Early versus late Gamma Knife radiosurgery for Cushing's disease after prior resection: results of an international, multicenter study

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OBJECTIVE The optimal time to perform stereotactic radiosurgery after incomplete resection of adrenocorticotrophic hormone (ACTH)–producing pituitary adenoma in patients with Cushing's disease (CD) remains unclear. In patients with persistent CD after resection of ACTH-producing pituitary adenoma, the authors evaluated the association of the interval between resection and Gamma Knife radiosurgery (GKRS) with outcomes.

METHODS Pooled data from 10 institutions participating in the International Radiosurgery Research Foundation were used in this study.

RESULTS Data from 255 patients with a mean follow-up of 65.59 ± 49.01 months (mean $\pm$ SD) were analyzed. Seventy-seven patients (30%) underwent GKRS within 3 months; 46 (18%) from 4 to 6 months; 34 (13%) from 7 to 12 months; and 98 (38%) at > 12 months after the resection. Actuarial endocrine remission rates were higher in patients who underwent GKRS ≤ 3 months than when treatment was > 3 months after the resection (78% and 65%, respectively; $p = 0.017$). Endocrine remission rates were lower in patients who underwent GKRS at > 12 months versus ≤ 12 months after the resection (57% vs 76%, respectively; $p = 0.006$). In multivariate Cox regression analyses adjusted for clinical and treatment characteristics, early GKRS was associated with increased probability of endocrine remission (hazard ratio [HR] 1.518, 95% CI 1.039–2.218; $p = 0.031$), whereas late GKRS (HR 0.641, 95% CI 0.448–0.919; $p = 0.015$) was associated with reduced probability of endocrine remission. The incidence of some degree of new pituitary deficiency ($p = 0.922$), new visual deficits ($p = 0.740$), and other cranial nerve deficits ($p = 0.610$) was not significantly related to time from resection to GKRS.

ABBREVIATIONS ACTH = adrenocorticotrophic hormone; CD = Cushing's disease; CKRS = CyberKnife SRS; GKRS = Gamma Knife radiosurgery; HR = hazard ratio; LINAC = linear accelerator; SRS = stereotactic radiosurgery; UFC = urinary free cortisol.

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CONCLUSIONS Early GKRS is associated with an improved endocrine remission rate, whereas later GKRS is associated with a lower rate of endocrine remission after pituitary adenoma resection. Early GKRS should be considered for patients with CD after incomplete pituitary adenoma resection.

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KEYWORDS Cushing's disease; stereotactic radiosurgery; remission; pituitary surgery

CUSHING's disease (CD) is caused by an adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma resulting in uncontrolled cortisol hypersecretion by the adrenal glands. Persistent hypercortisolemia is associated with increased risk for numerous somatic and psychiatric morbidities, including central obesity, diabetes, hypertension, mood changes, and accelerated cognitive decline.^{3,21}

Furthermore, patients with CD have up to a 5-fold increased mortality risk when compared with the general population.^{7,9} The greater morbidity and mortality risk of patients with CD is associated with greater duration of hypercortisolemia,⁸ lower rate of endocrine remission after pituitary adenoma resection (i.e., failed pituitary surgery),⁴ and higher number of prior treatments.² Therefore, timely and adequate control of cortisol hypersecretion is important for a favorable prognosis in these patients.

The first-line treatment for patients with established CD is resection of the ACTH-producing pituitary adenoma, and this is usually accomplished via a transsphenoidal route.^{15,16,23} However, up to 35% of patients with CD do not achieve endocrine remission after pituitary surgery, and an additional significant proportion of patients experience tumor progression and/or recurrence of hypercortisolemia.^{18,19} Persistent hypercortisolemia after initial adenoma resection can sometimes be successfully managed with lifelong medical therapy.²⁰ However, lifelong medical treatment for hypercortisolemia can be expensive, places patients at increased risk for treatment-related adverse events, and does not cure CD.²⁰ Repeated resection of residual and/or recurrent ACTH-producing pituitary adenomas is sometimes attempted; however, it has a lower success rate and greater complication risk when compared with initial surgery.^{1,10,17} Consequently, stereotactic radiosurgery (SRS) is currently recommended for the management of patients with CD who have persistent hypercortisolemia and/or post-SRS tumor recurrence.¹⁵ SRS has an acceptable safety profile and often leads to durable endocrine remission in up to 80% of patients.¹³ However, there are no large studies evaluating the optimal time from adenoma resection to SRS. This knowledge may have important clinical implications for treatment guidance after incomplete resection or after disease recurrence.

