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Early versus late Gamma Knife radiosurgery following transsphenoidal surgery for nonfunctioning pituitary macroadenomas: a multicenter matched-cohort study

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Abstract

OBJECTIVE—Gamma Knife radiosurgery (GKRS) is frequently used to treat residual or recurrent nonfunctioning pituitary macroadenomas. There is no consensus as to whether GKRS should be used early after surgery or if radiosurgery should be withheld until there is evidence of

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Disclosures

Dr. Grills reports owning stocks in Greater Michigan Gamma Knife. Dr. Lunsford reports owning stock in Elekta and being a consultant for Insightec.

Author Contributions

Conception and design: Sheehan, Pomeraniec, Dallapiazza, Jane. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Sheehan, Pomeraniec, Dallapiazza, Jane. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sheehan. Statistical analysis: Sheehan, Pomeraniec, Dallapiazza, Jane. Administrative/technical/material support: all authors. Study supervision: all authors.

imaging-defined progression of tumor. Given the high incidence of adenoma progression after subtotal resection over time, the present study intended to evaluate the effect of timing of radiosurgery on outcome.

METHODS—This is a multicenter retrospective review of patients with nonfunctioning pituitary macroadenomas who underwent transsphenoidal surgery followed by GKRS from 1987 to 2015 at 9 institutions affiliated with the International Gamma Knife Research Foundation. Patients were matched by adenoma and radiosurgical parameters and stratified based on the interval between last resection and radiosurgery. Operative results, imaging data, and clinical outcomes were compared across groups following early (≤ 6 months after resection) or late (> 6 months after resection) radiosurgery.

RESULTS—After matching, 222 patients met the authors' study criteria (from an initial collection of 496 patients) and were grouped based on early (n = 111) or late (n = 111) GKRS following transsphenoidal surgery. There was a greater risk of tumor progression after GKRS (p = 0.013) and residual tumor (p = 0.038) in the late radiosurgical group over a median imaging follow-up period of 68.5 months. No significant difference in the occurrence of post-GKRS endocrinopathy was observed (p = 0.68). Thirty percent of patients without endocrinopathy in the early cohort developed new endocrinopathies during the follow-up period versus 27% in the late cohort (p = 0.84). Fourteen percent of the patients in the early group and 25% of the patients in the late group experienced the resolution of endocrine dysfunction after original presentation (p = 0.32).

CONCLUSIONS—In this study, early GKRS was associated with a lower risk of radiological progression of subtotally resected nonfunctioning pituitary macroadenomas compared with expectant management followed by late radiosurgery. Delaying radiosurgery may increase patient risk for long-term adenoma progression. The timing of radiosurgery does not appear to significantly affect the rate of delayed endocrinopathy.

Keywords

stereotactic radiosurgery; Gamma Knife; pituitary surgery; transsphenoidal surgery; macroadenoma; nonfunctioning pituitary adenoma

Nonfunctioning pituitary adenomas (NFPAs) account for approximately 15%–30% of all pituitary tumors and typically grow slowly before the patient presents with visual deficits, headache, and hypopituitarism from compression of the optic apparatus and normal pituitary gland.[9,14] Transsphenoidal surgery and decompression of the optic chiasm is highly effective in providing symptomatic relief and the possibility of a long-term cure, but historic rates of total resection vary substantially. Complete resection can be limited due to adenoma volume and propensity for microscopic infiltration of the surrounding architecture.[3,5,28,29,41,55]

With the advent of transsphenoidal techniques, the distant consequences of slow-growing pituitary tumors have emerged. Long-term outcomes of surgically treated NFPAs demonstrate that tumor recurrence at distant follow-up can be upwards of 20% after gross-total resection[6–8, 12, 17, 19,31,41,43,58,64,66] and 50%–60% after subtotal resection without adjuvant treatment.[6–8,12,17,19,20,31,41,43,44,58, 64,66] The modern surgical armamentarium may

afford more options for patients with nonfunctioning tumors, including secondary operations and/or adjuvant treatment of residual or progressive disease.[8]

Standard management options for residual or recurrent NFPAs range from expectant management with serial clinical and imaging follow-up to repeat adenomectomy and/or stereotactic radiosurgery (SRS). Furthermore, for adenomas that invade laterally beyond the medial wall of the cavernous sinus, aggressive debulking can pose undue risk to neurovascular structures. In these latter cases (subtotal resections and recurrent nonfunctioning macroadenomas), SRS has been repeatedly reported as a clinically safe and scientifically viable management option.[4,21–25, 30,32, 35, 42,44–46,49,50,52,62,65] SRS helps reduce the conventional risks of radiotherapy, including hypopituitarism, radiation-induced tumors, carotid stenosis, and stroke, as well as neurocognitive side effects.[2,27,36,37,55]

The utility of SRS in treating residual and recurrent adenomas has been demonstrated across various large patient series with tumor control rates approaching 90%.[42,50] One of the largest multicenter studies included 512 patients treated with GKRS and demonstrated overall tumor control in 93.4% of patients at last-follow-up with actuarial tumor control rates of 98%, 95%, 91%, and 85% at 3, 5, 8, and 10 years postradiosurgery, respectively.[52] Despite mounting evidence of the long-term efficacy of SRS, the inherent tradeoff between potential treatment complications and residual tumor growth has limited the understanding of and consensus for radiosurgery along the spectrum of disease and therapy. Clinicians often face difficult decisions regarding administering SRS early after initial transsphenoidal debulking or after some time of expectant management during which the patient experiences further adenoma growth.

Importance of Study

To the best of our knowledge, this is the largest multicenter matched-cohort review with long-term clinical and radiological follow-up for comparing radiosurgery for pituitary macroadenomas based on the time interval from subtotal resection. The present study evaluated a large patient cohort from multiple institutions to better elucidate safe and effective treatment strategies following subtotal resection of NFPAs and the risk-benefit tradeoff of additional procedures versus expectant management. Early GKRS appears to decrease the risk of imaging-defined progression of subtotally resected tumors compared with expectant management. The timing of adjuvant GKRS does not appear to significantly affect the rate of postradiosurgical endocrinopathy over the long-term.

The lack of consensus for the timing of SRS for residual adenoma stems largely from concern for radiation-induced endocrinopathy. The present study represents a multicenter attempt to validate a prior single-institution study of a matched cohort of 64 patients in which differences in early versus late GKRS outcomes were observed. [47] The purpose of this review is to more comprehensively evaluate a large patient cohort from multiple institutions to better elucidate safe and effective treatment strategies following subtotal resection of NFPA and the risk-benefit profile of early intervention with radiosurgery versus expectant management.

Methods

Data Collection

Nine medical centers affiliated with the International Gamma Knife Research Foundation received respective institutional review board approvals to submit outcomes analyses of patients who underwent transsphenoidal surgery followed by GKRS for residual nonfunctioning pituitary macroadenoma. The following centers contributed data: University of Pittsburgh Medical Center (110 patients), NYU Langone Medical Center (14), Taipei Veterans General Hospital (114), Na Homolce Hospital Prague (73), Cleveland Clinic Foundation (45), Universite de Sherbrooke (27), Beaumont Health System (53), West Virginia University (7), and University of Virginia (64). All patients who received GKRS after subtotal resection during the period from 1987 to 2015 were evaluated for inclusion in this study. A database with predefined variables was created at the University of Virginia and sent to all participating centers that then subsequently reviewed patient medical records and entered data into the spreadsheet. Under institutional review board approval, pooled and de-identified data were screened by an independent third party and transmitted to the first author who drafted this report on behalf of the International Gamma Knife Research Foundation. In total, 496 patients were treated with GKRS for residual tumors. Patients who presented with hormonally active tumors and/or an unknown histological subtype (146 patients) were excluded. Patients with unknown information regarding the interval between surgery and GKRS and/or follow-up were also excluded (10 patients). Of the remaining 340 patients with adequate presenting and follow-up information, patients were subsequently matched on the basis of histological subtype, GKRS target volume, margin dose, and maximum dose. This yielded a final analysis of 222 patients. All of the patients included in this review demonstrated residual adenoma after resection and before GKRS treatment. Data were collected prospectively and reviewed retrospectively, including baseline demographics, symptoms, imaging reports before and after surgery, treatment information, histology reports, and clinical notes during the course of follow-up.

