Acta Neurochirurgica (2021) 163:1949–1956
https://doi.org/10.1007/s00701-021-04823-1

ORIGINAL ARTICLE - BRAIN TUMORS

Stereotactic radiosurgery before bilateral adrenalectomy is associated with lowered risk of Nelson's syndrome in refractory Cushing's disease patients

Adomas Bunevicius[1] · Karen Lavezzo[1] · Philip W. Smith[2] · Mary Lee Vance[3] · Jason Sheehan[1]

Received: 23 February 2021 / Accepted: 18 March 2021 / Published online: 24 March 2021

Abstract

Background Nelson's syndrome is a rare but challenging sequelae of Cushing's disease (CD) after bilateral adrenalectomy (BLA). We sought to determine if stereotactic radiosurgery (SRS) of residual pituitary adenoma performed before BLA can decrease the risk of Nelson's syndrome.

Methods Consecutive patients with CD who underwent BLA after non-curative resection of ACTH secreting pituitary adenoma and had at least one follow-up visit after BLA were studied. Nelson's syndrome was diagnosed based on the combination of rising ACTH levels, increasing volume of the pituitary adenoma and/or hyperpigmentation.

Results Fifty patients underwent BLA for refractory CD, and 43 patients (7 men and 36 women) had at least one follow-up visit after BAL. Median endocrine, imaging, and clinical follow-up were 66 months, 69 months, and 80 months, respectively. Nine patients (22%) were diagnosed with the Nelson's syndrome at median time after BLA at 24 months (range: 0.6–119.4 months). SRS before BLA was associated with reduced risk of the Nelson's syndrome (HR = 0.126; 95%CI [0.022–0.714], p=0.019), while elevated ACTH level within 6 months after BLA was associated with increased risk for the Nelson's syndrome (HR = 9.053; 95%CI [2.076–39.472], p=0.003).

Conclusions SRS before BLA can reduce the risk for the Nelson's syndrome in refractory CD patients requiring BLA and should be considered before proceeding to BLA. Elevated ACTH concentration within 6 months after BLA is associated with greater risk of the Nelsons' syndrome. When no prior SRS is administered, those with a high ACTH level shortly after BLA may benefit from early SRS.

Keywords Cushing's disease · Nelson's syndrome · Bilateral adrenalectomy · Stereotactic radiosurgery · Gamma Knife

Introduction

Cushing's disease (CD) is rare but challenging disorder caused by an adrenocorticotropic hormone (ACTH) secreting pituitary adenoma [18, 32]. Inadequately controlled CD can lead to somatic and psychiatric morbidities, and it is associated with up to 5-fold increased mortality risk when compared with the general population [7, 17, 18]. Treatment goals of multidisciplinary management of CD include normalization of cortisol production and management of CD associated comorbidities [25]. Surgical resection of ACTH producing pituitary adenomas is a cornerstone treatment for CD. However, complete resection of ACTH secreting pituitary adenoma is often not technically possible because of the adenoma's often infiltrative growth and small size. Therefore up to 35% of CD patients fail to achieve sustained endocrine remission after pituitary surgery [25, 29, 31]. Stereotactic radiosurgery (SRS) is commonly used for patients after failed adenoma resection or recurrence, and it offers the possibility of endocrine remission and tumor control in the majority of CD patients [4, 5, 12, 20, 25].

This article is part of the Topical Collection on *Brain Tumors*

✉ Jason Sheehan
jsheehan@virginia.edu

[1] Department of Neurosurgery, University of Virginia, Charlottesville, VA 22908, USA

[2] Department of Surgery, University of Virginia, Charlottesville, VA, USA

[3] Department of Medicine, University of Virginia Health System, Charlottesville, VA, USA

Bilateral adrenalectomy (BLA) is the definitive treatment for refractory CD and results in prompt control of hypercortisolemia. BLA is often reserved for patients after non-curative adenoma resection with severe CD when control of hypercortisolemia cannot be rapidly achieved with medical management or the latency period typical of SRS [25]. However, from 8 to 43% of CD patients develop Nelson's syndrome after BLA [14, 26, 28, 33]. Nelson's syndrome is associated with expansion of the pituitary adenoma, hyperpigmentation, and usually increasing plasma ACTH levels. However, a consensus of definition of the Nelson's syndrome is lacking [1, 10, 27]. Studies using more sensitive imaging techniques have documented tumor progression without other accompanying features of the Nelson's syndrome in almost 50% of CD patients after BLA [2]. Irradiation of residual pituitary adenoma and/or sellar region before BLA can reduce the risk of Nelson's syndrome [11, 13, 21, 24, 28]. In our previous series of 20 patients with established CD who underwent BLA after the SRS, we found that only one patient (5%) developed Nelson's syndrome after BLA [21]. However, prior studies exploring the possible impact of pituitary irradiation on the subsequent risk of Nelson's syndrome were limited by small sample sizes and limited follow-up duration and did not include a control group of patients without pituitary irradiation or used less conformal radiation techniques. In this study, we sought to determine if SRS to the pituitary before BLA is associated with a decreased risk of developing Nelson's syndrome.

