Title

Stereotactic Radiosurgery for Non-Functioning Pituitary Adenomas: Meta-Analysis and International Society of Stereotactic Radiosurgery (ISRS) Practice Opinion

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Stereotactic radiosurgery for non-functioning pituitary adenomas: meta-analysis and International Stereotactic Radiosurgery Society practice opinion

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Abstract

Background. This systematic review reports on outcomes and toxicities following stereotactic radiosurgery (SRS) for non-functioning pituitary adenomas (NFAs) and presents consensus opinions regarding appropriate patient management.

Methods. Using the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, a systematic review was performed from articles of ≥10 patients with NFAs published prior to May 2018 from the Medline database using the key words "radiosurgery" and "pituitary" and/or "adenoma." Weighted random effects models were used to calculate pooled outcome estimates.

Results. Of the 678 abstracts reviewed, 35 full-text articles were included describing the outcomes of 2671 patients treated between 1971 and 2017 with either single fraction SRS or hypofractionated stereotactic radiotherapy (HSRT). All studies were retrospective (level IV evidence). SRS was used in 27 studies (median dose: 15 Gy, range: 5–35 Gy) and HSRT in 8 studies (median total dose: 21 Gy, range: 12–25 Gy, delivered in 3–5 fractions). The 5-year random effects local control estimate after SRS was 94% (95% CI: 93.0–96.0%) and 97.0% (95% CI: 93.0–98.0%) after HSRT. The 10-year local control random effects estimate after SRS was 83.0% (95% CI: 77.0–88.0%). Post-SRS hypopituitarism was the most common treatment-related toxicity observed, with a random effects estimate of 21.0% (95% CI: 15.0–27.0%), whereas visual dysfunction or other cranial nerve injuries were uncommon (range: 0–7%).

Conclusions. SRS is an effective and safe treatment for patients with NFAs. Encouraging short-term data support HSRT for select patients, and mature outcomes are needed before definitive recommendations can be made. Clinical practice opinions were developed on behalf of the International Stereotactic Radiosurgery Society (ISRS).

Key Points

1. SRS is an effective and safe treatment for patients with NFAs.
2. Single fraction SRS is associated with long-term (10-year) disease control for NFAs.
3. HSRT can be used in select patients with NFAs with encouraging short-term results.

Importance of the Study

SRS is commonly used for patients with non-functioning adenomas. However, the reports on the treatment techniques and clinical outcomes, both efficacy and safety, are retrospective in nature, and therefore it is difficult to make broad conclusions by individually assessing studies. Therefore, on behalf of the ISRS, it was the objective of this report to provide a high-quality critical analysis of the literature to evaluate this treatment approach and provide key opinions for patient management. After an extensive review, we determined that single fraction SRS is associated with high control rates with long-term pooled outcomes, and hypofractionated approaches (3–5 fractions) are also associated with excellent, short-term, outcomes. New-onset hypopituitarism is the most common side effect following treatment, although the time course for its development and clinical sequelae require better reporting. Cranial nerve dysfunction following treatment is rare.

Pituitary adenomas represent 10–20% of all tumors of the central nervous system, of which approximately one-third are non-functioning.[1] Multiple options exist for patients with newly diagnosed non-functioning adenomas (NFAs), including conservative management, resection, conventionally fractionated external beam radiotherapy (EBRT), and stereotactic radiosurgery (SRS). Developments in SRS techniques have resulted in this becoming an alternative to resection for medically inoperable patients, an adjuvant treatment for those who have undergone a subtotal resection, or salvage treatment for those who experience growth of residual disease. Multiple retrospective series have demonstrated favorable control rates, often >90% five years following SRS; however, published institutional series often report on cases treated over an extended period of time, along with either functioning pituitary adenomas or with other benign base-of-skull tumors.[2] Moreover, the advent of hypofractionated approaches for complex cases near critical structures or larger tumors needs further systematic evaluation.

The purpose of this systematic review of the literature is to describe the demographics, patient characteristics, treatment details, control outcomes, and treatment-related toxicities specifically for patients with NFAs treated with SRS. Based on this review, consensus opinions were made in an effort to provide guidance and more uniform clinical management.

Methods

Selection of Articles

This systematic review of the literature was performed according to criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[3] Initial article selection was performed by searching the MEDLINE (PubMed) and Cochrane electronic bibliographic databases, and additional primary research studies were added based on a review of the bibliographies of the selected articles or other reviews of the literature. Given the reporting of outcomes of patients with NFAs in larger series of base-of-skull tumors or as selected cases in generalized series of pituitary adenomas (including functioning tumors), these generic key words were used: "radiosurgery" and "pituitary" and/or "adenoma." Full text articles published in the English language up until May 2018 were considered and no publishing date restrictions were used.