Patient Evaluation

Before surgery all patients underwent evaluation, which included MRI and neurological and endocrinological examinations. Clinical examination, including serum testing for pituitary function and/or formal ophthalmological visual field testing, was performed according to and varied by institutional practice. NFPAs were defined before surgery by imaging (e.g., sellar mass > 1 cm) and clinical and biochemical characteristics to preclude a diagnosis of a functioning tumor caused by a condition such as Cushing’s disease, acromegaly, or prolactinoma (e.g., nonappreciably elevated serum levels of prolactin [< 200 ng/ml], adrenocorticotrophic hormone [ACTH], growth hormone, and insulin-like growth factor 1). During the interval between surgery and GKRS, patients were again evaluated with imaging and on a neurological and endocrine basis. For planning purposes, patients underwent stereotactic MRI or CT at the time of GKRS. This information served as the baseline data for comparing longer-term clinical and imaging outcomes.

Clinical and Radiological Follow-Up

Patients were routinely followed up in the clinic with neurological examinations, endocrine evaluations, and biochemical assays and imaging of the sella (typically MRI). Whenever possible, patients underwent follow-up examination, endocrine testing, and neuroimaging at their respective treatment center. However, because all institutions were referral centers for broad geographic areas, some patients underwent follow-up evaluations by their referring physicians. In those cases, clinical notes, laboratory tests, and neuroimaging studies were sent to and reviewed by the treating neurosurgeons who performed GKRS. The follow-up images were compared with the images obtained at the time of GKRS. Comprehensive follow-up neurological and ophthalmological assessments served to evaluate new symptoms or progressive neurological deficits. Tumor response to treatment was demonstrated on serial neuroimaging (independently reviewed at the respective treatment centers), and endocrine testing was matched to these follow-up time points. Clinical and imaging outcomes were determined at 3 time points: after surgery, before GKRS, and at the last available examination. Tumor dimensions were measured in the axial, sagittal, and coronal planes. The dimensional indices of the tumors were measured and recorded in 3 orthogonal planes: transverse (TR), anteroposterior (AP), and craniocaudal (CC). The volumes of the tumors were estimated using the following formula: $V = (\pi \times [TR \times AP \times CC])/6$.[1,33] A change in tumor size was defined as a 15% or greater increase or decrease in tumor volume.[53] Adenomas that changed in volume by less than 15% were considered stable. New endocrinopathy was defined objectively by hormonal assays and physician recommendation for medical hormone replacement therapy.

Radiosurgical Technique

Models U, B, C, 4C, and Perfexion Gamma Knife units (Elekta AB) were used depending on the technology available and the time of treatment at the various participating centers. The radiosurgical techniques have been well detailed.[49,54,62] The procedure was performed using Leksell Gamma Unit (Elekta AB) model U before 2001 and model C thereafter with GammaPlan software (Elekta AB). Stereotactic Leksell G-frame placement was performed in the operating room under local anesthesia with or without additional intravenous conscious sedation. Following frame placement, treatment planning included high-resolution stereotactic MRI with pre- and postcontrast thin-slice (1-mm-thick) axial and coronal images through the sella with fat suppression as needed. For patients with rare contraindications to MRI, thin-slice stereotactic CT scans were obtained instead. SRS and dose planning were subsequently performed in consultation with a neurosurgeon, radiation oncologist, and medical physicist.[52,56] At each center, dose selection was based on a complex iteration of tumor volume, contiguity to the optic apparatus, and history of exposure to fractionated radiation therapy.

Statistical Analysis

Statistical analyses were performed using R (2014) (R Foundation for Statistical Computing). All statistical tests were 2-sided. For all statistical tests, a p value ≤ 0.05 was considered significant. In general, data are presented as the frequency for categorical variables and as the mean with SD or median with range for continuous variables.

Propensity score matching in a 1:1 fashion was conducted with nearest-neighbor matching, and patients with nonfunctioning pituitary macroadenomas who underwent GKRS within 6 months following the last resection (early GKRS cohort) were matched and blinded to the outcomes of the delayed group (late GKRS cohort), which included patients who underwent GKRS later than 6 months after last resection. Matching was conducted based on the following parameters: null cell, gonadotroph, thyrotroph, somatotroph, silent ACTH staining of a previously resected tumor, age at GKRS, target volume at GKRS, and radiosurgical margin dose.

Categorical data were compared between the 2 cohorts using Pearson's chi-square test, and continuous data were compared using the Student t-test. Kaplan-Meier analysis was performed with the log-rank test to determine the statistical significance of the actuarial tumor progression rate over time after radiosurgery. Univariate Cox proportional hazards regression analysis was performed on the early and late GKRS cohorts, and age at GKRS and the radiosurgical variables were used to determine the factors significantly associated with the tumor progression rate. Three hundred fifty-seven patients had complete data regarding histological staining. Following propensity score matching, 111 patients comprised each group.

Results

Patient Demographics and Presenting Symptoms

After matching, a total of 222 patients met the study criteria and were included in the analysis. Forty-seven patients (21.2%) from the prior single-institution study were included. Patients were stratified into 2 cohorts based on the interval between resection and radiosurgery: early (≤ 6 months) (n = 111) and late (> 6 months) (n = 111) groups. The average ages at transsphenoidal surgery and GKRS were 51.1 years and 53.0 years, respectively. In total, 31 patients underwent more than 1 resection before radiosurgery: 22 patients underwent 2 resections and 9 patients underwent 3 resections. The median clinical and imaging follow-up periods were 62.3 months and 51.6 months, respectively (Table 1). The vast majority of the 222 total patients presented with symptoms commonly associated with pituitary macroadenoma. Only 9 patients in the early cohort and 3 patients in the late cohort presented with incidental findings observed on imaging for unrelated clinical workup. For symptomatic patients, visual disturbance was the most common presenting symptom (n = 139; 62.6%) followed by headache (n = 122; 55.0%), fatigue and weakness (n = 41; 18.5%), and sexual dysfunction (n = 27; 12.2%). Endocrine function at presentation was determined by a combination of serum hormone levels and/or patient medications. Sixty patients (27.1%) presented with prior endocrinopathy. The only difference in symptoms at presentation was fatigue and weakness (24.3% in the early group vs 12.6% in the late group). Significantly more patients in the early cohort presented with hypothyroidism (18.9% of the early group vs 7.2% of the late group), and there were no other differences in presenting endocrine function between groups (Table 1).

Tumor Characteristics at the Time of Initial Presentation for Resection

All tumors at the time of surgery were macroadenomas and classified according to their volumetric dimensions, extent of invasion into surrounding structures, and histopathologic characteristics (Table 2). Preoperatively, most tumors (60.4% of the early cohort and 39.6% of the late cohort) measured 2–4 cm in maximum diameter. There was no difference in average tumor volume between the early cohort (12.4 cm^3; range 1.0–100.4 cm^3) and the late cohort (13.4 cm^3; range 1.0–115.0 cm^3). Thirty-seven (33.3%) tumors measured > 10 cm^3 in the early cohort versus 35 (31.5%) in the late cohort. The majority (79.7%) of patients had tumors with a suprasellar component, and 161 patients (72.5%) exhibited involvement of the cavernous sinus (78.4% in the early group vs 66.7% of the late group; $p = 0.07$). Histologically, adenomas were most commonly null cell (n = 113; 50.9%) followed by gonadotrophic (28.4%) and silent corticotrophic tumors (21.2%). There were no significant differences in the histopathologic findings between groups after matching.