From a large consecutive sample of patients with established CD, we investigated the possible association of the interval between the resection of ACTH-producing pituitary adenoma and SRS with the treatment outcomes reported.

Methods

Patient Population

Patients were identified from institutions affiliated with

the International Radiosurgery Research Foundation (protocol R-16-10) who were treated with Gamma Knife radiosurgery (GKRS) between 1990 and 2014. Data collection was approved by institutional review boards at each of the participating centers. A database with variables of interest was established by investigators at the University of Virginia and sent to all participating centers. Individual patient data were de-identified and pooled for the analyses. For the purpose of this study, we considered only patients who were diagnosed with CD according to the existing guidelines and who underwent pituitary adenoma resection before GKRS, via either transsphenoidal approach or craniotomy. Patients who did not have previous surgery for a pituitary adenoma were excluded. Also, patients were required to have at least one follow-up evaluation including endocrine testing and neuroimaging testing after GKRS to be included in the study. In the delayed postoperative GKRS group, all patients had documented endocrine evidence of active CD. In the early postoperative GKRS cohort, patients had active CD reflected by the lack of a serum cortisol nadir after resection, elevated cortisol concentration, and/or persistent CD symptoms.

As described previously, the diagnosis of CD was established according to existing guidelines¹⁵ and included testing of serum cortisol, ACTH, 24-hour urinary free cortisol (UFC), and other tests as appropriate.¹³

Radiosurgical Approach

Single-session GKRS was performed using models U, B, C, 4C, and Perfexion of Gamma Knife units (Elekta AB). Frame-based stereotaxy was performed using the Leksell model G frame (Elekta AB), which was placed under local anesthesia with or without conscious sedation. Imaging studies for radiosurgical planning typically included high-resolution 1-mm thickness pre- and postcontrast T1-weighted MRI scans. In rare cases in which MRI was contraindicated, stereotactic CT was used for GKRS planning. GKRS dose planning was performed by a multidisciplinary team that included a neurosurgeon, radiation oncologist, and medical physicist. At each center, planning was tailored toward individual patient needs and imaging findings. However, the maximal radiation dose to the optic nerve, chiasm, and tracts was generally kept below 8–12 Gy. Radiosurgical parameters, including the margin and maximum dose, optic apparatus maximal dose, isodose line, tumor volume, and number of isocenters, were recorded.

Clinical and Radiological Follow-Up

The interval from the most recent pituitary adenoma operation until initial GKRS was recorded in all patients. Although clinical and endocrine follow-up varied across

practices, follow-up typically included 24-hour UFC, and MRI at 6-month intervals for the first 2 years and annually thereafter. Endocrine remission was defined as normalization of UFC or morning serum cortisol (as determined by institutional reference ranges) with the patient off of medication to control hypercortisolism. The interval from GKRS to endocrine remission was recorded in all patients. Endocrine recurrence was defined as increase of 24-hour UFC or serum morning cortisol concentration above institutional reference ranges. Tumor progression or response was defined as an increase of tumor volume by 20% or a decrease by 20%, respectively. Adverse radiation events and other treatments were carefully monitored.

Statistical Analyses

Statistical analyses were performed with IBM SPSS Statistics for Windows version 25.0 (IBM Corp.). All identified patients were stratified into 4 cohorts based on the interval between surgical tumor resection and GKRS: 1) ≤ 3 months; 2) from 4 to 6 months; 3) from 7 to 12 months; and 4) later than 12 months. Categorical data were compared using the Pearson chi-square test, and continuous data using the ANOVA. Kaplan-Meier analysis with log-rank test was performed to analyze the possible association of endocrine remission rate with interval from tumor surgery until GKRS. Next, univariate Cox regression analysis was carried out to evaluate the association between the prespecified intervals from tumor surgery to GKRS (≤ 3 months vs > 3 months and ≤ 12 months vs > 12 months) and endocrine remission rates at 6 months, 1 year, 2 years, 5 years, and at later times after SRS. Significant associations in univariate Cox regression analyses were then adjusted for patient age, sex, pre-GKRS fractionated radiation therapy, medical treatment at time of GKRS, pre-GKRS UFC concentration, volume treated, maximal GKRS dose (Gy), margin dose (Gy), indication for GKRS (residual or recurrent disease), and treatment of the whole sella and cavernous sinuses.

