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Review

Stereotactic radiotherapy and radiosurgery for non-functioning and secreting pituitary adenomas

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ABSTRACT

Radiotherapy (RT) is frequently employed in patients with residual or recurrent pituitary adenoma with excellent rates of tumor control and remission of hormonal hypersecretion. Advances in RT have improved with the use of stereotactic techniques either as fractionated stereotactic radiotherapy (FSRT) or stereotactic radiosurgery (SRS), all aiming to improve the dose distribution to the tumor while reducing the amount of normal brain receiving significant doses of radiation. We provide an overview of the recent published literature on the long-term efficacy and adverse effects of stereotactic irradiation in nonfunctioning and secreting pituitary adenomas. Both techniques are associated with excellent clinical outcomes; however, advantages and drawbacks of each of these techniques in terms of local control, hormonal excess normalization, and radiation-induced toxicity remain a matter of debate. In clinical practice, single-fraction SRS may represent a convenient approach to patients with small and medium-sized pituitary adenoma away at least 2 mm from the optic chiasm, whereas FSRT is preferred over SRS for lesions >2.5–3 cm in size and/or involving the anterior optic pathway.

1. Background

Radiotherapy (RT) has traditionally been used in patients with residual or recurrent secreting and nonfunctioning pituitary adenomas after surgery, resulting in a variable long-term tumor control of 80–97%[1–5] and normalization of elevated hormone levels in 40–70% of patients.[6–10] Hypopituitarism occurs in 30–60% of patients 5–10 years after irradiation, while other toxicities, including radiation-induced optic neuropathy, cerebrovascular accidents, and second tumors have been reported in 0–3%.[10–13]

Stereotactic techniques have been developed with the aim to deliver more localized irradiation and minimize the long-term consequences of treatment. The techniques used for treatment of pituitary adenomas involve either photon energy

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with cobalt-60 radiation-emitting sources (Gamma Knife, GK) or a modified linear accelerator (LINAC), and are given as a single-fraction stereotactic radiosurgery (SRS) or as fractionated stereotactic radiotherapy (FSRT).[14] Data from published literature indicate that either SRS or FSRT may achieve excellent long-term tumor control and hormone hypersecretion normalization; however, advantages and disadvantages of the different stereotactic techniques in the management of patients with pituitary adenomas and their optimal indications are still a matter of debate.

In this review, we present an update of the recent available literature on the use of stereotactic techniques in patients with pituitary adenoma. The efficacy, safety, and optimal indications for SRS and FSRT in nonfunctioning and secreting adenomas, including GH-secreting adenomas, ACTH-secreting adenomas and prolactinomas are discussed.

2. Stereotactic techniques

Stereotactic techniques are a refinement of high conformal RT with further improvement in immobilization, imaging and treatment delivery. The principal advances of stereotactic techniques are improved immobilization with either a frame-based or a frameless mask stereotactic system that act as a fiducial reference system, leading to a submillimetric accuracy in terms of patient movement. Stereotactic irradiation can be delivered as single-fraction SRS, multi-fraction SRS (2–5 fractions), and as FSRT when a conventional fractionation of 1.8–2.0 Gy per fraction is used.

In the multiheaded cobalt unit Gamma Knife (GK), 201 small Cobalt sources of gamma rays are arrayed in a hemisphere. A primary collimator aims the radiation emitted by these sources to a common focal point. A second external collimator helmet, which fits within the primary collimator, has an array of removable tungsten collimators (one per source) with circular apertures from 4 to 18 mm in size that are used to create different diameter fields at the focus point. In the new version of the machine (Gamma Knife Perfexion), the external helmet collimators have been replaced by a single internal collimation system: the cobatl-60 sources move along the collimator body to locations, where 4 mm, 8 mm, and 16 mm apertures have been created. High degree of conformity for larger non-spherical pituitary adenomas can be achieved through complex multi-isocenter computer planning that defines the optimum combinations of number, aperture and position of the collimators. The dose is typically prescribed at 50% isodose to obtain the maximum dose at the center of each pinpointed target and the prescribed dose at the target edge. Instead of using an array of cobalt sources, LINAC SRS utilizes X-rays which are derived from colliding accelerated electrons with a target metal. Linac FSRT uses multiple fixed fields or arcs at each daily session, shaped with a multileaf collimator (MLC). All fields and arcs conform to the shape of the tumor allowing a sharp dose gradient between the target and normal brain tissue. Dose conformity can be improved by the use of intensity modulation of the beams, lengths and dynamic collimator optimization of arcs, use of micro-multileaf collimator, and multiple isocenter.

CyberKnife (Accuray, Sunnyvale, CA) is a relatively new technological device that combines a mobile linear accelerator mounted on a robotic arm with an image-guided robotic system.[15] The treatment couch also has movements in six degrees of freedom. It has got 3 translation movements (longitudinal, lateral and vertical) and 3 rotational movements (pitch, roll and yaw). Patients are fixed in a thermoplastic mask and the treatment can be delivered as single-fraction or multi-fraction SRS. Single isocenters are used for spherical lesions, whereas irregularly shaped lesions are usually treated with a non-isocentric technique. A variable number of overlapping beams (up to 200) are delivered non-isocentrically to the target, resulting in excellent dose coverage to the target and conformity. The set of beam directions and analysis of dose distribution are chosen through an inverse planning process.

The superiority in terms of dose delivery and distribution for each of these techniques remains a matter of debate. Dose distribution to the target delivered by LINAC-based SRS is usually more homogeneous as compared to CyberKnife and GK SRS, and this may represent an advantage when treating larger tumors that include radiation-sensitive brain structures. By contrast, GK and CyberKnife may achieve a better conformity when irradiating irregularly shaped targets as compared to LINAC-based SRS. Regardless of the advantages claimed for each of these radiosurgical techniques, the reported clinical efficacy and toxicity are similar.

In FSRT, the delivered total dose is the same as in conventional RT (45–55 Gy in 25–33 daily fractions over a period of 5–6 weeks). Patients are usually immobilized in a high precision frameless stereotactic mask fixation system with a reported accuracy of 1–3 mm.[16] The principal aim of FSRT is to deliver more localized irradiation as compared with conventional RT, leading to a reduction of the volume of normal brain tissue irradiated to high radiation doses, possibly minimizing the long-term consequences of treatment.

The principal difference between SRS and FSRT is in the number of fractions. Large single doses of radiation as used in SRS are more toxic to normal brain structures than similar doses given in a fractionated manner, as used in FSRT. A dose-dependent risk of radiation optic neuropathy exists following single doses of irradiation. A few retrospective studies have indicated that the incidence of radiation-induced optic neuropathy is about 2% for single doses of 8–12 Gy, and becomes >10% for doses of 12–15 Gy to the optic apparatus.[17–20] Leavitt et al.[20] have recently reviewed 222 patients treated with GK SRS for a benign tumor adjacent to the anterior visual pathway. The risk of optic neuropathy was 0% for patients receiving a maximum dose of 8–12 Gy and 10% for those receiving >12 Gy, respectively, suggesting that small portions of anterior visual pathway in the range of 0.02–0.04 cm^3 may receive doses up to 12 Gy. The reported tolerance of cranial nerves in the cavernous sinus after single-fraction SRS is 16–18 Gy,[17,18] whereas a maximum dose of 12–13 Gy in a single fraction to the brainstem is recommended. By contrast, there is no restriction to the size of pituitary adenoma suitable for FSRT, since the delivered doses of 45–55 Gy using a conventional fractionation are within the tolerance of normal brain structures, including the optic nerves and chiasm.