Surgical Outcomes After Resection

Transsphenoidal surgery achieved average tumor reductions of 66.2% (8.3 cm^3) and 78.7% (10.7 cm^3) in the early and late cohorts, respectively. At 2 months following surgery, most patients (n = 159; 71.6%) exhibited residual tumor with no statistical difference between groups ($p = 0.79$). There was no difference in average residual tumor volume at that time (4.1 cm^3 in the early group [n = 89] vs 2.7 cm^3 in the late group [n = 70]; $p = 0.16$). Of 60 patients, 11 (18.3%) experienced resolution of preoperative endocrinopathy. Resolution of preexisting endocrinopathy ($p = 1.00$) or the development of new endocrinopathy after surgery ($p = 0.63$) did not differ between groups (Table 3).

GKRS Parameters

In the early cohort, median time to radiosurgery from prior resection was 4.0 months (range 0.1–6.0 months). In the late cohort, median time to radiosurgery from resection was 19.9 months (range 6.1–156.4 months). In the late cohort, 35 patients (31.5%) received treatment within 6–12 months after subtotal resection, 25 (22.5%) patients received treatment within 12–24 months, and 51 patients (46.0%) received treatment > 24 months after subtotal resection. There were no significant differences in radiosurgical parameters between groups. The median maximum dose to the tumor was 29 Gy across both cohorts (range 10–50 Gy). The median tumor margin dose was 15 Gy (range 5–25). The target volume was on average higher in the early cohort (5.7 cm^3) than the late cohort (5.3 cm^3), but without significant difference ($p = 0.67$). The maximum dose to the visual pathways (optic apparatus) was typically limited to a median of 7.2 Gy (range 1.0–13.7 Gy) (Table 4). To limit radiation to the optic apparatus, shielding was employed as needed.

Radiological Outcome

Patients in the early cohort had an average of 46.5 months of imaging follow-up after transsphenoidal resection (range 5.3–194.2 months) and 40.3 months after GKRS (range 2.8–189.2 months). Patients in the late cohort had an average of 82.9 months of imaging follow-up after transsphenoidal resection (range 13.1–214.3 months) and 49.8 months after GKRS (range 2.5–181.1 months), with the increase in follow-up being a result of the

extended interval between resection and time to SRS. In the early cohort, 30 patients (27.0%) received > 5 years and 6 patients (5.4%) received > 10 years of imaging follow-up. In the late cohort, 71 patients (63.9%) received > 5 years and 26 patients (23.4%) received > 10 years of imaging follow-up. More patients in the late cohort (n = 76; 93.8%) demonstrated residual tumor on imaging at the last follow- up versus the early cohort (n = 81; 83.5%) (p = 0.038). While most (82.2%) residual tumors (81.5% in the early group and 82.9% in the late group) did not significantly change in size over this follow-up period, there was a greater risk of tumor progression after GKRS in the late treatment group (p = 0.013 according to the log-rank test) over the median neuroimaging follow-up of 64.8 months. The actuarial adenoma progression rates were 2.8%, 6.1%, and 9.1% at 2 years, 4 years, and 6 years following SRS in the early cohort, respectively, while the rates were 7.8%, 14.3%, and 21.2%, respectively, in the late cohort (Fig. 1). The late cohort exhibited a significantly higher proportion of residual tumor at last follow-up (p = 0.038) as well as tumor growth or new tumor residual relative to postoperative imaging (Table 5).

Endocrine Outcome

Pituitary insufficiency was observed in 108 of 222 patients (48.6%) at the time of GKRS (p = 0.89). There was no significant difference between groups in the proportion of patients without endocrinopathy before GKRS who subsequently developed new endocrinopathy during the follow-up period: 6 of 51 patients (11.8%) in the early cohort compared with 5 of 53 patients (9.4%) in the late cohort (p = 0.76). This was also true regarding new endocrinopathies after presentation (before transsphenoidal resection): 19 patients (30.2%) in the early cohort compared with 15 patients (26.8%) in the late cohort (p = 0.84). There was no difference in endocrinopathy at last clinical follow-up (58.7% of the early cohort vs 55.5% of the late cohort; p = 0.68) (Table 5).

There was also no difference in resolved endocrinopathy across groups: 13.9% after presentation and 10.0% after GKRS in the early group compared with 25.0% after presentation (p = 0.32) and 12.1% after GKRS (p = 0.78) for the late group. Improvement in endocrinopathy was analyzed with more granularity by type, including hypogonadism, hypocortisolism, hypothyroidism, and panhypopituitarism. In the early group, 1 patient with hypogonadism, 5 patients with hypocortisolism, 2 patients with hypothyroidism, and 2 patients with panhypopituitarism had improvement or resolution after GKRS. In the late cohort, 6 patients with hypogonadism, 2 patients with hypocortisolism, 2 patients with hypothyroidism, and 2 patients with panhypopituitarism showed evidence of clinical resolution. Resolution of symptoms did not differ across groups (Table 5).

Discussion

NFPAs, which are hormonally quiescent and typically slow growing, can expand significantly and alter pituitary function by compressing normal glandular tissue.[11,61] Transsphenoidal surgery has become a mainstay of effective treatment for NFPA and can be curative for some patients. Still, technical difficulty and potential undue risk often preclude complete resection of locally invasive adenomas (i.e., adenomas that invade the cavernous sinus, sphenoid bone, or diaphragm sella).[40] SRS has been shown to be a safe and effective

adjuvant therapy for residual adenomas or progressive disease not amenable to gross-total resection by surgery alone (and, in rare cases, as initial treatment). Despite moderate advances in the modal spectrum of such therapy, significant cumulative lifetime morbidity presents a real clinical burden for both therapeutic regimens.[55]

The current study draws from 9 different institutions and includes a matched cohort of 222 patients who underwent transsphenoidal surgery followed by GKRS for residual nonfunctioning pituitary macroadenomas. All patients had residual tumor observed at the time of resection. GKRS was performed as an adjunct therapy in cases of residual adenomas that were observed on serial neuro-imaging after resection or exhibited local invasion to the cavernous sinus, bone, or dura, or GKRS was performed when recurrence was reasonably and clinically ascertained by the return of symptoms and the tumor was considered unlikely to respond to additional resection.[34] As a multiinstitutional follow-up to a prior study of 64 patients at the University of Virginia that revealed early GKRS within 6 months of resection was associated with less risk for tumor progression and endocrinopathy, a similar time frame was analyzed.[47] This time interval permits patients to recover from surgery, postsurgical changes on MRI to subside, and more optimal imaging for radiosurgical targeting purposes. Patients who exhibit equivocal changes on MRI at 2–3 months following surgery are typically followed up with routine care and subsequent imaging over the next 3–5 months. This contemporary treatment paradigm offers natural allocation between the early (≤ 6 months) and late (> 6 months) patient cohorts.

In concordance with the previous single-center study, early GKRS demonstrated better tumor control compared with expectant management followed by radiosurgery.[47] In the prior study, early GKRS conferred significantly higher radiological resolution of the residual tumor (median maximum dose of 32 Gy and tumor margin dose of 16 Gy across both cohorts); however, this was not observed in this multiinstitutional study. One possible explanation for the long-term radiological differences between the early and late treatment groups rests with the inherent tumor characteristics. If patients with growing adenomas are in fact harboring more aggressive yet ill-defined tumor biology, then these adenomas could be less effectively controlled by GKRS. Still, tumor biology (beyond type and subtype of adenoma) did not necessarily differ between the early and late cohorts because patients were effectively matched for these criteria. Early GKRS (within 6 months after resection) may simply not offer enough time for patients with most adenomas to reliably demonstrate tumor growth. Alternately, because volume is well known to affect outcomes in SRS, the larger volume adenoma may be less effectively controlled. However, there were no differences in the average tumor volume treated, either preoperatively or at the time of GKRS (or any other radiosurgical parameters), between the 2 groups.

