Outcomes of Pituitary Radiation for Cushing Disease

Natasha Ironside, MBChB[a], Ching-Jen Chen, MD[b], Cheng-Chia Lee, MD[c], Daniel M. Trifiletti, MD[d], Mary Lee Vance, MD[e], Jason P. Sheehan, MD, PhD[b,*]

KEYWORDS

• Cushing disease • Stereotactic radiosurgery • Radiation therapy • Endocrine • Remission

KEY POINTS

- For patients with persistent or recurrent Cushing disease after transsphenoidal resection, ionizing radiation delivery to the pituitary is the primary adjuvant treatment.
- More recently, single-session stereotactic radiosurgery has been popularized over conventional fractionated external beam radiotherapy as the treatment of choice.
- Endocrine remission rates, times to remission, and tumor control rates between stereotactic radiosurgery and external beam radiotherapy are comparable among major series.
- Heterogeneity in endocrine remission and recurrence rates highlights a need for investigation. Potential contributing factors include differences in patient selection, treatment parameters, and use of adjuvant medication.
- New pituitary hormone deficiency is the most frequent adverse effect after stereotactic radiosurgery and external beam radiotherapy. Other complications, including cranial neuropathy and visual deficit, are uncommon.

INTRODUCTION

Biochemical remission with the preservation of normal pituitary function is the primary goal in the treatment of Cushing disease.[1] Transsphenoidal resection remains the gold

Disclosure Statement: The authors have nothing to disclose.
[a] Department of Neurosurgery, Auckland City Hospital, Private Bag 92 024, Auckland Mail Center, Auckland 1142, New Zealand; [b] Department of Neurological Surgery, University of Virginia Health System, PO Box 800-212, Charlottesville, VA 22908, USA; [c] Department of Neurosurgery, Taipei Veterans General Hospital, 17 Floor, No. 201, Sec. 2, Shipai Road, Beitou District, Taipei 11217, Taiwan; [d] Department of Radiation Oncology, Mayo Clinic, 4500 San Pablo Road South, Jacksonville, FL 32224, USA; [e] Division of Endocrinology and Metabolism, University of Virginia Health System, 2 Floor, Suite 2100, 415 Ray C Hunt Drive, Charlottesville, VA 22908, USA
* Corresponding author. Department of Neurological Surgery, Health Sciences Center, Box 800-212, Charlottesville, VA 22908.
E-mail address: jps2f@virginia.edu

Endocrinol Metab Clin N Am ■ (2018) ■–■
https://doi.org/10.1016/j.ecl.2018.01.002 **endo.theclinics.com**

standard of treatment, offering remission rates that range from 59% to 97%.[2–5] Despite the high rates of initial remission that can be achieved with transsphenoidal resection, delayed recurrences have been reported in up to 50% of patients, as late as 30 years after surgical resection.[6–8] This finding presents a significant challenge to the long-term management of Cushing disease. Radiation targeting residual tumor cells represents an important adjuvant treatment for patients with persistent or recurrent Cushing disease.[8] In select patients who are poor surgical candidates or unwilling to undergo surgery, upfront radiation therapy may also be considered.[9,10] The administration of ionizing radiation includes conventional external-beam fractionated radiation therapy (XRT) and stereotactic radiosurgery (SRS), the latter of which can be delivered via linear accelerator-based systems, gamma knife, proton beam, and various other commercially available units.[11] In recent years, for tumors located in the sellar and parasellar regions, SRS has become a modality of choice for radiation delivery. SRS permits the administration of focused, high-dose treatment in a single session, while limiting the exposure of nearby critical neurovascular structures to unwanted radiation.[10,12] This review outlines the indications, outcomes, and adverse effects associated with radiation treatment of Cushing disease.

Techniques Used for Radiation Delivery to the Pituitary Gland

SRS is characterized by the delivery of a high-dose of hypofractionated radiation to a precise target using a multiheaded cobalt-based unit (Gamma Knife, Elekta AB, Stockholm, Sweden), linear particle accelerator, or proton beam unit.[10,12,13] In gamma knife radiosurgery (GKRS), numerous radiation beams are focused on the target using a crossfire technique.[14] Gamma rays, produced by radioactive decay of cobalt-60 sources, are converged on an isocenter within the tumor using a collimator. A high central radiation dose with submillimeter accuracy can be achieved through various combinations of the beam number, aperture size, and position.[11,15] Typically prescribed at a 50% isodose line, the cobalt system can achieve steep radiation dose fall-off just beyond target margins.[11,14,15] In linear accelerator-based SRS systems (CyberKnife, Edge, Novalis TX, Trilogy, and Axesse), x-rays are derived from the collision of an accelerated electron with a high *z* target. An isodose line of 80% to 90% is frequently prescribed to encompass the target volume, resulting in a greater penumbra effect and a lower maximum dose when compared with GKRS.[13,14,16,17] Proton beam therapy takes advantage of the Bragg phenomenon, in which the peak energy transferred by an accelerated proton occurs immediately before it comes to rest, sparing the deeper tissues of unwanted radiation.[18] Although proton beam use has increased, most centers do not currently offer this treatment, owing to the size, technical challenges, and cost of construction of these proton beam units for radiosurgical delivery.[10,11,18,19]

XRT delivers ionizing radiation in multiple fractionated doses (25–30 daily treatments) and can be used in patients who are not candidates for SRS owing to safety concerns associated with large tumor size, irregular geometry, extrasellar extension, or proximity to the optic apparatus.[12] However, the use of multisession SRS in treating those with large tumors or tumors in close proximity to critical neurovascular structures has recently demonstrated promising results.[14,20–22]

Illustrative Case

A 43-year-old woman who presented with clinical stigmata of Cushing disease underwent microscopic transsphenoidal resection of an adrenocorticotropic hormone-secreting pituitary adenoma in April 2006 (**Fig. 1**). She experienced postoperative persistence of hypercortisolism and received GKRS in November 2006. This