Methods

Patients

Consecutive patients who underwent BLA for persistent CD at the University of Virginia from July 1995 until February 2019 were identified from the institutional database and considered for this study. Patients were included in the study irrespective of prior therapies before BLA. Individual patient data were de-identified and pooled for the analyses. We updated our previously reported cohort of CD patients treated with SRS before BLA by including new patients treated in the interim and appreciably updating follow-up information of previously reported cohort [21]. We have also included a new cohort of CD patients who were not treated with SRS before BLA.

The data were collected retrospectively with approval from the Institutional Review Board of the University of Virginia. Due to the retrospective study design, informed consent was not required from patients included in the report.

Radiosurgery procedure

SRS was performed using models U, C, Perfexion, and Icon of Gamma Knife devices (Elekta AB, Stockholm, Sweden) as described previously [4, 6]. SRS was performed using frame-based stereotaxy using the Leksell Model G-frame (Elekta AB, Stockholm, Sweden) that was placed under local anesthesia with conscious sedation. Hypofractionated SRS (5Gy in 5 fractions) was delivered using thermoplastic mask–based system and was considered for adenomas within 3 mm or abutting the optic apparatus. CT imaging was initially used for SRS radiosurgical planning, and around the year 2000, high-resolution MRI became the standard neuro-imaging modality for planning. Radiosurgical imaging typically includes high-resolution pre- and post-contrast T1-weighted 3T MRI scans performed in 1 mm thickness. SRS target planning, and dose selection was performed by a multidisciplinary team that included a neurosurgeon, radiation oncologist, and medical physicist. In all cases, SRS planning was tailored toward individual patient and imaging findings. We treated pituitary adenoma when there was evidence of a discrete tumor on planning MRI or when there was clear evidence of laterality of the adenoma during resection (e.g., infiltration of unilateral cavernous sinus). We treated the whole sella when there was no discrete adenoma seen on planning MRI nor any evidence of tumor laterality during the resection (Fig. 1). For discrete adenomas, we covered at least 98% of the target volume with the prescription dose, while for the whole sella treatment, we covered all sella content. For single-fraction SRS, maximal radiation dose to the optic nerve, chiasm, and optic tracts was generally kept below 8 to 12 Gy and kept to $\underline{<}$25Gy in 5 fraction cases. Radiosurgical parameters, including the margin and maximum dose, optic apparatus maximal dose, the prescription isodose line, the tumor volume, and the number of isocenters, were recorded.

BLA procedure

Bilateral laparoscopic adrenalectomy was primarily performed using a laparoscopic transabdominal approach prior to 2011 and using either the retroperitoneoscopic or the transabdominal approach as determined to be most suited for the patient anatomically after 2011 [34]. All procedures were performed under general anesthesia. For all cases, care was taken to achieve complete clearance of the adrenal and surrounding fatty tissue to ensure complete resection of any extra-adrenal rests.

For the laparoscopic transabdominal approach, the patient was positioned in the left lateral decubitus position and four subcostal ports were placed, the liver was medialized, and the entirety of the adrenal and surrounding fatty tissue in the suprarenal fossa was resected. The patient was repositioned in the right lateral decubitus position, and the splenic flexure,