Subtotal resection without adjuvant treatment reportedly results in high recurrence rates of 50%–60% within 10 years of surgery.[8,20,31,41,43,45] More recent investigations and meta-analyses place the incidence of macroadenoma growth at 12.5 per 100 person-years.[16] O'Sullivan et al. studied 159 patients with nonfunctioning adenomas who underwent resection without adjuvant radiation or radiosurgery and found tumor growth or recurrence in 33.5% of patients at a median follow-up of 4.1 years (range 1–20.7 months). The 5- and 10-year actuarial rates of recurrence or growth of residual adenoma were 24.4% and 51.5%,

respectively. [41] This is consistent with other surgical series that suggest 10-year recurrence rates ranging from 19% to 78% after resection.[10,11,41,42,59] Because recurrence is recognizably common after subtotal surgical resection, other techniques such as radiosurgery have been effective in treating patients with aggressive neuropathological attributes (such as silent ACTH-secreting adenomas) and in younger populations with recurrent or residual tumors.[52]

SRS offers a high rate of tumor control, with most studies citing a 90% control rate with a low rate of new neurological or endocrinological deficits.[4,13, 15,18,21–26,30,32,35,38,39,42,44–46, 48, 49,52,55,61,63,65] SRS has also become widely recognized as a reasonable alternative to repeat resection and fractionated radiation therapy.[52] Nonetheless, the promise of GKRS has been tempered in practice due to results being largely reported from single-center retrospective studies.[4,15, 18,21–26,30,32,35,39,42,44–46,49,54, 61,65] Despite favorable data from contemporary large-scale multicenter studies, the optimal role and timing of GKRS for patients with recurrent or residual growing NFPAs remains uncertain.[52] In a recent series of 140 consecutive patients with nonfunctioning pituitary macroadenomas treated with GKRS at the University of Virginia, the overall tumor control and actuarial 5-year progression-free survival rates were 90% and 97%, respectively. Tumor control correlated directly with radiosurgical target volume, which testifies to the lasting effects of microsurgical resection prior to GKRS for macroadenomas.[55] This purview was partially laid out by Mingione et al. in 2006, who proposed a propensity for nonfunctioning pituitary macroadenomas to either grow or decrease over longer follow-up periods.[35] Comparable long-term effectiveness of GKRS was achieved by Park et al. who demonstrated a 90% tumor control rate in 125 patients with nonfunctioning adenomas over a mean follow-up of 62 months.[42] Gopalan et al. achieved a tumor control rate of 83% over a median follow-up of 95 months.[18] These studies were similar in suggesting that tumor volume predicted neurological decline, including delayed hypopituitarism. [35,42,55] One may reason that providing suboptimal radiosurgical doses to larger adenomas in close proximity to radiation-sensitive structures may allow for tumor growth after GKRS.

Residual pituitary adenomas tend to progress slowly over time without further radiosurgery.[47,52] Despite this commonality, some patients with residual disease never exhibit radiological or clinical progression despite long follow-up intervals. The timing of adjuvant therapy aside, clinicians may not be able to predict with any reasonable reliability those patients who will have stable tumor volume after subtotal resection alone from those who will have progressive tumor growth over a shorter interval after surgery. A central and persistent contention against early GKRS rests on the basis that many residual adenomas may not in fact progress and that such treatment would need-lessly expose patients to potential complications. Additionally, there is debate regarding the effectiveness of GKRS for actively growing adenomas relative to radiologically stable ones.

The current study offers another salient observation and departure from prior findings of long-term endocrinopathy based on the interval between last subtotal resection and GKRS. In the previous study, late adjuvant GKRS treatment was associated with significantly higher rates of endocrinopathy secondary to higher rates of tumor growth during the observational

period prior to GKRS.[47] Patients in the late cohort (64%) without baseline endocrinopathy were more likely to develop new endocrinopathy following radiosurgery relative to the early cohort (17%).[47] In the current study, this difference disappeared both in terms of new endocrinopathy after presentation (30% of patients in the early cohort vs 27% of patients in the late cohort) and after GKRS (12% of patients in the early cohort vs 9% of patients in the late cohort). Fifty-nine percent of patients in the early cohort and 56% of patients in the late cohort experienced endocrine dysfunction at the last clinical follow-up ($p = 0.68$). The rates of new endocrinopathy after presentation ($p = 0.84$), new endocrinopathy after GKRS ($p = 0.76$), and resolved endocrinopathy after presentation ($p = 0.32$) and GKRS ($p = 0.78$) were comparable between groups.

The present study draws from several unique strengths, including the large number of patients drawn from multiple institutions and the longitudinal nature of the follow-up relative to other reports in the literature. To the best of our knowledge, this is the largest multicenter matched-cohort study to use propensity scorematching to reduce bias. Despite these efforts, this study is not without weakness. As a retrospective analysis with inherent referral pattern bias for both the patient and clinician, the selection criteria and dose-planning techniques were nonuniform across treatment centers. Patient bias could have been introduced by preferring early treatment versus opting to be followed for a longer period before electively proceeding with radiosurgery. We can also now use more modern SRS devices to administer hypofractionated treatments to treat some larger adenomas and more optimally deliver an effective margin dose to the tumor while still respecting constraints to critical structures (e.g., the optic apparatus). Comparing visual function after surgery and radiosurgery and over the long term would also yield valuable insight into the symptomatic course; unfortunately, while we did have reliable visual function data across all participating sites, formal visual field and acuity testing was not performed uniformly or regularly at some centers. Finally, the median follow-up was 5.2 years and some patients had a relatively short follow-up, which may have precluded complete assessment of delayed endocrine dysfunction and/or tumor control.

While the preresection and preradiosurgical growth rates were not the focus of the study, further tumor classification might provide valuable insight into the differences observed between the 2 groups. All of the patients in this study harbored histologically confirmed NFPAs. The Ki-67 rates were not reliably collected for all patients in this review, but Ki-67 tends to be low in nonfunctioning adenomas. In a study by Thapar et al., the mean growth fraction for nonfunctioning adenomas was 2.09%, while functioning adenomas had a growth rate of 3.25% and pituitary carcinomas had 11.91%.[57] Most series have shown no difference in tumor control after SRS in functioning versus nonfunctioning adenomas.[51] Thus, even if these nonfunctioning adenomas exhibited a slightly higher Ki-67 rate than typical that placed them at the level of functioning adenomas, growth control after radiosurgery should still have been high because achieving growth control in functioning adenomas with radiosurgery is quite likely. The nonfunctioning adenomas herein were not pituitary carcinomas, which respond less well to ionizing radiation, and no pituitary carcinomas were included in the study.

The 6-month time interval of the current analysis was based on the findings of a prior single-institutional study.[47] Unfortunately, given the variability in the timing of SRS in the late group, finding an adequate later time point that would allow for case matching in the current cohort is not practical. The 6-month cutoff point may in fact be arbitrary, and findings simply suggest a difference in outcome with earlier versus later treatment. Further studies are required to better define the point at which SRS is given after resection that will result in a worse outcome to the patient. Testing multiple time points would likely require a more prospective study or at least multiple matched analyses, which goes beyond the presently available data for this multicenter group.

