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Neurocognitive Changes in Pituitary Adenoma Patients After Gamma Knife Radiosurgery: A Preliminary Study
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Neurocognitive Changes in Pituitary Adenoma Patients After Fractionated External Beam Radiotherapy versus Gamma Knife Radiosurgery

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In the current issue of **WORLD NEUROSURGERY**, the publication by Tooze et al. evaluates gamma knife radiosurgery (GKRS) treatment and its effect on the cognitive function of 14 patients with pituitary adenomas. Specifically, 2 patient subsets were analyzed regarding these effects, i.e., 9 patients with Cushing disease and 5 with nonfunctioning pituitary adenomas. This is the first report in the literature to examine this topic. The authors' results indicate that no neurocognitive differences were found between the GKRS-treated patients who all had preceding transsphenoidal (TS) surgeries (5 patients) versus participants not treated with GKRS, the latter 9 patients undergoing either TS resection (7 patients) or conservative tumor management (2 patients). Similarly, no appreciable neurocognitive differences were demonstrated between patients with nonfunctioning adenomas as compared with those who had Cushing disease, the latter patients with elevated cortisol levels that may have caused further impairment.

A literature review for this Perspective statement was undertaken to ascertain whether any differences in neurocognitive outcomes existed between the above patients treated with GKRS versus patients in the literature who were treated prior to the emergence of radiosurgery for pituitary adenomas using fractionated external beam radiotherapy (FEBRT). PubMed was used, and the search terms "pituitary adenomas" and "neurocognition" were utilized. The results of this literature search follow. Before this evaluation, a general review of the symptoms and neurological presentations of radiation-induced brain injury is in order.

Three phases of radiation encephalopathy, each with a separate pathophysiology, have been recognized and include 1) an acute phase; 2) an early delayed, also termed subacute, phase; and 3) a late delayed phase, which is additionally termed a chronic phase. The acute phase develops days to weeks after FEBRT and is manifested by drowsiness, headaches, nausea, emesis, and worsening of neurological deficits (5, 11). Possible underlying mechanisms for this phase include blood-brain barrier disruption by endothelial apoptosis and increased cerebral edema and intracranial pressure. Dexamethasone treatment results in symptomatic improvement in these symptoms and findings (2, 5). Early delayed or subacute effects occur 1-2 to 6 months postradiation and also are reversible. Symptoms and findings for this phase are similar to those of the acute phase with, apropos to the present report and this Perspective, changes in cognitive functioning. Subacute encephalopathy is secondary to transient diffuse demyelination, and the syndrome resolves within several months (5, 11). Late delayed effects appear 6 months to many years after treatment and often produce irreversible and progressive damage to the central nervous system. This phase's white matter damage is due to vascular injury causing ischemia, demyelination, and necrosis. Presenting symptoms are seizures, increased intracranial pressure, neuroanatomic-specific effects, and radiation necrosis (5, 11).

Key words
- Cognitive function
- Cushing
- Memory
- Nonfunctioning adenoma
- Radiosurgery

Abbreviations and Acronyms
AVLT: Auditory-Verbal Learning Test
CVLT: California Verbal Learning Test
FEBRT: Fractionated external beam radiotherapy
GH: Growth hormone
GKRS: Gamma knife radiosurgery
TS: Transsphenoidal
WRMT-faces: Warrington Recognition Memory Test for Faces

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During FEBRT treatment of pituitary tumors, the limbic system is within the radiation field and receives approximately 50% to 100% of the radiation that the pituitary gland receives, amounting to about 22.5 to 45 Gy. The hippocampus receives approximately 50% to 75% of the radiation therapy dose, whereas the mammillary bodies receive approximately 95% of the total dose. The prefrontal field also receives radiation from 1 field. One of the most common side effects of this therapeutic pituitary FEBRT is damage to blood vessels, particularly small vessels, which is dose dependent (12).

The current report comments on the differences in techniques between GKRS and FEBRT, which potentially could result in differences in neurocognitive outcomes between the two treatments. The quoted publication by Minniti et al. (6) concluded that the localized irradiation in GKRS is achieved by shaping the radiation beams to conform to the tumor's shape. More surrounding normal tissue is thus spared. Minniti et al. also stated that "there is a general belief that increasing the number of beams leads to a greater dose differential with a steeper dose gradient between the target and normal brain tissue." A statement is also made that this, however, "leads to a greater volume of tissue receiving low radiation doses." Thus, per Tooze et al., increasing the number of beams of radioactive sources in GKRS projects many beams through the medial temporal lobe and frontal lobe structures. Per these latter authors, it is therefore possible that the cognitive outcomes of patients treated with GKRS could be expected to be worse than those of patients treated with FEBRT. Thus, an analysis follows of the overall cognitive findings of patients with pituitary tumors treated with FEBRT as outlined in pertinent publications obtained from the literature search mentioned earlier.