Results

Patient Characteristics

Two hundred fifty-five patients with CD who underwent GKRS after resection of an adenoma were identified by 10 participating institutions. The mean age of the study patients at the time of GKRS was 41.36 ± 13.54 years (mean $\pm$ SD, range 10–81 years), and the majority (79%) of patients were women (Table 1). Seventy-seven (30%) patients underwent GKRS within 3 months after resection; 46 (18%) from 4 to 6 months after resection; 34 (13%) from 7 to 12 months after resection; and 98 (38%) at more than 12 months after surgery. Patients who underwent GKRS at more than 12 months after prior resection were more often subjected to GKRS for recurrent adenoma ($p < 0.001$) and had a greater prevalence of pre-GKRS radiation therapy for their adenomas ($p = 0.015$; Table 1). Patients who underwent GKRS within 3 months of surgery had a lower prevalence of a history of medical treatment ($p = 0.021$) and were less likely to use medical therapy at the time of GKRS ($p < 0.001$). Distribution of age, sex, histories of surgery, prevalence of pre-GKRS pituitary defi-

ciency, visual deficits, and concentrations of 24-hour UFC and morning serum cortisol were similar as a function of the interval between surgery and GKRS.

Radiosurgical Parameters

Patients treated with GKRS within 3 months after surgery were more likely to have GKRS to the cavernous sinus or sinuses ($p < 0.002$), and their isodose line (%) was lower relative to other groups of patients ($p < 0.001$; Table 2). Other GKRS characteristics were similar among the 4 groups of patients stratified according to GKRS timing.

Endocrine Remission

Following GKRS, the mean endocrine follow-up in the entire cohort of patients was 65.59 ± 49.01 months (median 51 months), and it was similar among the 4 groups of patients stratified according to GKRS timing ($p = 0.382$; Table 1). In the total sample of patients, actuarial endocrine remission rates at 1, 2, and 5 years and at last follow-up after GKRS were 43%, 57%, 68%, and 69%, respectively. In patients treated with GKRS within 3 months of resection, remission rates at 1, 2, and 5 years and at last follow-up after GKRS were 52%, 70%, 77%, and 78%, respectively. Endocrine remission rates at 1, 2, and 5 years and at last follow-up were 48%, 64%, 75%, and 76%, respectively, among patients treated with GKRS at ≤ 12 months after the resection, and 36%, 45%, 56%, and 69%, respectively, among patients treated with GKRS at > 12 months after the resection. In the total sample of patients, there was a significant association of time interval from surgery to GKRS (≤ 3 months vs from 4 to 6 months vs from 7 to 12 months vs later than 12 months) with actuarial endocrine remission rates at last follow-up visit (log-rank test = 12.644, $p = 0.005$). Specifically, Kaplan-Meier analyses showed that when compared with CD patients who were treated with GKRS > 3 months after resection of the adenoma, patients who were treated with GKRS ≤ 3 months after resection had higher actuarial endocrine remission rates at 6 months (20% vs 33%, respectively); at 2 years (51% vs 70%, respectively); and at last follow-up (65% vs 78%, respectively; log-rank test = 5.716, $p = 0.017$; Fig. 1 upper). On the other hand, in patients with CD who were treated with GKRS > 12 months after resection when compared to those who were treated with GKRS ≤ 12 months after pituitary adenoma resection, actuarial endocrine remission rates were lower at 6 months (25% vs 21%, respectively); at 2 years (64% vs 45%, respectively); and at last follow-up (76% vs 57%, respectively; log-rank test = 7.457, $p = 0.006$; Fig. 1 lower).

In univariate Cox regression analyses an interval between prior resection and an initial GKRS of ≤ 3 months was associated with statistically significantly greater hazard ratios (HRs) for endocrine remission at 6 months, 2 years, and last follow-up after GKRS, whereas an interval from resection to GKRS of > 12 months was associated with lower likelihood for endocrine remission at 2 years and last follow-up after the GKRS (Table 3). After adjusting for patient age, sex, pre-GKRS fractionated radiation therapy, medical treatment at time of GKRS, pre-GKRS UFC concentration, volume treated, maximal GKRS dose

TABLE 1. Baseline clinical and demographic characteristics as a function of time between resection and radiosurgery in 255 patients with CD