Patients in the late treatment cohort were treated for a multitude of reasons including tumor presence, symptomatic presence (e.g., headaches), patient preference in the setting of persistent disease, and tumor progression. This could have introduced bias if the analyses were not matched for tumor volume and pre-GKRS endocrinopathy between the early and late treatment groups. Adenoma volume and preexisting endocrinopathies have been shown to impact post-GKRS outcomes. Because these factors were matched, they should not have led to the observed differences in outcome. Nevertheless, we acknowledge that selection biases or the inherent failings of a propensity matched analysis could have led to unintended biases in the results.

This is a multiinstitutional matched-cohort review and does not substitute for prospective trials. Further prospective studies, or analysis of data accrued by large, prospective registries with propensity score matching along with central radiographic review, would more definitively unearth any differences in tumor control and endocrine outcomes based on treatment timing. Innovations in treatment modalities and providing patient care would assuredly benefit from more interdisciplinary and longitudinal follow-up studies of the natural history of surgically treated tumors.

Conclusions

In the largest multicenter matched-cohort review of adjuvant GKRS for nonfunctioning pituitary macroadenomas to date, early GKRS is associated with a decreased risk of imaging-defined progression of subtotally resected tumors compared with expectant management. The timing of adjuvant GKRS does not appear to significantly affect the rate of postradiosurgical endocrinopathy over the long term.

ABBREVIATIONS

ACTH	adrenocorticotrophic hormone
AP	anteroposterior
CC	craniocaudal
GKRS	Gamma Knife radiosurgery
NFPA	nonfunctioning pituitary adenoma

SRS	stereotactic radiosurgery
TR	transverse

References

1. Attanasio R, Epaminonda P, Motti E, Giugni E, Ventrella L, Cozzi R, et al. Gamma-Knife radiosurgery in acromegaly: a 4-year follow-up study. J Clin Endocrinol Metab. 2003; 88:3105–3112. [PubMed: 12843150]
2. Brada M, Rajan B, Traish D, Ashley S, Holmes-Sellors PJ, Nussey S, et al. The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. Clin Endocrinol (Oxf). 1993; 38:571–578. [PubMed: 8334743]
3. Brochier S, Galland F, Kujas M, Parker F, Gaillard S, Raftopoulos C, et al. Factors predicting relapse of nonfunctioning pituitary macroadenomas after neurosurgery: a study of 142 patients. Eur J Endocrinol. 2010; 163:193–200. [PubMed: 20460423]
4. Castro DG, Cecílio SA, Canteras MM. Radiosurgery for pituitary adenomas: evaluation of its efficacy and safety. Radiat Oncol. 2010; 5:109. [PubMed: 21083925]
5. Chandler WF, Schteingart DE, Lloyd RV, McKeever PE, Ibarra-Perez G. Surgical treatment of Cushing's disease. J Neurosurg. 1987; 66:204–212. [PubMed: 3806203]
6. Chang EF, Zada G, Kim S, Lamborn KR, Quinones-Hinojosa A, Tyrrell JB, et al. Long-term recurrence and mortality after surgery and adjuvant radiotherapy for nonfunctional pituitary adenomas. J Neurosurg. 2008; 108:736–745. [PubMed: 18377253]
7. Comtois R, Beauregard H, Somma M, Serri O, Aris-Jilwan N, Hardy J. The clinical and endocrine outcome to transsphenoidal microsurgery of nonsecreting pituitary adenomas. Cancer. 1991; 68:860–866. [PubMed: 1855185]
8. Dallapiazza RF, Grober Y, Starke RM, Laws ER Jr, Jane JA Jr. Long-term results of endonasal endoscopic transsphenoidal resection of nonfunctioning pituitary macroadenomas. Neurosurgery. 2015; 76:42–53. [PubMed: 25255271]
9. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J Clin Endocrinol Metab. 2006; 91:4769–4775. [PubMed: 16968795]
10. Dekkers OM, Pereira AM, Roelfsema F, Voormolen JH, Neelis KJ, Schroijen MA, et al. Observation alone after transsphenoidal surgery for nonfunctioning pituitary macroadenoma. J Clin Endocrinol Metab. 2006; 91:1796–1801. [PubMed: 16507632]
11. Dekkers OM, Pereira AM, Romijn JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. J Clin Endocrinol Metab. 2008; 93:3717–3726. [PubMed: 18682516]
12. Ebersold MJ, Laws ER Jr, Scheithauer BW, Randall RV. Pituitary apoplexy treated by transsphenoidal surgery. A clinicopathological and immunocytochemical study. J Neurosurg. 1983; 58:315–320. [PubMed: 6827315]
13. El-Shehaby AM, Reda WA, Tawadros SR, Abdel Karim KM. Low-dose Gamma Knife surgery for nonfunctioning pituitary adenomas. J Neurosurg. 2012; 117(Suppl):84–88. [PubMed: 23205793]
14. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al. The prevalence of pituitary adenomas: a systematic review. Cancer. 2004; 101:613–619. [PubMed: 15274075]
15. Feigl GC, Pistracher K, Berghold A, Mokry M. Pituitary insufficiency as a side effect after radiosurgery for pituitary adenomas: the role of the hypothalamus. J Neurosurg. 2010; 113(Suppl): 153–159.
16. Fernández-Balsells MM, Murad MH, Barwise A, Gallegos-Orozco JF, Paul A, Lane MA, et al. Natural history of nonfunctioning pituitary adenomas and incidentalomas: a systematic review and metaanalysis. J Clin Endocrinol Metab. 2011; 96:905–912. [PubMed: 21474687]
17. Ferrante E, Ferraroni M, Castrignanò T, Menicatti L, Anagni M, Reimondo G, et al. Non-functioning pituitary adenoma database: a useful resource to improve the clinical management of pituitary tumors. Eur J Endocrinol. 2006; 155:823–829. [PubMed: 17132751]