The initial query identified 678 articles that were subsequently screened for relevance to the objectives of the present report by thorough review of the article titles, abstracts, and manuscripts, as necessary. Specific inclusion criteria included: retrospective or prospective case series of >10 adult patients, SRS or hypofractionated stereotactic radiotherapy (HSRT; 2–5 fractions), and description of clinical or treatment-related toxicity outcomes specific to NFA patients. Exclusion criteria included: non-clinical reports (ie, dosimetric, physics, or basic science research only); expert opinion, commentary or review studies which did not provide unique data on >10 patients; studies on patients with sellar tumors of different disease entities (ie, craniopharyngiomas, pituitary carcinomas, and metastases), pediatric-only case series, or studies which had fewer than 10 patients with NFAs. As some series included updates on prior reports from the same institution or multi-institutional studies with inclusion of already published patient cohorts, duplicate studies were assessed for any updated data on treatment efficacy or toxicity with the latest report of the largest number of patients included in the final analysis. The search strategy used for this report and the methodology for study inclusion is outlined in Supplementary Fig. 1.

Outcome Measures and Statistical Analysis

The primary outcomes were local control at 5 and 10 years. In addition, key treatment-related toxicities were evaluated, such as new hypopituitarism, optic neuropathy, and other cranial nerve (CN) injury. R Studio v1.1.423 was used for statistical analyses and the R package "metafor" (v2.0-0)[4] was used for meta-analyses, tests for heterogeneity, analysis of publication bias, and meta-regressions. Study variances for overall estimate and for meta-regression were calculated using the DerSimonian–Laird method.[5,6] Weighted random effects models were used to calculate pooled estimates for 5-year local control, 10-year local control, and new hypopituitarism. Since the studies involved patient treatment decisions, the random effects model was considered superior to the fixed effects model when calculating pooled estimates. In addition, due to the selected studies spanning numerous years, in a number

of different populations and in varied geographical locations, the random effects model was considered to be better than the fixed effects model.[7,8] Nevertheless, we reported both estimates in the figures. The I^2 statistic was used for identifying heterogeneity: I^2 of 0%, 25%, 50%, and 75% were interpreted as absent, low, moderate, and high heterogeneity, respectively.[9] Funnel plots and the Egger test ($P < 0.05$ indicating presence of bias) were used for identifying publication bias. Finally, meta-regression analyses were performed to identify potential associations between outcomes including 5-year local control, 10-year local control, and new hypopituitarism as a function of tumor volume given the potential for bias in treatment fractionation selection.

Results

After a comprehensive review of the published literature, 35 unique studies met the inclusion and exclusion criteria for this systematic review. All included studies were retrospective in nature and provided low-quality evidence. There was no presence of publication bias ($P > 0.05$) across the included studies regarding the primary outcomes evaluated in this meta-analysis (Supplementary Fig. 2). A majority of studies ($n = 31$, 89%) represented single-institution reports, and 4 studies (11%) were multi-institutional collaborations. Eleven reports (31%) were published from institutions in the United States, whereas the majority of reports originated from institutions outside of the United States ($n = 24$, 69%). The median number of patients evaluated in single institution reports was 31 (range: 10–272 patients).

Basic study details and patient characteristics are presented in Table 1.[10–44] Across all studies, 51% of patients were men, and the median age was 53 years (range: 43–69). Few patients were treated definitively with SRS (median 5.5%, range: 0–100%), and only 2 reports ($n = 62$ and $n = 69$) described the outcomes of patients who were treated definitively due to medical inoperability or refusal of resection.[19,20] The median value across all studies for the proportion of patients who had undergone resection prior to SRS was 95% (range: 0–100%). For these patients, 15 studies (43%) reported the percentage of patients who were treated adjuvantly (immediately after resection for residual disease or within an interval without radiographic evidence of disease growth) or in the salvage setting. For the studies reporting this distinction, the median proportion of patients treated adjuvantly was 47% (range: 17–96%), and the median proportion of patients treated in the salvage setting was 53% (range: 2–83%). For most patients, SRS represented the first course of radiotherapy received; the range of proportions of patients who received prior radiotherapy was 9–17%. Given the substantial number of patients who had undergone resection as first-line treatment for their disease, the overall proportion of patients who had hypopituitarism prior to first SRS was 45% (range: 0–83%).