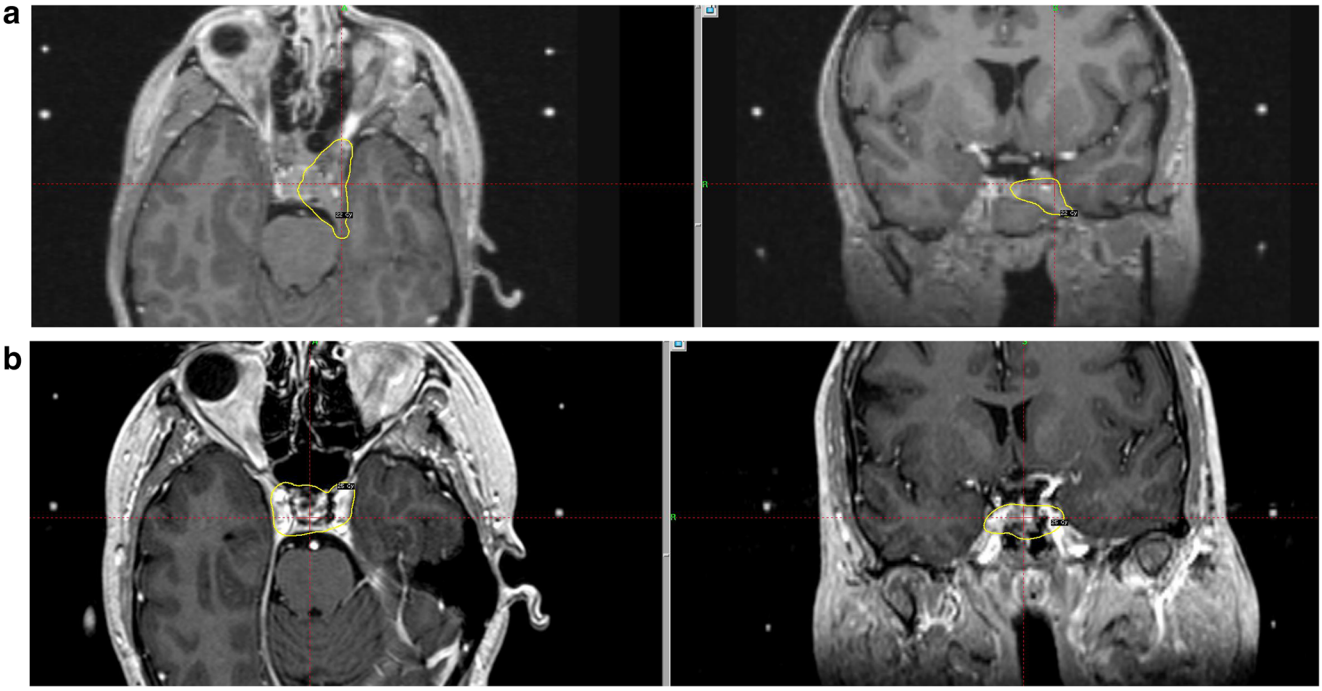

Fig. 1 Treatment plans of discrete adenoma as seen on SRS planning brain MRI (panel **a**) and the whole sella in a patient without clearly evident adenoma on SRS planning brain MRI (panel **b**). Yellow line indicated 50% prescription isodose line that was 22 Gy and 25 Gy for panels **a** and **b**, respectively

spleen, tail of pancreas, and stomach were medialized. The entirety of the adrenal and surrounding fatty tissue in the suprarenal fossa was resected. The adrenal vein on both sides was secured either with clips or the LigaSure device.

For the retroperitoneoscopic (laparoscopic retroperitoneal approach), the patient was positioned supine on a spinal frame to minimized lumbar lordosis. Access was obtained by direct entry into the retroperitoneum, and three subcostal ports were placed on each side. Gerota's fascia was opened, and the kidney was mobilized inferior medially on its hilum. The inferior limb of the adrenal was mobilized from the renal hilum. The adrenal arteries and veins were ligated with the LigaSure device. The entirety of the adrenal and surrounding fatty tissue in the suprarenal fossa was resected.

Imaging and clinical assessment and follow-up

Post-SRS imaging follow-up was typically performed using brain MRI performed at regular intervals of 6 months for the first 2 years and then yearly thereafter. Brain MRI imaging protocol for patients with pituitary adenomas typically included high-field T1w brain MRI performed with and without contrast using small FOV in coronal and sagittal planes, in addition to structural whole brain MRI sequences. Endocrine and clinical follow-ups were typically performed at or around the same time as radiological follow-up. Endocrine evaluation routinely included serum ACTH, thyroid-stimulating hormone, free thyroxine, and insulin-like growth factor–I levels. Serum testosterone levels were followed in men.

Diagnosis of the Nelson's syndrome was established based on the combination of rising ACTH levels, increasing volume of pituitary adenoma, and/or hyperpigmentation according to relevant international, national, and institutional guidelines [1, 10, 27]. The interval between BLA and development of the Nelson's syndrome was recorded in all patients. We also recorded any other treatment or treatments that were used for the management of Nelson's syndrome after BLA. Endocrine remission at last follow-up was defined as ACTH concentrations of 7–63 pg/mL.

Statistical analysis

Statistical analyses were performed with the IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp). For all statistical tests, a p value of <0.05 was considered statistically significant. Categorical data were compared using the Pearson chi-squared test and continuous data using the analysis of variance (ANOVA).

We compared baseline clinical and demographic characteristics between patients who underwent SRS before BAL vs. those who did not. Next, Kaplan-Meier analysis with log-rank test was performed to analyze the association of SRS before BLA (yes vs. no) with time to developing Nelson's syndrome. Univariate Cox regression analyses were performed to examine risk factors for the Nelson's syndrome, including age at

BLA, gender, ACTH concentration before BLA (pg/mL), cortisol concentration before BLA (mcg/dL), ACTH concentration 6 months after BLA (pg/mL), highest ACTH concentration after BLA of >300 pg/mL, 24-h urine-free cortisol before BLA, pathology results (ACTH positive, negative/unavailable), and number of pituitary adenoma operation. Significant predictors in univariate Cox regression analyses were entered into a multivariate Cox regression model. Results of Cox regression analysis are presented as Hazard ratio (HR), 95% confidence interval (95% CI), and *p* value.