18. Gopalan R, Schlesinger D, Vance ML, Laws E, Sheehan J. Long-term outcomes after Gamma Knife radiosurgery for patients with a nonfunctioning pituitary adenoma. Neurosurgery. 2011; 69:284–293. [PubMed: 21792138]
19. Greenman Y, Ouaknine G, Veshchev I, Reider-Groswasser II, Segev Y, Stern N. Postoperative surveillance of clinically nonfunctioning pituitary macroadenomas: markers of tumour quiescence and regrowth. Clin Endocrinol (Oxf). 2003; 58:763–769. [PubMed: 12780754]
20. Greenman Y, Stern N. How should a nonfunctioning pituitary macroadenoma be monitored after debulking surgery? Clin Endocrinol (Oxf). 2009; 70:829–832. [PubMed: 19222490]
21. Hayashi M, Chernov M, Tamura N, Nagai M, Yomo S, Ochiai T, et al. Gamma Knife robotic microradiosurgery of pituitary adenomas invading the cavernous sinus: treatment concept and results in 89 cases. J Neurooncol. 2010; 98:185–194. [PubMed: 20411299]
22. Höybye C, Rähn T. Adjuvant Gamma Knife radiosurgery in non-functioning pituitary adenomas; low risk of long-term complications in selected patients. Pituitary. 2009; 12:211–216. [PubMed: 19152112]
23. Iwai Y, Yamanaka K, Yoshioka K. Radiosurgery for nonfunctioning pituitary adenomas. Neurosurgery. 2005; 56:699–705. [PubMed: 15792508]
24. Iwata H, Sato K, Tatewaki K, Yokota N, Inoue M, Baba Y, et al. Hypofractionated stereotactic radiotherapy with CyberKnife for nonfunctioning pituitary adenoma: high local control with low toxicity. Neuro Oncol. 2011; 13:916–922. [PubMed: 21665918]
25. Kajiwara K, Saito K, Yoshikawa K, Kato S, Akimura T, Nomura S, et al. Image-guided stereotactic radiosurgery with the CyberKnife for pituitary adenomas. Minim Invasive Neurosurg. 2005; 48:91–96. [PubMed: 15906203]
26. Kobayashi T. Long-term results of stereotactic Gamma Knife radiosurgery for pituitary adenomas. Specific strategies for different types of adenoma. Prog Neurol Surg. 2009; 22:77–95. [PubMed: 18948721]
27. Langsenlehner T, Stiegler C, Quehenberger F, Feigl GC, Jakse G, Mokry M, et al. Long-term follow-up of patients with pituitary macroadenomas after postoperative radiation therapy: analysis of tumor control and functional outcome. Strahlenther Onkol. 2007; 183:241–247. [PubMed: 17497095]
28. Laws ER, , JrEbersold MJ, Piepgras DG, Randall RV, Salassa RM. The results of transsphenoidal surgery in specific clinical entities. In: Laws ER, , JRRandall RV, Kern EB. , et al., editorsManagement of Pituitary Adenomas and Related Lesions with Emphasis on Transsphenoidal Microsurgery. New York: Appleton-Century-Crofts; 1982. 277–305.
29. Laws ER Jr, Vance ML. Radiosurgery for pituitary tumors and craniopharyngiomas. Neurosurg Clin N Am. 1999; 10:327–336. [PubMed: 10099097]
30. Liscák R, Vladyka V, Marek J, Simonová G, Vymazal J. Gamma Knife radiosurgery for endocrine-inactive pituitary adenomas. Acta Neurochir (Wien). 2007; 149:999–1006. [PubMed: 17676409]
31. Losa M, Mortini P, Barzaghi R, Ribotto P, Terreni MR, Marzoli SB, et al. Early results of surgery in patients with nonfunctioning pituitary adenoma and analysis of the risk of tumor recurrence. J Neurosurg. 2008; 108:525–532. [PubMed: 18312100]
32. Losa M, Valle M, Mortini P, Franzin A, da Passano CF, Cenzato M, et al. Gamma Knife surgery for treatment of residual nonfunctioning pituitary adenomas after surgical debulking. J Neurosurg. 2004; 100:438–444. [PubMed: 15035279]
33. Mak HK, Lai SW, Qian W, Xu S, Tong E, Vance ML, et al. Effective time window in reducing pituitary adenoma size by Gamma Knife radiosurgery. Pituitary. 2015; 18:509–517. [PubMed: 25261330]
34. Meij BP, Lopes MB, Ellegala DB, Alden TD, Laws ER Jr. The long-term significance of microscopic dural invasion in 354 patients with pituitary adenomas treated with transsphenoidal surgery. J Neurosurg. 2002; 96:195–208. [PubMed: 11838791]
35. Mingione V, Yen CP, Vance ML, Steiner M, Sheehan J, Laws ER, et al. Gamma surgery in the treatment of nonsecretory pituitary macroadenoma. J Neurosurg. 2006; 104:876–883. [PubMed: 16776330]
36. Minniti G, Gilbert DC, Brada M. Modern techniques for pituitary radiotherapy. Rev Endocr Metab Disord. 2009; 10:135–144. [PubMed: 18787957]

37. Minniti G, Jaffrain-Rea ML, Osti M, Cantore G, Enrici RM. Radiotherapy for nonfunctioning pituitary adenomas: from conventional to modern stereotactic radiation techniques. Neurosurg Rev. 2007; 30:167–176. [PubMed: 17483973]
38. Minniti G, Scaringi C, Poggi M, Jaffrain Rea ML, Trillò G, Esposito V, et al. Fractionated stereotactic radiotherapy for large and invasive non-functioning pituitary adenomas: long-term clinical outcomes and volumetric MRI assessment of tumor response. Eur J Endocrinol. 2015; 172:433–441. [PubMed: 25627653]
39. Muacevic A, Uhl E, Wowra B. Gamma knife radiosurgery for nonfunctioning pituitary adenomas. Acta Neurochir Suppl. 2004; 91:51–54. [PubMed: 15707025]
40. Oldfield EH. Editorial. Management of invasion by pituitary adenomas. J Neurosurg. 2014; 121:501–503. [PubMed: 25014439]
41. O'Sullivan EP, Woods C, Glynn N, Behan LA, Crowley R, O'Kelly P, et al. The natural history of surgically treated but radiotherapy-naïve nonfunctioning pituitary adenomas. Clin Endocrinol (Oxf). 2009; 71:709–714. [PubMed: 19302582]
42. Park KJ, Kano H, Parry PV, Niranjan A, Flickinger JC, Lunsford LD, et al. Long-term outcomes after Gamma Knife stereotactic radiosurgery for nonfunctional pituitary adenomas. Neurosurgery. 2011; 69:1188–1199. [PubMed: 21552167]
43. Park P, Chandler WF, Barkan AL, Orrego JJ, Cowan JA, Griffith KA, et al. The role of radiation therapy after surgical resection of nonfunctional pituitary macroadenomas. Neurosurgery. 2004; 55:100–107. [PubMed: 15214978]
44. Petrovich Z, Yu C, Giannotta SL, Zee CS, Apuzzo ML. Gamma Knife radiosurgery for pituitary adenoma: early results. Neurosurgery. 2003; 53:51–61. [PubMed: 12823873]
45. Picozzi P, Losa M, Mortini P, Valle MA, Franzin A, Attuati L, et al. Radiosurgery and the prevention of regrowth of incompletely removed nonfunctioning pituitary adenomas. J Neurosurg. 2005; 102(Suppl):71–74. [PubMed: 15662784]
46. Pollock BE, Cochran J, Natt N, Brown PD, Erickson D, Link MJ, et al. Gamma Knife radiosurgery for patients with nonfunctioning pituitary adenomas: results from a 15-year experience. Int J Radiat Oncol Biol Phys. 2008; 70:1325–1329. [PubMed: 18029107]
47. Pomeraniec IJ, Dallapiazza RF, Xu Z, Jane JA Jr, Sheehan JP. Early versus late Gamma Knife radiosurgery following transsphenoidal resection for nonfunctioning pituitary macroadenomas: a matched cohort study. J Neurosurg. 2016; 125:202–212. [PubMed: 26517773]
48. Runge MJ, Maarouf M, Hunsche S, Kocher M, Ruge MI, El Majdoub F, et al. LINAC-radiosurgery for nonsecreting pituitary adenomas. Long-term results. Strahlenther Onkol. 2012; 188:319–325. [PubMed: 22349709]
49. Sheehan JP, Kondziolka D, Flickinger J, Lunsford LD. Radiosurgery for residual or recurrent nonfunctioning pituitary adenoma. J Neurosurg. 2002; 97(5 Suppl):408–414.
50. Sheehan JP, Niranjan A, Sheehan JM, Jane JA Jr, Laws ER, Kondziolka D, et al. Stereotactic radiosurgery for pituitary adenomas: an intermediate review of its safety, efficacy, and role in the neurosurgical treatment armamentarium. J Neurosurg. 2005; 102:678–691. [PubMed: 15871511]
51. Sheehan JP, Pouratian N, Steiner L, Laws ER, Vance ML. Gamma Knife surgery for pituitary adenomas: factors related to radiological and endocrine outcomes. J Neurosurg. 2011; 114:303–309. [PubMed: 20540596]
52. Sheehan JP, Starke RM, Mathieu D, Young B, Sneed PK, Chiang VL, et al. Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. J Neurosurg. 2013; 119:446–456. [PubMed: 23621595]
53. Snell JW, Sheehan J, Stroila M, Steiner L. Assessment of imaging studies used with radiosurgery: a volumetric algorithm and an estimation of its error. Technical note. J Neurosurg. 2006; 104:157–162.
54. Starke RM, Nguyen JH, Rainey J, Williams BJ, Sherman JH, Savage J, et al. Gamma Knife surgery of meningiomas located in the posterior fossa: factors predictive of outcome and remission. J Neurosurg. 2011; 114:1399–1409. [PubMed: 21214335]
55. Starke RM, Williams BJ, Jane JA Jr, Sheehan JP. Gamma Knife surgery for patients with nonfunctioning pituitary macroadenomas: predictors of tumor control, neurological deficits, and hypopituitarism. J Neurosurg. 2012; 117:129–135. [PubMed: 22577749]