Characteristic	Total Sample	Time Interval Between Resection and Radiosurgery				p Value
		≤3 Mos	4–6 Mos	7–12 Mos	>12 Mos	
No. of patients	255	77 (30%)	46 (18%)	34 (13%)	98 (38%)	
Sex						1.691 (0.639)
Men	54 (21%)	19 (25%)	7 (15%)	8 (23%)	20 (20%)	
Women	201 (79%)	58 (75%)	39 (85%)	26 (77%)	78 (80%)	
Age at GKRS, yrs	41.36 ± 13.54	41.57 ± 12.27	40.39 ± 14.76	43.82 ± 15.25	40.82 ± 13.38	0.511 (0.675)
Radiosurgery indications						28.199 (<0.001)
Residual	221 (87%)	76 (99%)	42 (91%)	31 (91%)	72 (73%)	
Recurrent	34 (13%)	1 (1%)	4 (9%)	3 (9%)	26 (27%)	
Pre-GKRS transsphenoidal resection						4.274 (0.233)
Yes	248 (97%)	77 (100%)	45 (98%)	33 (97%)	93 (95%)	
No	7 (3%)	0 (0%)	1 (2%)	1 (3%)	5 (5%)	
Pre-GKRS craniotomy						4.726 (0.193)
Yes	11 (4%)	2 (3%)	0 (0%)	2 (6%)	7 (7%)	
No	244 (96%)	75 (97%)	46 (100%)	32 (94%)	91 (93%)	
Pre-GKRS fractionated radiation therapy						10.403 (0.015)
Yes	16 (6%)	3 (4%)	0 (0%)	1 (3%)	12 (12%)	
No	239 (94%)	74 (96%)	46 (100%)	33 (97%)	86 (88%)	
Pre-GKRS medical therapy						9.726 (0.021)
Yes	120 (47%)	25 (33%)	24 (52%)	17 (50%)	54 (55%)	
No	135 (53%)	52 (67%)	22 (48%)	17 (50%)	44 (45%)	
Medical therapy at time of GKRS						25.589 (<0.001)
Yes	83 (32%)	8 (10%)	17 (37%)	14 (41%)	44 (45%)	
No	172 (68%)	69 (90%)	29 (63%)	20 (58%)	54 (55%)	
Pituitary deficiency before GKRS*						
Any	70 (28%)	23 (30%)	10 (23%)	10 (30%)	27 (28%)	0.890 (0.828)
Hypothyroidism	50 (20%)	18 (24%)	5 (11%)	9 (27%)	18 (19%)	3.786 (0.286)
Estrogen/testosterone deficiency	18 (7%)	7 (9%)	3 (7%)	2 (6%)	6 (6%)	0.618 (0.892)
GH deficiency	8 (3%)	3 (4%)	1 (2%)	2 (6%)	2 (2%)	1.462 (0.691)
Diabetes insipidus	13 (5%)	5 (7%)	2 (5%)	2 (6%)	4 (4%)	0.543 (0.909)
Visual deficits before GKRS						3.505 (0.743)
None	220 (86%)	68 (88%)	41 (89%)	29 (85%)	82 (84%)	
Visual field deficit	25 (10%)	5 (7%)	4 (9%)	3 (9%)	13 (13%)	
Diplopia	10 (4%)	4 (5%)	1 (2%)	2 (6%)	3 (3%)	
Pretreatment 24-hr UFC, µg†	278.2 ± 490.4	181.4 ± 181.9	384.2 ± 839.3	209.1 ± 193.1	320.6 ± 488.2	1.758 (0.156)
Pretreatment morning serum cortisol, µg/dL‡	25.5 ± 19.6	24.0 ± 16.1	26.0 ± 21.0	25.6 ± 24.9	26.5 ± 19.6	0.215 (0.886)
Time between resection and GKRS, mos	23.17 ± 37.19	2.18 ± 0.68	5.09 ± 0.86	8.88 ± 1.87	53.10 ± 49.23	57.958 (<0.001)
Endocrine follow-up, mos	65.59 ± 49.01	62.57 ± 44.70	70.79 ± 52.96	76.42 ± 54.34	61.75 ± 48.36	1.024 (0.382)

GH = growth hormone.

Values are expressed as the mean ± SD or the number (%). The p values (in parentheses) were calculated as follows: categorical data were compared using the Pearson chi-square test, and continuous data using the ANOVA (F statistic). Boldface type indicates statistical significance.

* Data available for 247 patients.

† Data available for 208 patients.

‡ Data available for 227 patients.