Results

Baseline characteristics

Between 1995 and 2019, 50 patients underwent BLA for established CD, and 43 patients (36 women and 7 men) had a least one follow-up visit after BLA and were included in this study (Table 1). Fifty-one percent of patients had histories of one pituitary adenoma resection, and 49% of patients had two or three pituitary operations. Pathology results were available in 27 patients, and the majority was diagnosed with an ACTH-positive pituitary adenoma by immunohistochemistry. Thirty-three patients underwent SRS for residual/recurrent disease before BLA, and 10 patients were not treated with SRS before BLA. One patient underwent hypofractionated SRS delivering 5Gy in each of 5 fractions. The remaining patients were treated using single-fraction SRS, and median prescription dose was 25 Gy (range: 18–30 Gy). Median isodose line was 50% for all patients. Median number of isocenters was 7 (range: 2–18). We treated pituitary adenoma when there was evidence of a discrete tumor on planning MRI (*n*=15 patients) or whole sella when there was no discrete adenoma seen on MRI (*n*=16 patients). SRS treatment data was not available for 2 patients. Demographic and clinical characteristics were similar in patients who underwent SRS before BAL and those who did not, with the exception of age at BLA.

Endocrine, clinical, and imaging follow-up

Endocrine follow-up was available for 43 patients with median duration of post-BLA endocrine follow-up of 66 months (range: 0.03–285 months). Median imaging follow-up was 70 months (range: 6–286 months), and median clinical follow-up was 80 months (range 0.3 to 228 months). Median duration of post-BLA endocrine, imaging, and clinical follow-up was similar in patients who were treated with SRS before BLA and those who were not. Nine patients (22%) in the total cohort were diagnosed with the Nelson's syndrome based on endocrine and imaging criteria. All patients diagnosed with the Nelson's syndrome had rising/elevated ACTH levels, progressive/residual adenoma on brain MRI was documented in six patients, and four patients had hyperpigmentation. Median time from BLA to the diagnosis of Nelson's syndrome was 24 months (range: 0.6–119.4 months). Nine patients (21%) achieved endocrine remission defined as normal ACTH concentrations. The proportion of patients achieving endocrine remission is not statistically significantly different in patients who were treated with SRS before BLA and those who were not (30% vs. 11%, p=0.25).

Five (12%) patients died during the study follow-up. Two deaths were in the pre-BLA SRS group, and three deaths were in the BLA-only group. Two patients died of pneumonia, one patient experienced sudden death of unknown cause, and causes of death were not available for two patients.

Predictors of Nelson's syndrome

Kaplan-Meier analysis showed that the incidence of Nelson's syndrome was significantly lower in CD patients who underwent pituitary SRS before BLA when compared with patients who did not undergo SRS before BLA (log-rank=5.528, p=0.019; Fig. 2). In univariate Cox regression analysis, SRS before BLA was associated with reduced risk for the Nelson's syndrome (HR = 0.224; 95% CI [0.058–0.869], p=0.03). Higher serum cortisol concentration before BLA (p=0.047), higher ACTH level after BLA (p=0.027), and the ACTH level within 6 months after BLA of >300 pg/mL (p=0.004) were associated with increased risk for development of Nelson's syndrome (Table 2). In multivariate Cox regression analysis considering significant predictors in univariate models, we found that SRS before BLA remained associated with reduced risk of developing Nelson's syndrome after BLA (HR = 0.126; 95%CI [0.022–0.714], p=0.019). Greater ACTH level after BLA (HR = 1.002; 95%CI [1.000–1.003], p=0.023) and ACTH level of >300 pg/mL after BLA (HR = 9.053; 95%CI [2.076–39.472], p=0.003) also emerged as independent predictors of the Nelson's syndrome in adjusted Cox regression models.

Adverse events

The incidence of hypothyroidism requiring thyroid hormone replacement therapy at last post-SRS endocrine follow-up visit was higher in patients who underwent SRS before BLA versus those who did not (88% vs. 40%, respectively, p<0.001; data available for 42 patients). New thyroid hormone deficiency after pre-BLA SRS developed in 10 out of 20 patients (50%) with available thyroid hormone assessment before the SRS. The proportion of patients diagnosed with growth hormone deficiency and/or requirement for hormone replacement therapy at last follow-up visit was higher in