56. Steiner LSJ, Lindquist C, Stroila M, Steiner M. Gamma surgery in cerebral vascular lesions, malformations, tumors, and functional disorders. In: Schmidek HH, Roberts DW, editorsSchmidek & Sweet Operative Neurosurgical Techniques: Indications, Methods, and Results. 5. Vol. 1. Philadelphia: Saunders; 2006. 530–576.
57. Thapar K, Kovacs K, Scheithauer BW, Stefaneanu L, Horvath E, Pernicone PJ, et al. Proliferative activity and invasiveness among pituitary adenomas and carcinomas: an analysis using the MIB-1 antibody. Neurosurgery. 1996; 38:99–107. [PubMed: 8747957]
58. Turner HE, Stratton IM, Byrne JV, Adams CB, Wass JA. Audit of selected patients with nonfunctioning pituitary adenomas treated without irradiation—a follow-up study. Clin Endocrinol (Oxf). 1999; 51:281–284. [PubMed: 10469006]
59. van den Bergh AC, van den Berg G, Schoorl MA, Sluiter WJ, van der Vliet AM, Hoving EW, et al. Immediate postoperative radiotherapy in residual nonfunctioning pituitary adenoma: beneficial effect on local control without additional negative impact on pituitary function and life expectancy. Int J Radiat Oncol Biol Phys. 2007; 67:863–869. [PubMed: 17197121]
60. Vance ML. Pituitary adenoma: a clinician's perspective. Endocr Pract. 2008; 14:757–763. [PubMed: 18996799]
61. Voges J, Kocher M, Runge M, Poggenborg J, Lehrke R, Lenartz D, et al. Linear accelerator radiosurgery for pituitary macroadenomas: a 7-year follow-up study. Cancer. 2006; 107:1355–1364. [PubMed: 16894526]
62. Williams BJ, Yen CP, Starke RM, Basina B, Nguyen J, Rainey J, et al. Gamma Knife surgery for parasellar meningiomas: long-term results including complications, predictive factors, and progression-free survival. J Neurosurg. 2011; 114:1571–1577. [PubMed: 21314269]
63. Wilson PJ, De-Loyde KJ, Williams JR, Smee RI. A single centre's experience of stereotactic radiosurgery and radiotherapy for non-functioning pituitary adenomas with the linear accelerator (Linac). J Clin Neurosci. 2012; 19:370–374. [PubMed: 22277561]
64. Woollons AC, Hunn MK, Rajapakse YR, Toomath R, Hamilton DA, Conaglen JV, et al. Non-functioning pituitary adenomas: indications for postoperative radiotherapy. Clin Endocrinol (Oxf). 2000; 53:713–717. [PubMed: 11155093]
65. Wowra B, Stummer W. Efficacy of Gamma Knife radiosurgery for nonfunctioning pituitary adenomas: a quantitative follow up with magnetic resonance imaging-based volumetric analysis. J Neurosurg. 2002; 97(5 Suppl):429–432. [PubMed: 12507069]
66. Zhang X, Fei Z, Zhang J, Fu L, Zhang Z, Liu W, et al. Management of nonfunctioning pituitary adenomas with suprasellar extensions by transsphenoidal microsurgery. Surg Neurol. 1999; 52:380–385. [PubMed: 10555844]

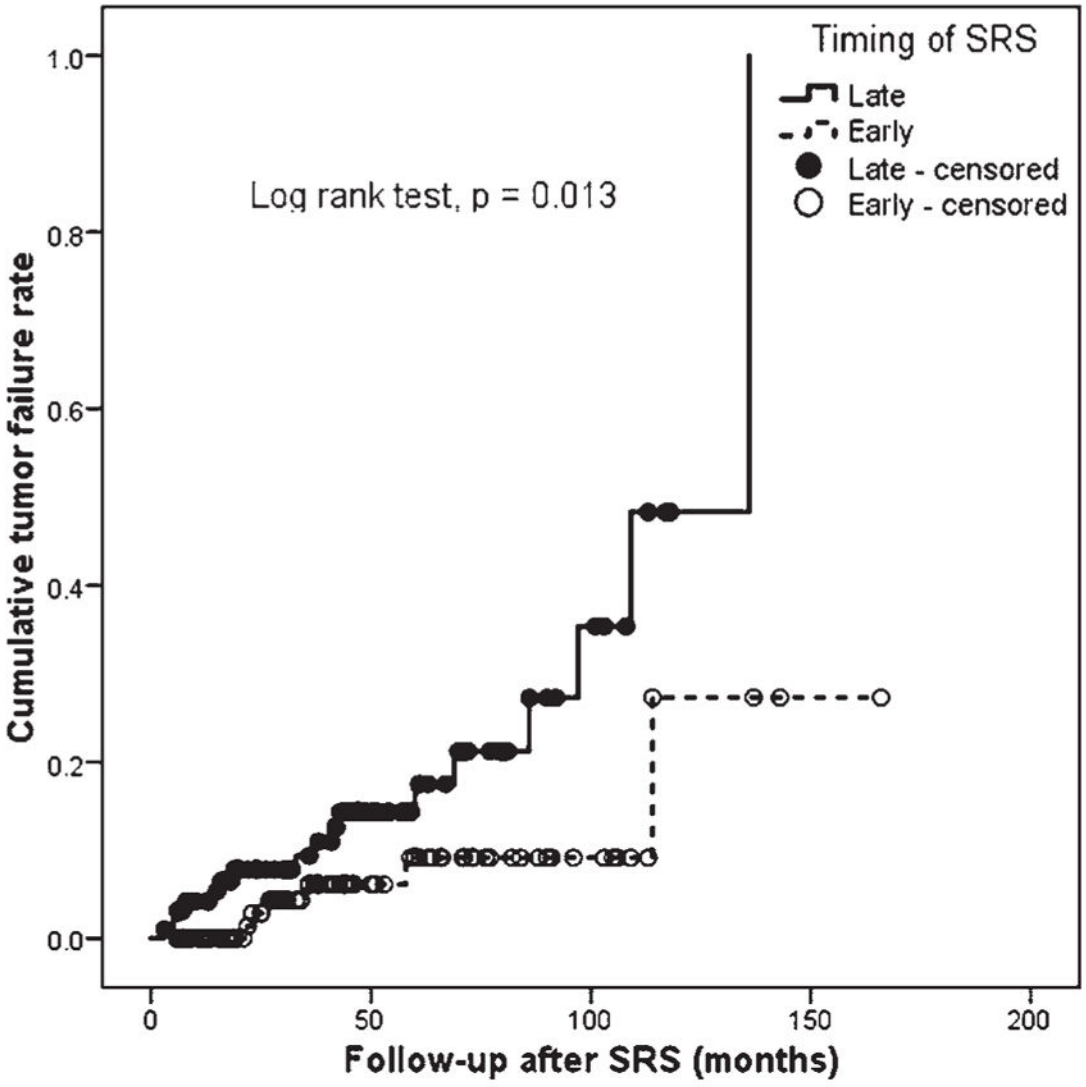

FIG. 1.