(Gy), margin dose (Gy), indication for GKRS (residual or recurrent tumor), and treatment of the whole sella, an interval from resection to GKRS of ≤ 3 months remained associated with a greater probability for endocrine remission at 2 years (HR 1.561, 95% CI 1.033–2.359; $p = 0.034$)

and at last follow-up (HR 1.518, 95% CI 1.039–2.218; $p = 0.031$). The interval from resection to GKRS of > 12 months was associated with reduced likelihood of endocrine remission at 2 years (HR 0.637, 95% CI 0.424–0.957; $p = 0.030$) and at the last follow-up (HR 0.641, 95%

TABLE 2. Tumor and treatment characteristics as a function of treatment time after surgery in 255 patients with CD

Characteristic	Total Sample	Time Interval Between Resection and Radiosurgery				p Value
		≤3 Mos	4–6 Mos	7–12 Mos	>12 Mos	
No. of patients	255	77 (30%)	46 (18%)	34 (13%)	98 (38%)	
Tumor vol, cm ³	1.55 ± 2.00	1.65 ± 1.68	1.76 ± 2.48	1.59 ± 1.74	1.37 ± 2.10	0.488 (0.691)
Vol treated, cm ^{3*}	2.24 ± 2.21	2.52 ± 1.65	2.43 ± 3.14	2.48 ± 2.33	1.87 ± 1.94	1.449 (0.229)
Cavernous sinus targeted	126 (49%)	52 (68%)	20 (44%)	15 (44%)	39 (40%)	14.769 (<0.002)
Suprasellar component targeted	40 (16%)	14 (18%)	7 (15%)	4 (12%)	15 (15%)	0.776 (0.855)
Whole sella targeted	70 (28%)	19 (25%)	10 (22%)	8 (24%)	33 (34%)	3.219 (0.359)
Margin dose, Gy	23.21 ± 6.02	22.10 ± 1.17	23.68 ± 7.01	24.69 ± 6.54	23.34 ± 6.49	1.679 (0.172)
Maximal dose, Gy	45.55 ± 12.21	46.23 ± 8.27	45.33 ± 14.82	47.49 ± 13.25	44.44 ± 13.13	0.637 (0.592)
Isodose line, %	51.74 ± 9.10	48.23 ± 6.16	52.87 ± 7.93	53.03 ± 8.74	53.52 ± 10.86	5.837 (<0.001)
No. of isocenters	7.43 ± 5.40	8.59 ± 4.99	7.43 ± 5.46	7.91 ± 6.68	6.37 ± 5.06	2.573 (0.055)
Maximal dose to optic chiasm, Gy†	5.67 ± 2.69	5.16 ± 2.47	5.67 ± 2.89	6.07 ± 2.83	5.97 ± 2.71	1.446 (0.230)

Values are expressed as the mean ± SD or the number (%). The p values (in parentheses) were calculated as follows: categorical data were compared using the Pearson chi-square test, and continuous data using the ANOVA (F statistic). Boldface type indicates statistical significance.

* Data available for 232 patients.

† Data available for 226 patients.

CI 0.448–0.919; $p = 0.015$). However, when the treatment volume included the cavernous sinus, only treatment with GKRS > 12 months after the pituitary adenoma resection remained associated with a lower probability of endocrine remission (HR 0.683, 95% CI 0.475–0.980; $p = 0.039$).

CD recurrence was documented in 18% of patients among the 175 who initially achieved endocrine remission after GKRS. Endocrine recurrence rates were not different as a function of the interval from resection to GKRS.

Imaging Outcomes and Adverse Events

The mean time from GKRS to the most recent MRI scan was 56.0 ± 44.1 months (median 48 months), and this time was balanced across the 4 treatment groups ($p = 0.806$; Table 4). In 13 patients (5%), there was an increase of the adenoma size by at least 20% during the follow-up period, whereas the adenoma remained stable or decreased in volume by at least 30% after GKRS in 98 (41%) and 127 (53%) patients, respectively. Imaging outcomes were not different as a function of time from resection to GKRS.

Incidences of some degree of new pituitary deficiency or new visual and other cranial nerve deficits were not significantly related to time from resection to GKRS (Table 4). The need for additional resection or medical therapy was not related to the interval between resection and GKRS. Twenty patients died during the study period, and the overall mortality rate was similar among the 4 study groups ($p = 0.615$).

Discussion

To the best of our knowledge, this is the first study that evaluated the association of the interval between resection and GKRS with treatment outcomes in patients with CD. In this large multiinstitutional series of consecutive patients with CD who underwent GKRS after resection of

an ACTH-secreting pituitary adenoma, we found that early GKRS (≤ 3 months after surgery) was associated with greater endocrine remission rates, whereas late GKRS (> 12 months after surgery) was associated with a reduced probability of endocrine remission. Both early and delayed GKRS had a similar safety profile that was acceptable.