Table 1 Demographic and clinical characteristics of the study cohort

Demographic and clinical characteristics	All patients (*n*=43)	SRS before BAL (*n*=33)	No SRS before BAL (*n*=10)	*p*-value
Age at bilateral adrenalectomy				0.047
Median [range]	42.05 [20.22–82.86]	41.68 [22.02–63.62]	48.11 [20.22–82.86]	
Mean ± SD	44.16±14.01	41.84±10.40	51.82±21.12	
Gender				0.180
Men	7 (16%)	4 (12%)	3 (30%)	
Women	36 (84%)	29 (87%)	7 (70%)	
Number of pituitary adenoma resection surgeries				0.101
One	22 (51%)	14 (42%)	8 (80%)	
Two	17 (40%)	15 (46%)	2 (20%)	
Three	4 (9%)	4 (12%)	0	
SRS treatment				-
Whole Sella	-	16 (48%)	-	
Discrete tumor	-	15 (46%)	-	
Data not available	-	2 (6%)		
Pituitary adenoma pathology results				0.119
ACTH positive	16 (37%)	14 (42%)	2 (20%)	
ACTH negative	11 (26%)	6 (18%)	5 (50%)	
Not done/not available	16 (37%)	13 (40%)	3 (30%)	
SRS prescription dose (Gy)				-
Median [range]		25 [18–30]		
Mean ± SD		23.82±2.72		
Highest ACTH concentration within 6 months before BLA (pg/mL)				0.793
Mean ± SD	127.74±271.18	135.25±315.72	108.20±92.30	
Median [range]	68.50 [14.00–1665.0]	68.5 [14.0–1665.0]	72.50 [25.0–292]	
Highest cortisol concentration within 6 months before BLA (ug/dL)				0.234
Median [range]	25.30 [1.60–90.00]	21.85 [1.6–90.0]	30.0 [13.3–59.0]	
Mean ± SD	27.97±19.22	25.95±20.30	34.73±13.95	
Highest 24-h urine-free cortisol concentration within 6 months before BLA (ug/24 h)				0.107
Median [range]	93.0 [10–2782.0]	78.0 [10.0–852.0]	120.5 [80.4–2782.0]	
Mean ± SD	253.96±579.0	137.80±202.41	583.07±1080.79	
Highest ACTH concentration within 6 months after BLA (pg/mL)				0.688
Median [range]	140 [3–3302]	115.0 [3.0–3302.0]	238.0 [109.0–597.0]	
Mean ± SD	343.23±578.76	362.48±645.03	268.63±165.13	
Normal ACTH concentration at last follow-up (<63 pg/mL)	11 (26%)	10 (30%)	9 (9%)	0.246
Imaging follow-up after BLA (months)				0.438
Median [range]	70.20 [6.13–285.74]	93.15 [6.13–206.32]	49.26 [4.39–206.33]	
Mean ± SD	91.12±73.50	95.98±74.36	72.91 ± 71.89	
Clinical follow-up after BLA (months)				0.578
Median [range]	80.49 [0.30–228.36]	85.57 [1.05–228.36]	70.85 [0.30–222.03]	
Mean ± SD	92.66±70.52	89.31±64.69	103.71±90.28	
Endocrine follow-up after BLA (months)				0.587
Median [range]	66.49 [0.03–285.54]	73.18 [0.04–285.54]	63.85 [15.80–213.67]	
Mean ± SD	81.65±72.70	85.57±70.79	101.31±82.34	

BLA bilateral adrenalectomy, *SRS* stereotactic radiosurgery

patients who underwent SRS before BLA vs. those who did not (90% vs. 10%, respectively, p=0.02; data available for 34 patients). There were no patients with permanent post-SRS cranial nerve neuropathy, carotid stenosis, or radiation-induced neoplasia during post-SRS imaging surveillance.

Treatment for Nelson's syndrome after BLA

Treatment of the Nelson's syndrome included stereotactic radiosurgery in five patients, fractionated radiation therapy in one patient, and repeat transsphenoidal resection in

Table 2 Predictors of risk of developing Nelson's syndrome (HR [95%confidence interval]; *p*-value)

	Cox regression analysis	
	Univariate	Multivariate
SRS before BLA	**0.224 (0.058–0.869), 0.03**	**0.126 (0.022–0.714), 0.019**
Age at BLA	1.074 (0.443–2.606), 0.874	-
Gender	0.467 (0.094–2.335), 0.354	-
ACTH concentration before BLA	1.001 (0.998–1.004), 0.461	-
Cortisol concentration before BLA	**1.030 (1.000–1.060), 0.047**	1.034 (0.998–1.071), 0.062
ACTH concentration 6 months after BLA (pg/mL)	**1.001 (1.000–1.002), 0.027**	**1.002 (1.000–1.003), 0.023**[A]
ACTH concentration after BLA >300 pg/mL	**7.887 (1.931–32.216), 0.004**	**9.053 (2.076–39.472), 0.003**[A]
24h Urine free cortisol before BLA	1.001 (1.000–1.002), 0.074	-
Pathology results[B]	0.514 (0.221–1.197), 0.123	-
Number of pituitary adenoma resection surgeries	1.074 (0.443–2.606), 0.874	-

ACTH adrenocorticotropic hormone, *BLA* bilateral adrenalectomy

[A] Considered separately in multivariate Cox regression models

[B] ACTH positive, negative, or not available

one patient. Two patients were treated with temozolomide, and one patient also received bevacizumab and sunitinib. Radiologic tumor control was achieved in all patients; however, ACTH levels at last endocrine follow-up remained elevated in 4 out of the 5 patients who had BLA without prior SRS. One patient died during follow-up due to progressive disease.

Discussion

In patients with established CD, SRS for residual pituitary adenoma before BLA was associated with reduced risk for developing Nelson's syndrome, independently of CD severity. Elevated concentration of ACTH within 6 months after BLA was also associated with an elevated risk for developing Nelsons' syndrome in adjusted regression models.