Kaplan-Meier plot of tumor progression over time. This plot compares the cumulative tumor failure rate over time between the early (GKRS ≤ 6 months after resection) and late (GKRS > 6 months after resection) groups.

TABLE 1

Patient demographics

Characteristic	Early GKRS (≤6 mos)	Late GKRS (>6 mos)	p Value
No. of patients	111 (50.0)	111 (50.0)	
Sex			
Male	43 (38.7)	48 (43.2)	1.00
Female	47 (42.3)	53 (47.7)	
Unknown	21 (18.9)	10 (9.0)	
Age at procedure, mean (SD), yrs			
Surgery	52.5 (12.4)	49.7 (12.5)	
GKRS	53.3 (12.4)	52.6 (13.2)	
Follow-up after last trans-sphenoidal resection, median (range), mos			
Clinical	42.2 (5.6–202.4)	85.6 (9.1–217.0)	
Imaging	37.8 (5.3–194.2)	75.1 (13.1–214.3)	
Presenting symptoms			
Visual deficit	72 (64.9)	67 (60.4)	0.58
Headache	66 (59.5)	56 (50.5)	0.22
Endocrinopathy	36 (32.4)	24 (21.6)	0.10
Fatigue/weakness	27 (24.3)	14 (12.6)	**0.04**
Sexual dysfunction	17 (15.3)	10 (9.0)	0.22
Incidental	9 (8.1)	3 (2.7)	0.14
Unknown	11 (9.9)	31 (27.9)	**0.001**
Endocrine function*			
Hypogonadism	11 (9.9)	11 (9.9)	1.00
Hypocortisolism	5 (4.5)	6 (2.4)	1.00
Hypothyroidism	21 (18.9)	8 (7.2)	**0.02**
Panhypopituitarism	10 (9.0)	8 (7.2)	0.81
No endocrinopathy	63 (56.8)	56 (50.5)	0.42
Unknown	12 (10.8)	31 (27.9)	**0.002**

Values are reported as number (%) of patients unless specified otherwise.

Boldface type indicates statistical significance.

*These findings are not mutually exclusive, e.g., 1 patient could have 2 or more endocrine abnormalities that were separately counted.

TABLE 2

Preoperative tumor characteristics

Characteristic	Early GKRS (≤6 mos)	Late GKRS (>6 mos)	p Value
Maximum tumor diameter, cm			
1–1.9	10 (9.0)	11 (9.9)	1.00
2–2.9	39 (35.1)	23 (20.7)	**0.02**
3–4.0	28 (25.2)	21 (18.9)	0.33
>4.0	19 (17.1)	18 (16.2)	1.00
Unknown	15 (13.5)	38 (34.2)	**0.001**
Mean tumor volume			
<10 cm^3	52 (46.8)	36 (32.4)	0.34
>10 cm^3	37 (33.3)	35 (31.5)	
Unknown	22 (19.8)	40 (36.0)	
Involvement			
Suprasellar involvement	93 (83.8)	84 (75.7)	0.18
Cavernous sinus invasion	87 (78.4)	74 (66.7)	0.07
Histopathology *			
Null cell	52 (46.8)	61 (55.0)	0.28
Gonadotrophic	34 (30.6)	29 (26.1)	0.55
Silent corticotrophic	26 (23.4)	21 (18.9)	0.51
Thyrotrophic	3 (2.7)	3 (2.7)	1.00
Somatotrophic	3 (2.7)	4 (3.6)	1.00

All values are presented as number (%) of patients. Boldface type indicates statistical significance.

* These findings are not mutually exclusive, e.g., 13 patients had plurihormonal stains and each was counted separately.

TABLE 3

Surgical treatment

Characteristic	Early GKRS (≤6 mos)	Late GKRS (>6 mos)
Tumor volume, cm^3		
Preop	12.4	13.4
Postop	4.1	2.7
Size reduction, % change *	66.2	78.7
Endocrinopathy, no. of cases (%)		
Preop information	100 (90.1)	82 (73.9)
Preop endocrinopathy	36 (36.0)	24 (29.3)
Postop information	111 (100)	111 (100)
Postop endocrinopathy	50 (45.0)	49 (44.1)
Resolved endocrinopathy	5 (4.5)	6 (5.4)
New endocrinopathy	11 (9.9)	8 (7.2)
No change endocrinopathy	31 (27.9)	18 (16.2)

* Calculated as the average of each patient's individual volume reduction.

TABLE 4

Radiosurgical parameters

Parameter	Early GKRS (≤6 mos)	Late GKRS (>6 mos)	p Value
Margin dose, Gy	14.8 (10.0–25.0)	14.5 (5.0–25.0)	0.41
Maximum dose, Gy	29.4 (19.2–50.0)	28.3 (10.0–50.0)	0.18
Target volume, cm^3	5.7 (0.0–57.3)	5.3 (0.3–37.6)	0.63
Maximum dose to optic chiasm, Gy	7.3 (1.0–12.3)	7.8 (1.2–12.6)	0.31
Maximum dose to optic tract, Gy	6.2 (1.5–12.0)	6.6 (1.2–12.0)	0.53
Maximum dose to optic nerve, Gy	7.5 (1.4–13.7)	7.2 (1.2–12.3)	0.44

All values are shown as the median (range).

TABLE 5

Summary of patient outcomes

Outcome	Early GKRS (≤6 mos)	Late GKRS (>6 mos)	p Value
Residual tumor at last follow-up *			
Yes	81 (83.5)	76 (93.8)	**0.0375**
No	16 (16.5)	5 (6.2)	
Unknown	14		
Tumor status after GKRS			
Stable †	66 (81.5)	63 (82.9)	0.84
Growth	15 (18.5)	13 (17.1)	
Growth >15%	11 (13.6)	8 (10.5)	0.63
Post-GKRS endocrinopathy ‡			
Yes	64 (58.7)	61 (55.5)	0.68
No	45 (41.3)	49 (44.5)	
Unknown	2	1	
New endocrinopathy after presentation §	19 (30.2)	15 (26.8)	0.84
New endocrinopathy after GKRS ¶	6 (11.8)	5 (9.4)	0.76
Resolved endocrinopathy after presentation **	5 (13.9)	6 (25.0)	0.32
Resolved endocrinopathy after GKRS ††	6 (10.0)	7 (12.1)	0.78
New endocrinopathy after GKRS §§			
Hypogonadism	6 (5.4)	6 (5.4)	1.00
Hypocortisolism	3 (2.7)	6 (5.4)	0.49
Hypothyroidism	6 (5.4)	9 (8.1)	0.59
Panhypopituitarism	6 (5.4)	6 (5.4)	1.00
Resolved endocrinopathy after GKRS §§			
Hypogonadism	1 (0.9)	6 (5.4)	0.12
Hypocortisolism	5 (4.5)	2 (1.8)	0.45
Hypothyroidism	2 (1.8)	2 (1.8)	1.00
Panhypopituitarism	2 (1.8)	2 (1.8)	1.00

All values are presented as number (%) of patients. Boldface type indicates statistical significance.

* Shown as the percentage of patients with residual tumor information (97 patients in the early group and 81 patients in the late group).

† Change of volume ≤ 15% after GKRS.

‡ Shown as the percentage of patients with known postop endocrinopathy information (109 patients in the early group and 110 in the late group).

§ Shown as the percentage of patients with no endocrinopathy at presentation (63 patients in the early group and 56 patients in the late group).

¶ Shown as the percentage of patients with no pre-GKRS endocrinopathy (51 patients in the early group and 53 patients in late group).

** Shown as the percentage of patients with endocrinopathy at presentation (36 patients in the early group and 24 patients in the late group).

[††] Shown as the percentage of patients with pre-GKRS endocrinopathy (60 patients in the early group and 58 patients in the late group).

[§§] Shown as the percentage of each cohort.