Our most important observation is that in CD after noncurative resection of an ACTH-producing pituitary adenoma or disease recurrence, early GKRS (≤ 3 months of resection) was associated with improved endocrine remission, whereas delayed GKRS (i.e., > 12 months after surgery) was associated with less favorable outcomes. These associations were independent of patients' sociodemographic and clinical characteristics, tissue volume treated, and maximal and margin doses of radiation. Thus, for patients with CD in whom complete adenoma resection cannot be achieved, with a resulting remission documented by endocrine testing, such patients can benefit from early rather than delayed GKRS. Earlier endocrine remission after SRS has important clinical benefits, including shorter duration of hypercortisolemia and medical treatment and possibly fewer medical treatments, which were implicated as important factors for the long-term prognosis and survival of patients with CD.^{2,7} To the best of our knowledge, there are no studies exploring the optimal timing of GKRS after unsuccessful resection of an ACTH-producing pituitary adenoma. A small study in 7 patients with CD treated with CyberKnife SRS (CKSRS) found that all 4 patients who received CKSRS treatment within 14 months (range 3–14 months) after resection achieved endocrine remission, whereas all 3 patients who were treated with CKSRS more than 14 months (range 15–85 months) after resection had active CD at a follow-up of 55 months.¹⁴ We studied only those patients who underwent GKRS after an incomplete resection and a failure to achieve remission following surgery, and this approach is consistent with current CD treatment guidelines.¹⁵ Therefore, early SRS should be considered in pa-

FIG. 1. Kaplan-Meier analyses of the association of time between resection and GKRS to endocrine remission. **Upper:** Patients dichotomized into groups of ≤ 3 months and > 3 months. **Lower:** Patients dichotomized into groups of ≤ 12 months and > 12 months.

tients with CD after an incomplete resection and persistent CD after surgery in order to optimize endocrine control and overall prognosis.

The benefits of treating patients with early SRS after resection are likely multifactorial. Early SRS is when the target volume is at its smallest; a smaller target volume has generally been associated with more favorable outcomes following SRS. Also, resection is in essence a controlled trauma at the operative site. Trauma has been associated with the production of tumor necrosis factor, proinflammatory cytokines, and microvascular disruption, and performing a resection even with great care probably leads to at least a temporary cascade of proinflammatory cytokines

and microvascular disruption in the sellar region, thereby placing residual pituitary adenoma cells under stress.^{11,22} Delivering SRS early after surgery, when the remaining pituitary adenoma cells are more vulnerable, may induce a higher degree of postradiosurgical inactivation of ACTH production, and this could translate to the improved rate of remission seen with early GKRS in this study.

In our series, actuarial endocrine remission rates ranged from 57% in the late (> 12 months) GKRS group to 78% in the early (≤ 3 months) GKRS group, and this underscores the clinically meaningful differences of treatment success as a function of time from resection to GKRS. Endocrine recurrence rates were similar among the treatment groups.

TABLE 3. Association of interval between resection and GKRS with remission in univariate and multivariate Cox regression analyses in 255 patients with CD

Time From Surgery to GKRS	Univariate	Multivariate*	Multivariate†
Dependent variable: endocrine remission at 6 mos after GKRS			
≤3 mos after GKRS	1.686 (1.009–2.817), 0.046	0.227	—
4–6 mos after GKRS	0.570 (0.259–1.254), 0.162	—	—
7–12 mos after GKRS	0.908 (0.413–1.998), 0.811	—	—
>12 mos after GKRS	0.851 (0.501–1.447), 0.552	—	—
Dependent variable: endocrine remission at 2 yrs after GKRS			
≤3 mos after GKRS	1.571 (1.121–2.204), 0.009	1.561 (1.033–2.359), 0.034	0.190
4–6 mos after GKRS	0.766 (0.490–1.196), 0.241	—	—
7–12 mos after GKRS	1.444 (0.924–2.256), 0.107	—	—
>12 mos after GKRS	0.637 (0.446–0.908), 0.013	0.637 (0.424–0.957), 0.030	0.115
Dependent variable: endocrine remission anytime during the follow-up			
≤3 mos after GKRS	1.450 (1.060–1.984), 0.02	1.518 (1.039–2.218), 0.031	0.215
4–6 mos after GKRS	0.850 (0.577–1.253), 0.412	—	—
7–12 mos after GKRS	1.490 (0.994–2.234), 0.053	—	—
>12 mos after GKRS	0.650 (0.472–0.893), 0.008	0.641 (0.448–0.919), 0.015	0.683 (0.475–0.980), 0.039

— = not done.