The most important finding of our study is that SRS before BLA is associated with a reduced risk for Nelson's syndrome in patients with persistent CD requiring BLA, suggesting that irradiation of residual pituitary adenoma and/or sellar region should be considered prior to proceeding with BLA. Other studies have reported with mixed findings with regard to the potential impact of pituitary irradiation for developing Nelson's syndrome after BLA. Some authors have reported that pituitary irradiation before or immediately after BLA is associated with lowered risk of the Nelson's syndrome [11, 13, 21, 24, 28], while others found that pituitary irradiation before BLA does not affect the risk for the Nelson's syndrome [22, 30, 35]. However, these studies were limited by small sample sizes, absence of control group of CD patients who did not receive SRS prior to BLA, and use of non-SRS pituitary irradiation techniques that are rarely used for contemporary pituitary irradiation. For example, Jenkins and colleagues reported their experience with 56 patients who underwent BLA for ACTH-dependent CD between 1946 and 1993 [13]. Patients who received prophylactic radiotherapy were less likely to develop Nelson's syndrome compared with those who did not (25% vs. 50%), and the authors recommended prophylactic pituitary radiotherapy. Another series of 39 CD patients reported 11 (28%) cases of Nelson's syndrome at median of 15 months after BLA; none of the Nelson's syndrome patients was treated with prophylactic pituitary irradiation [11]. We reported previously only one case of Nelson's syndrome in a consecutive cohort of 20 CD patients who were treated with SRS after pituitary surgery but before BLA [21]. While a prospective randomized study could provide more definitive evidence regarding the potential value of pituitary irradiation before BLA, however, such a study would present significant logistic challenges given the rarity of persistent CD requiring BLA. Nevertheless, our findings suggest that irradiation of the pituitary adenoma should be considered for refractory CD patients after failed pituitary surgery but before proceeding to BLA [4, 5, 12, 20, 25]. As expected, SRS was associated with a greater incidence of hypothyroidism at last follow-up, but this was successfully managed using thyroid hormone replacement therapy. None of the SRS patients in this series was diagnosed with cranial neuropathy or radiation-induced tumors. Given the latency from SRS to endocrine remission of CD, medical treatment can be considered for bridging therapy. BLA is often reserved for those CD patients who experience life-threatening hypercortisolemia necessitating immediate endocrine control, those who cannot tolerate medical management, or those who fail to achieve endocrine remission after SRS.

We also found that higher ACTH concentrations after BLA were associated with increased risk for the Nelson's syndrome. These findings are in line with other studies

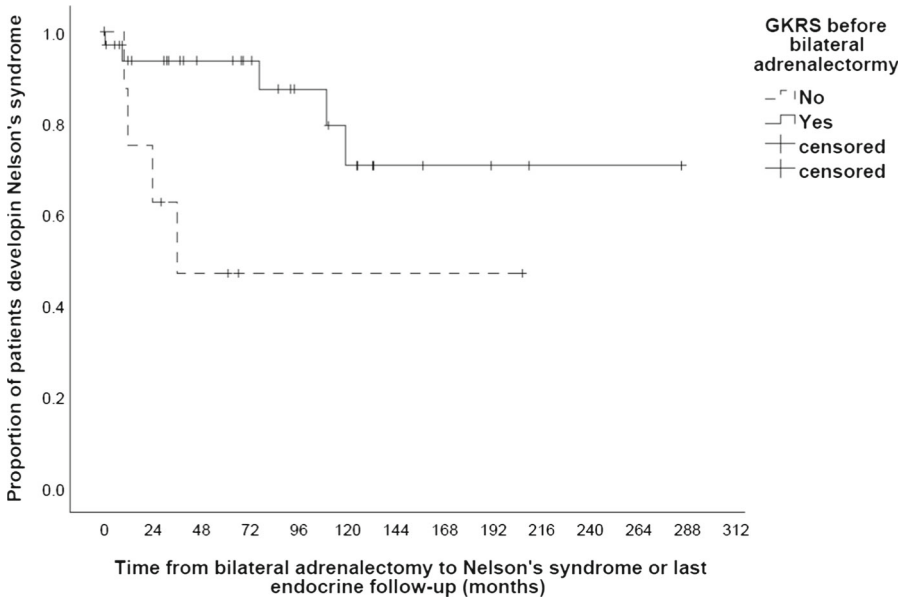

Fig. 2. Incidence of Nelson's syndrome as a function of pituitary SRS before bilateral adrenalectomy

documenting that elevated concentration of ACTH is a well-established predictive factor of Nelson's syndrome after BLA [3, 9, 13, 28, 30]. Furthermore, greater increment of ACTH within the first year after BLA has been shown to be associated with greater risk of the Nelson's syndrome [9]. Therefore, early SRS after BLA can be considered for those CD patients who did not have prior pituitary irradiation but exhibit elevated ACTH concentration after BLA or experience raising ACTH levels within the first year after BLA.

