appearance of various lesions suggestive of radiation effect in different tumors was neither significantly related with the histopathological type of the irradiated neoplasm nor with the time interval between radiosurgery and craniotomy. Considering the temporal development of radiation-induced tissue and organ reactions, there are immediate (milliseconds to hours), early (days to weeks) and delayed (months to years after exposure) responses. However, the morphological and clinical types can be described as acute, subacute or chronic. The acute type histological reaction may develop early or during the delayed period, but chronic type tissue response evolves only in a delayed manner [56].

Histopathological changes attributable to radiosurgery were observed within the tumor parenchyma, connective tissue stroma and vessels. These changes were either degenerative or proliferative. The main histopathological characteristics are summarized in table 1. Degenerative alterations occurred mostly in the parenchyma of different tumors, while proliferative processes took place first of all in the connective tissue stroma and vessels of neoplasms. The basic histopathological alteration evoked by the ionizing energy of high-dose radiation was recognized as a well-circumscribed lesion with sharp demarcation towards surrounding tissues according to the steep radiation fall-off (fig. 1a). Regarding the histological and cellular composition of these gamma radio-lesions, three main types were obtained following GK treatment. In the *acute type* reaction, coagulation necrosis constituted the center with a network of acidophilic fibrinoid material and amorphous homogeneous tissue or cellular debris (fig. 1b). No cellular reaction, or scanty basophilic hyperchromatic apoptotic cells characterized by nuclear fragmentation and pyknosis intermingled with scattered polymorphonuclear leukocytes and some dilated postcapillary venules surrounded this necrotic core (fig. 1c). There was no prominent macrophage or lymphocytic infiltration, reactive gliosis or scar tissue formation. The necrosis in this targeted volume was usually circumscribed, homogeneous and sharply
demarcated from surrounding remaining tumor tissue (fig. 1a) as compared to other necrotic tumor areas outside of the focused irradiation which had an irregular multifocal appearance and entrapped tumor islands (fig. 1d). A similar histological picture of the acute type lesion could be observed either at an early or a delayed time interval after radiosurgery. These parenchymal changes were accompanied with alterations of stromal vessels around the necrotic core characterized by endothelial destruction, fibrinoid necrosis, undulation of the internal elastic membrane, and vacuolation and accumulation of eosinophilic material (transudation) in the vessel wall (fig. 1e, f).

The second group of gamma radiolesions had the characteristics of subacute type pathological reactions that were observed several months to years after radiosurgery. The main histological feature of these lesions was an inflammatory tissue response. The central coagulation necrotic core was surrounded by a macrophage rim (fig. 2a). These macrophages revealed phagocytotic activity and mainly CD68 (PGM1) but sometimes CD31 immunohistochemical reactivity as well (fig. 2b). A granulation tissue zone was situated outside of the macrophage layer containing abundant small vessels, capillaries, arterioles and venules accompanied by inflammatory cells, fibrocytes and fibroblasts expressing vimentin positivity (fig. 2c, d). Postirradiation vasculopathy was

<table>
<thead>
<tr>
<th>Type</th>
<th>Parenchymal changes</th>
<th>Stromal alterations</th>
<th>Vasculopathy</th>
<th>Temporal development</th>
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<tbody>
<tr>
<td>Acute</td>
<td>sharply demarcated coagulation necrosis</td>
<td>no cellular reaction or scattered apoptotic cells and polymorphonuclear leukocytes around the necrosis</td>
<td>dilated small venules; endothelial destruction, undulation of internal elastic membrane, fibrinoid changes in vessels’ wall, vacuolar degeneration</td>
<td>early or delayed</td>
</tr>
<tr>
<td>Subacute</td>
<td>well-circumscribed coagulation necrosis</td>
<td>macrophage reaction around the necrosis; granulation tissue; reactive gliosis</td>
<td>proliferative vasculopathy with narrowing of the lumen</td>
<td>early or delayed</td>
</tr>
<tr>
<td>Chronic</td>
<td>replaced by scar tissue</td>
<td>focal lymphocytic infiltration; hyaline degenerated scar tissue, calcification</td>
<td>subendothelial cell proliferation; subtotal or complete lumen obliteration; hyaline degeneration in the wall</td>
<td>delayed</td>
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Table 1. Histopathological characteristics of gamma radiolesions
Fig. 1. Histological characteristics of acute type gamma radiolesions. 

a–d Metastatic non-small cell carcinoma 4 months after GKRS. 

a. Sharply demarcated coagulation necrosis in tumor parenchyma (HE, ×100). 
b. Fibrinoid mesh in the center of the radiolesion (HE, ×300). 
c. Scattered pyknotic cells at the periphery of the lesion (HE, ×300). 
d. Irregular tumor necrosis outside of the irradiated target volume (HE, ×300). 

e, f Metastatic small cell lung carcinoma 3 months following GKRS. 

e. Fibrinoid necrosis in vessel’s wall (HE, ×300). 
f. Endothelial destruction, undulation of internal elastic membrane, vacuolar degeneration of vessel’s wall (HE, ×300).