Values are expressed as HR (95% CI), p value. Boldface type indicates statistical significance.

* Adjusted for patient age, sex, pre-GKRS fractionated radiation therapy, medical treatment at time of GKRS, pre-GKRS UFC concentration, volume treated, maximal GKRS dose (Gy), margin dose (Gy), and indication for GKRS (residual or recurrent tumor).

† Addition of cavernous sinus treatment as predictor variable.

Others have reported endocrine remission rates of 35%⁶ to 72%⁵ after GKRS, 57% after CKRS,¹⁴ 22%²⁶ to 59%²⁵ after linear accelerator (LINAC)-based SRS, and 54% after proton beam therapy,²⁴ with the median post-SRS follow-up in all studies exceeding 2 years. However, the association of time between resection and SRS with treatment outcomes was reported in only one study.¹⁴ Findings from the present study indicate that time between resection and SRS therapy should be considered when reporting SRS outcomes of patients with CD.

Management of patients with residual or refractory CD is challenging.¹ Patients with refractory CD can be managed with repeated resection, SRS, or medical management, but unfortunately all 3 options provide limited and variable success.¹⁵ Our study indicates the importance of GKRS for the management of patients with CD after noncurative surgery. A previous study in 20 patients with CD who had disease recurrence after initial SRS found that endocrine remission was achieved in 60% of patients after a second SRS treatment at a mean follow-up of 6.6 years (range 1.4–19.1 years).¹² Hence, SRS is important for the management of residual or recurrent CD.

Adenoma growth on neuroimaging was low (5%) and similar among the 4 treatment groups. High control of growth rates in ACTH-producing pituitary adenomas was previously reported after GKRS,⁵ CKRS,¹⁴ LINAC-based systems,²⁶ and proton beam therapy.²⁴ Although tumor control after SRS is beneficial for avoiding growth that may lead to cranial nerve and normal pituitary gland dysfunction, the primary goal of SRS management of CD is control of hypercortisolemia in order to prevent long-term metabolic complications and improve prognosis.¹⁵

Limitations and Strengths of the Study

This study has limitations. Due to the retrospective study design, we were unable to reliably identify underlying medical reasons that prompted the decision to change from medical management to GKRS. There were differences in prior treatments and tumor characteristics as a function of the interval from surgery to GKRS; however, the majority of them could be systematically accounted for only by performing a randomized controlled trial, which would be challenging for this rare disorder. Volumes of pituitary adenomas were small but different between cohorts of patients with early and late treatment; however, in a larger study with pituitary adenomas in patients with CD treated with SRS, tumor volume within typical radio-surgical targets was not a prognostic factor in endocrine remission.¹³ Also, patients with delayed GKRS had more pre-GKRS fractionated radiation therapy, and this was largely a reflection of earlier treatment approaches and did not result in a significant lowering of the therapeutic GKRS dose to the target in either group. Furthermore, information regarding intraoperative findings in terms of tumor invasion of the cavernous sinus and preoperative imaging data was not always available; thus, we were unable to identify factors that precluded complete adenoma resection. Also, the timing from resection to GKRS was determined by the treating teams and probably varied among centers. Also, because we analyzed patients who were treated at 10 participating centers over 24 years, there have been substantial technological improvements of GKRS systems over time that could introduce variation in GKRS planning and delivery both within and among centers. However, the principles of GKRS planning, treat-