To determine whether there was a difference between the cognitive changes found in the current report using GKRS versus cognitive changes found in pituitary tumors treated with FEBRT, the PubMed search, as described earlier, yielded a report by Tooze et al. (12) who compiled 2 tables evaluating 8 such FEBRT articles. The 2 tables were combined into **Table 1** in the present Perspective, and 2 publications cited in the tables were discarded due to an indeterminate and very small number of pituitary tumor cases, respectively; another PubMed search FEBRT publication's results was added. During the search, there were no directly comparable publications to the present publication, i.e., articles that evaluated patients undergoing surgery, or surgery and FEBRT, who had only nonfunctioning pituitary adenomas or Cushing disease. All articles that evaluated neurocognitive function after undergoing FEBRT included multiple types of pituitary adenomas (**Table 1**). This, then, is a difficulty with attempts to compare neurocognitive outcomes in pituitary patients using FEBRT versus those after use of current radiosurgery systems.

Evaluating the results of authors included in the current Perspective's **Table 1**, Grattan-Smith et al. (3) used visual and verbal memory as well as executive function cognitive testing, the results of which are included in **Table 1**. In their study, in 27 patients who did not receive FEBRT and 38 who did, the latter including those having surgery followed by FEBRT and those having FEBRT alone, both did worse than 21 control subjects in verbal/visual memory testing and 1 test of executive function.

Peace et al. (10) evaluated 27 patients with pituitary tumors undergoing surgery followed either by FEBRT (18 patients) or by no FEBRT (9 patients), patients not having surgery (9 patients), and 36 healthy control subjects. Patients undergoing TS surgeries and transfrontal craniotomies and nonoperative patients fared worse than control subjects on the Warrington Recognition Memory Test for Faces (WRMT-faces) and on all tests of executive function. The authors thought that the differences may have resulted from endocrine status differences. No differences were found on any measures of cognitive function between the FEBRT patients versus those not undergoing FEBRT. No difference was found between type of surgery; however, there was a significant difference between those having surgery and those not undergoing surgery, which favored those not having surgery.

The authors Peace et al. (9) next evaluated patients who had TS operations and craniotomies both followed by FEBRT versus those having surgery without it. They evaluated TS versus craniotomy separately to establish any differences between the two procedures in cognitive functioning. No differences were found between the mean test scores of the two surgical groups on any of the measures of cognitive function. More craniotomy patients, however, had lower scores than the patients undergoing TS operations. In their study using the cognitive testing outlined in **Table 1**, the patients did worse than control subjects on Wechsler memory scale and Story Recall tests; surgery patients did worse than the nonsurgery patients on the Auditory-Verbal Learning Test (AVLT); and the control subjects did worse on the WRMT-faces. No significant differences were found between the surgical patients who had FEBRT and those who did not.

Regarding the study by Baum et al. (1), all of their patients had adult-onset growth hormone (GH) deficiency. Neurocognitive testing was performed at the patient's GH baseline and then again after the patient had received 18 months of GH replacement. At GH baseline, all patients scored within normal limits on all tests, except on the California Verbal Learning Test (CVLT), which measures learning and memory where they scored over 1 SD below the test norms. Patients with a history of FEBRT had similar results on cognitive tests as those not treated with FEBRT, except on the Controlled Oral World Association Test, on which patients with a FEBRT history actually scored higher. There were no changes in testing after 18 months of GH administration compared with those receiving a placebo.

Guinan et al. (4) evaluated 90 pituitary adenoma patients. Patients were grouped into those who underwent transfrontal craniotomy and FEBRT (20), TS surgery plus FEBRT (21), TS surgery alone (21), FEBRT alone (10), and bromocriptine therapy (18); there were 19 healthy control subjects. Anterograde memory quotients indicated that significant differences in anterograde memory were obtained on 2 measures, i.e., the Wechsler Memory Scale–Revised and WRMT-faces, and WRMT-words for all patient groups when compared with the healthy control subjects. Intellectual function as manifested by IQ testing remained intact in all groups. There was no difference between the effects of surgery and radiotherapy.