Management of Nelson's syndrome is challenging, and treatment alternatives include observation, medical therapy, radiation therapy, radiosurgery, and surgical resection [28]. In our series, SRS or hypofractionated SRS was attempted for all Nelson's syndrome patients who did not have a history of prior pituitary irradiation. Repeated pituitary surgery is traditionally considered first-line treatment option for the Nelson's syndrome especially in cases of macroadenomas causing optic pathway compression. However, curative resection is often not possible given infiltrative tumor growth in these pretreated patients, often with multiple histories of unsuccessful adenoma resections [15, 19, 28]. A multicentered study of 51 patients treated with single-fraction GKRS for the Nelson's syndrome reported that 29% of patients achieved endocrine remission and 63% of patients achieved reduction of ACTH levels, suggesting that SRS is a reasonable approach for treatment of the Nelson's syndrome [8]. Two of our patients were treated with temozolomide, sometimes considered for refractory Nelson's syndrome after exhaustion of available targeted therapies, such an approach may be reasonably effective and tolerated [16, 23, 28]. Treatment options for patients with Nelson's syndrome must be considered based in part on the patient's history and prior treatments.

Our study has limitations. Most importantly, this was a retrospective single-institution series subjecting our results to selection and recall biases, and also some SRS treatment parameters, such as conformity index, could not be evaluated for all patients. However, all patients were managed according to consistent approaches and contemporary clinical practice. Prospective randomized study would be logistically challenging. Secondly, small sample size limits statistical power of our study that could possibly be addressed via a larger multi-institutional series.