TABLE 4. Imaging outcomes and adverse events after GKRS in 255 patients with CD

Outcome	Total Sample	Time Interval Between Resection and Radiosurgery				p Value
		≤3 Mos	4–6 Mos	7–12 Mos	>12 Mos	
No. of patients	255	77 (30%)	46 (18%)	34 (13%)	98 (38%)	
Imaging outcomes after GKRS*						10.131 (0.340)
Stable	98 (41%)	28 (37%)	19 (43%)	15 (48%)	36 (40%)	
30% reduction	127 (53%)	45 (59%)	21 (48%)	13 (42%)	48 (53%)	
20% increase	13 (5%)	2 (3%)	2 (5%)	3 (10%)	6 (7%)	
Tumor not seen before GKRS	3 (1%)	1 (1%)	2 (5%)	0 (0%)	0 (0%)	
Interval from GKRS to last MRI, mos*	56.0 ± 44.1	56.7 ± 43.0	56.7 ± 45.2	61.9 ± 54.2	53.1 ± 41.0	0.327 (0.806)
Pituitary deficiency after GKRS						
Any	65 (26%)	21 (27%)	10 (22%)	9 (27%)	25 (26%)	0.487 (0.922)
Hypothyroidism	41 (16%)	11 (14%)	7 (15%)	7 (21%)	16 (16%)	0.726 (0.867)
Estrogen/testosterone deficiency	25 (10%)	9 (12%)	4 (9%)	3 (9%)	9 (9%)	0.453 (0.929)
GH deficiency	27 (11%)	9 (12%)	4 (9%)	7 (21%)	7 (7%)	5.093 (0.165)
Diabetes insipidus	5 (2%)	2 (3%)	0 (0%)	1 (3%)	2 (1%)	1.256 (0.740)
Hypocortisolism	21 (8%)	11 (14%)	3 (7%)	1 (3%)	6 (6%)	5.749 (0.125)
New visual deficits after GKRS	5 (2%)	2 (3%)	0 (0%)	1 (3%)	2 (2%)	1.256 (0.740)
New other cranial deficits after GKRS						10.072 (0.610)
CN III	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	
CN V	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	
CN VI	1 (0.4%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	
Multiple	1 (0.4%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	
Endocrine recurrence†	32 (18%)	7 (12%)	7 (23%)	7 (25%)	11 (20%)	3.056 (0.383)
Additional treatments after GKRS						
Repeat GKRS‡	32 (13%)	9 (12%)	6 (13%)	5 (16%)	12 (12%)	0.332 (0.954)
Pituitary adenoma surgery	21 (8%)	8 (10%)	3 (7%)	2 (6%)	8 (8%)	0.901 (0.825)
Adrenalectomy	17 (7%)	7 (9%)	4 (9%)	2 (6%)	4 (4%)	3.147 (0.790)
Fractionated radiotherapy	1 (1%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	6.467 (0.091)
Initiation of new medical therapy§	14 (6%)	1 (1%)	5 (11%)	2 (6%)	6 (6%)	5.245 (0.155)

CN = cranial nerve.

Values are expressed as the mean ± SD or the number (%). The p values (in parentheses) were calculated as follows: categorical data were compared using the Pearson chi-square test, and continuous data using the ANOVA (F statistic).

* Data available for 241 patients.

† In total, 175 patients initially achieved endocrine remission.

‡ Data available for 252 patients.

§ Data available for 251 patients.

ment volume calculation, and dose selection were homogeneous throughout the course of the study, and a detailed description of GKRS plan data was reported for all patients. Variations of clinical patient management and follow-up strategies both among institutions and within the same institution over time are another potential limitation of this retrospective study. The use of 4 predefined time periods from surgery to GKRS places our results at increased risk for a type I error.

On the other hand, the large sample size of patients with persistent CD, which is a rare but often devastating disease, is a significant strength of this multicenter study, and it allowed us to optimize statistical power and hence fortify the reliability of our findings. Furthermore, all patients included in this report underwent diagnostic and management procedures for CD (i.e., resection followed by GKRS) as outlined in contemporary CD treatment guidelines,¹⁵ and

they were subjected to rigorous biochemical and imaging follow-up—thus underscoring the clinical applicability of our results to contemporary clinical care of patients with persistent CD.

Conclusions

In patients with CD who have residual adenoma after resection, early GKRS is associated with improved endocrine remission, whereas delayed GKRS is associated with worse long-term disease control. Early and late GKRS have acceptable and similar safety profiles. Our findings suggest that early (ideally within 3 months, but not later than 12 months) GKRS should be considered in patients with CD after noncurative resection in order to achieve control of hypercortisolemia and possibly prevent long-term consequences of persistent CD.

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Conception and design: Sheehan. Acquisition of data: all authors. Analysis and interpretation of data: Sheehan, Bunevicius. Drafting the article: Bunevicius, Kano. Critically revising the article: Sheehan, Bunevicius, Kano, CC Lee, Nabeel, El-Shehaby, Abdel Karim, Martinez-Moreno, Mathieu, JYK Lee, Grills, Kondziolka, Martinez-Alvarez, Reda, Liscak, Su, Lunsford, Vance. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sheehan. Statistical analysis: Bunevicius, Krsek. Administrative/technical/material support: Sheehan. Study supervision: Sheehan.

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