TO THE EDITOR: We read with great interest the recent article by Gupta et al.1 (Gupta A, Xu Z, Kano H, et al: Upfront Gamma Knife radiosurgery for Cushing’s disease and acromegaly: a multicenter, international study. J Neurosurg [epub ahead of print August 17, 2018. DOI: 10.3171/2018.3.JNS18110]). The authors included 21 patients with Cushing’s disease (CD) and 25 patients with acromegaly undergoing upfront Gamma Knife radiosurgery (GKS). After a median endocrine follow-up of 69.5 months, patients with CD achieved a faster and far better remission rate compared to patients with acromegaly. The authors suggest a possible differential radiosensitivity of two kinds, and then further recommend upfront GKS in CD rather than in acromegaly. We commend the efforts of the authors in carrying out this interesting study. Yet from the perspective of neurosurgeons, some conclusions are questionable.

The biggest concern lies in the posttreatment remission criteria for CD that were used in this study. The authors defined remission as normalization of urinary free cortisol and morning serum cortisol levels, which is not recognized by most endocrinologists and neurosurgeons. According to the latest Endocrine Society Clinical Practice Guideline for CD, as well as other previous literature, remission is generally defined as morning serum cortisol values < 5 μg/dl, a stricter criterion than just normal range.2,5,7 One meta-analysis suggests that patients with CD in whom subnormal cortisol levels are found after treatment have a clearly lower risk of long-term recurrence compared to those within the normal range.8 The reduction of cortisol levels to the normal range after treatment does not necessarily represent the patient’s cure, but rather a higher recurrence rate.9 Regarding this condition as remission could give patients overly optimistic and misleading expectations, and may cause neglect of follow-up. Moreover, the use of different remission criteria hinders direct comparison of outcomes between this GKS study and other surgical treatment studies for CD.

Nevertheless, although the authors have used more easily achievable remission criteria for CD, the remission criteria for acromegaly (i.e., growth hormone [GH] level < 1 ng/ml in response to a glucose challenge) are much stricter and in accordance with the latest guideline.4 These varying degrees of rigor in criteria to assess CD and acromegaly may also make less convincing the conclusion that patients with CD achieve faster and better remission rates and that their disease is more sensitive to GKS than is the case in those with acromegaly.

In addition, this study did not mention the impact of radiotherapy on the growth of younger patients, especially when the youngest patient with CD included in this study was 14 years old. A radiotherapy study in pediatric CD reported that the incidence of GH deficiency after radiation therapy was 36%–68%, and most patients failed to reach the target height. In one study from the Mayo Clinic the investigators also believe that the risk of delayed hypopituitarism caused by radiotherapy is significant.9 The risk of this hypopituitarism exists for a lifetime.9 It is therefore recommended that this article add age factors when deriving the conclusion of efficacy for upfront GKS for CD and acromegaly treatment. Especially given the lack of long-term follow-up data, the conclusions should be more cautious for the sake of safety.

References
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The authors raise the issue of contemporary definitions of endocrine remission. Endocrine criteria for remission of CD and acromegaly have changed substantially over the 2.5 decades during which our study cohort was accrued. Although applying modern endocrine assays and definitions would be ideal, the approach would be impractical for such a clinical study, and its absence does not negate the significant findings of our study. Not surprisingly, this limitation also holds true for the largest surgical series of pituitary surgery for functioning adenomas. Moreover, given past experiences, the remission criteria and neuroendocrine assay technology are almost certain to be refined in the future. Thus, the remission criteria will remain a moving target.

Latent effects of radiotherapy are not the same in breadth or frequency as those experienced with GKS. For instance, in the CD and acromegaly studies by our group, as well as a review of the literature, we have not seen a single instance of symptomatic carotid stenosis leading to cerebral ischemia. This sharply contrasts with radiotherapy series for patients with pituitary adenoma. The same is true for radiation-induced neoplasia and neurocognitive deficits after radiosurgery as compared with radiotherapy for tumors of the sella. Nevertheless, one should always weigh the benefit-to-risk profile of GKS with those of other treatment options and take into account the natural history of the underlying disease state. For pituitary adenomas, the long-term consequences of action or inaction must be carefully considered.

A large, multicenter, prospective study of patients with pituitary adenomas would probably take at least 5 years from the accrual of patients for intermediate results to be meaningful and more than a decade for long-term results. Furthermore, such an undertaking would require hundreds of patients and millions of dollars to achieve study validity. During that time, it is likely that the study would be confounded by changing technologies (e.g., radiosurgery devices, radiology sequencing, endocrine assays), evolving medical and microsurgical approaches, varied treatment paradigms, and potentially changing criteria for endocrine remission. Until then, the pituitary adenoma radiosurgery studies by the International Radiosurgery Research Foundation (IRRF) will probably remain the highest level of evidence available to guide clinicians.

References

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