Conclusions

SRS performed before BLA is associated with reduced risk of the Nelson's syndrome and should be considered after failed resection of ACTH producing pituitary adenoma before proceeding to BLA. Elevated ACTH level after BLA (>300 pg/mL) is indicative of increased risk of developing Nelsons' syndrome, suggesting that patients with a high ACTH concentration after BLA should be considered for early SRS to decrease the chances of developing Nelson's syndrome.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Assié G, Bahurel H, Bertherat J, Kujas M, Legmann P, Bertagna X (2004) The Nelson's syndrome... revisited. Pituitary 7(4):209–215
2. Assié G, Bahurel H, Coste J et al (2007) Corticotroph tumor progression after adrenalectomy in Cushing's Disease: a reappraisal of Nelson's Syndrome. J Clin Endocrinol Metab 92(1):172–179
3. Barnett AH, Livesey JH, Friday K, Donald RA, Espiner EA (1983) Comparison of preoperative and postoperative ACTH concentrations after bilateral adrenalectomy in Cushing's disease. Clin Endocrinol (Oxf) 18(3):301–305
4. Bunevicius A, Kano H, Lee C-C, et al (2020) Early versus late Gamma Knife radiosurgery for Cushing's disease after prior resection: results of an international, multicenter study. J Neurosurg 1–9
5. Bunevicius A, Laws ER, Vance ML, Iuliano S, Sheehan J (2019) Surgical and radiosurgical treatment strategies for Cushing's disease. J Neurooncol 145(3):403–413
6. Bunevicius A, Sheehan D, Lee Vance M, Schlesinger D, Sheehan JP (2020) Outcomes of Cushing's disease following Gamma Knife radiosurgery: effect of a center's growing experience and era of treatment. J Neurosurg 1–8
7. Clayton RN, Jones PW, Reulen RC et al (2016) Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study. Lancet Diab Endocrinol 4(7):569–576
8. Cordeiro D, Xu Z, Li CE, et al (2019) Gamma Knife radiosurgery for the treatment of Nelson's syndrome: a multicenter, international study. J Neurosurg 1–6
9. Das L, Bhansali A, Pivonello R et al (2020) ACTH increment post total bilateral adrenalectomy for Cushing's disease: a consistent biosignature for predicting Nelson's syndrome. Pituitary. https://doi.org/10.1007/s11102-020-01047-x
10. Fountas A, Lim ES, Drake WM et al (2020) Outcomes of patients with Nelson's syndrome after primary treatment: a multicenter study from 13 UK pituitary centers. J Clin Endocrinol Metab. https://doi.org/10.1210/clinem/dgz200
11. Gil-Cárdenas A, Herrera MF, Díaz-Polanco A, Rios JM, Pantoja JP (2007) Nelson's syndrome after bilateral adrenalectomy for Cushing's disease. Surgery 141(2):147–151 discussion 151-152
12. Hughes JD, Young WF, Chang AY, Link MJ, Garces YI, Laack NN, Thompson GB, Pollock BE (2019) Radiosurgical management of patients with persistent or recurrent cushing disease after prior transsphenoidal surgery: a management algorithm based on a 25-year experience. Neurosurgery. https://doi.org/10.1093/neuros/nyz159
13. Jenkins PJ, Trainer PJ, Plowman PN, Shand WS, Grossman AB, Wass JA, Besser GM (1995) The long-term outcome after adrenalectomy and prophylactic pituitary radiotherapy in adrenocorticotropin-dependent Cushing's syndrome. J Clin Endocrinol Metab 80(1):165–171
14. Katznelson L (2015) Bilateral adrenalectomy for Cushing's disease. Pituitary 18(2):269–273
15. Kelly PA, Samandouras G, Grossman AB, Afshar F, Besser GM, Jenkins PJ (2002) Neurosurgical treatment of Nelson's syndrome. J Clin Endocrinol Metab 87(12):5465–5469
16. Kurowska M, Nowakowski A, Zieliński G, Malicka J, Tarach JS, Maksymowicz M, Denew P (2015) Temozolomide-induced shrinkage of invasive pituitary adenoma in patient with Nelson's syndrome: a case report and review of the literature. Case Rep Endocrinol. https://doi.org/10.1155/2015/623092
17. Lacroix A, Feelders RA, Stratakis CA, Nieman LK (2015) Cushing's syndrome. The Lancet 386(9996):913–927
18. Lindholm J, Juul S, Jørgensen JO et al (2001) Incidence and late prognosis of cushing's syndrome: a population-based study. J Clin Endocrinol Metab 86(1):117–123
19. Lüdecke DK, Breustedt HJ, Brämswig J, Köbberling J, Saeger W (1982) Evaluation of surgically treated Nelson's syndrome. Acta Neurochir (Wien) 65(1–2):3–13
20. Mehta GU, Ding D, Patibandla MR et al (2017) Stereotactic radiosurgery for Cushing disease: results of an international, multicenter study. J Clin Endocrinol Metab 102(11):4284–4291
21. Mehta GU, Sheehan JP, Vance ML (2013) Effect of stereotactic radiosurgery before bilateral adrenalectomy for Cushing's disease on the incidence of Nelson's syndrome. J Neurosurg 119(6):1493–1497
22. Moore TJ, Dluhy RG, Williams GH, Cain JP (1976) Nelson's syndrome: frequency, prognosis, and effect of prior pituitary irradiation. Ann Intern Med 85(6):731–734
23. Moyes VJ, Alusi G, Sabin HI, Evanson J, Berney DM, Kovacs K, Monson JP, Plowman PN, Drake WM (2009) Treatment of Nelson's syndrome with temozolomide. Eur J Endocrinol 160(1):115–119
24. Nagesser SK, van Seters AP, Kievit J, Hermans J, Krans HM, van de Velde CJ (2000) Long-term results of total adrenalectomy for Cushing's disease. World J Surg 24(1):108–113
25. Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A (2015) Treatment of Cushing's syndrome: an endocrine society clinical practice guideline summary of recommendations. J Clin Endocrinol Metab 100:2807–2831
26. Oßwald A, Plomer E, Dimopoulou C et al (2014) Favorable long-term outcomes of bilateral adrenalectomy in Cushing's disease. Eur J Endocrinol 171(2):209–215
27. Palermo NE, Ananthakrishnan S (2015) Re-examining Nelson's syndrome. Curr Opin Endocrinol Diabetes Obes 22(4):313–318
28. Patel J, Eloy JA, Liu JK (2015) Nelson's syndrome: a review of the clinical manifestations, pathophysiology, and treatment strategies. Neurosurg Focus 38(2):E14
29. Pendharkar AV, Sussman ES, Ho AL, Hayden Gephart MG, Katznelson L (2015) Cushing's disease: predicting long-term remission after surgical treatment. Neurosurg Focus 38(2):E13
30. Pereira MA, Halpern A, Salgado LR, Mendonça BB, Nery M, Liberman B, Streeten DH, Wajchenberg BL (1998) A study of patients with Nelson's syndrome. Clin Endocrinol (Oxf) 49(4):533–539
31. Petersenn S, Beckers A, Ferone D et al (2015) Therapy of endocrine disease: outcomes in patients with Cushing's disease undergoing transsphenoidal surgery: systematic review assessing criteria used to define remission and recurrence. Eur J Endocrinol 172(6):R227–R239
32. Ragnarsson O, Olsson DS, Chantzichristos D et al (2019) The incidence of Cushing's disease: a nationwide Swedish study. Pituitary 22(2):179–186
33. Ritzel K, Beuschlein F, Mickisch A, Osswald A, Schneider HJ, Schopohl J, Reincke M (2013) Clinical review: outcome of bilateral adrenalectomy in Cushing's syndrome: a systematic review. J Clin Endocrinol Metab 98(10):3939–3948
34. Smith PW, Turza KC, Carter CO, Vance ML, Laws ER, Hanks JB (2009) Bilateral adrenalectomy for refractory Cushing disease: a safe and definitive therapy. J Am Coll Surg 208(6):1059–1064
35. Sonino N, Zielezny M, Fava GA, Fallo F, Boscaro M (1996) Risk factors and long-term outcome in pituitary-dependent Cushing's disease. J Clin Endocrinol Metab 81(7):2647–2652