Most studies reported on the tumor dimensions at the time of SRS, summarized in Supplementary Table 1. For those studies reporting tumor diameter ($n = 10$, 29%), the median dimension was 2.2 cm (range: 0.1–10.5 cm). For those studies reporting tumor volume ($n = 30$, 86%), the median was 3.5 cc (range: 0.03–38.7 cc). A total of 27 studies (77%) reported on outcomes of 2451 patients treated with single fraction SRS to a median dose of 15 Gy (range: 5–25 Gy). Eight studies (23%) described the outcomes of patients treated with HSRT, to a median dose of 21 Gy (range: 12 Gy in 3 fractions to 25 Gy in 5 fractions). The radiosurgery delivery technologies included in this review are CyberKnife (Accuray) ($n = 6$) for HSRT, Gamma Knife ($n = 26$) (Elekta) for SRS or HSRT treatments, or other linear accelerator–based techniques ($n = 3$).

The disease control and treatment-related toxicity outcomes are presented in Table 2. The median follow-up was 42 months (range: 21–86 mo). The majority of studies ($n = 21$, 60%) reported crude, rather than actuarial, rates of local control ranging 90–100%. This is a possible confounder in terms of overestimating effect size. However, for the 10 studies reporting actuarial outcomes, the 5-year rate of progression-free survival (PFS) was 95% (range: 90–100%), identical to the studies utilizing non-actuarial reporting methodology. Random effects meta-analyses for 5-year local control for single fraction SRS and HSRT are shown in Fig. 1, with estimates of 94.0% (95% CI: 93.0–96.0%) and 97.0% (95% CI: 93.0–98.0%), respectively. Four studies reported 10-year rates of PFS ranging 79–100%. Fig. 2 shows the meta-analysis for 10-year local control after SRS with a random effects estimate of 83.0% (95% CI: 77.0–88.0%); HSRT outcomes were limited to <5 years. Reported salvage treatment included repeat SRS, EBRT, chemotherapy, or resection (Table 2).

Treatment-related toxicities that were evaluated in each of the selected articles included cerebrovascular accident (CVA) ($n = 0$), new-onset hypopituitarism ($n = 31$), optic pathway dysfunction ($n = 29$), other CN injury ($n = 29$), and secondary malignancy ($n = 0$) (Table 2). New-onset hypopituitarism ranged 0–32%. Random effects meta-analyses for new hypopituitarism following single fraction SRS and HSRT are shown in Fig. 3, with estimates of 21.0% (95% CI: 15.0–27.0%) and 3.0% (95% CI: 1.0%–8.0%), respectively. Twenty-four studies described dose constraints to the adjacent optic nerve or chiasm, with doses ranging 8–13.7 Gy in 1 fraction, and typically 25 Gy in 5 fractions. Declining visual function occurred 0–7% of the time as a result of radiotherapy, and in the absence of reported tumor progression. Similarly, the incidence of other cranial neuropathies ranged 0–7% and were most often temporary in nature. CN injuries frequently involved CN III, but were also seen in CNs IV, V, and VI.

Given the potential for SRS fractionation selection, local control, and treatment-related toxicity to be related to tumor volume, we investigated this correlation. Supplementary Fig. 3 shows meta-regression plots of median lesion volume versus 5- and 10-year local control and new hypopituitarism by SRS and HSRT. Meta-regression analysis did not identify a statistically significant relationship for 5- and 10-year local control or new hypopituitarism as a function of tumor volume.

Discussion

SRS for a pituitary adenoma was first described anecdotally in 1968 and since then this technique has been

Table 1 Non-functioning pituitary adenoma SRS study details and patient characteristics

Author	Year	Institution	Location	Years	Study Type	Evidence Quality	N	%Males	Age (y)	%Definitive	Prior Surgery	%Adjuvant	%Salvage	Prior RT	Time from Surgery to RT(mo)	% Hypopituitarism prior to RT
Graffeo	2018	Mayo Clinic	Rochester, MN, USA	2007–2014	RS	Low	57	45%*	50*	7%*	93%	–	–	None	–	0%
Narayan	2018	Louisiana State University Health Sciences Center	Shreveport, LA, USA	2000–2017	RS	Low	87	48%	57	7%	93%	61%	32%	None	12.6	34%
Pomeraniec	2017	Multi-institutional	IGKRF	1987–2015	RS	Low	222	–	53	0%	100%	50%	50%	None	–	46%
Cohen-Inbar	2017	Multi-institutional	IGKRF	1997–2015	RS	Low	357	–	55	0%	100%	0%	0%	None	–	–
ZibarTomsic	2017	University Hospital Centre Zagreb	Zagreb, Croatia	2003–2014	RS	Low	18	67%	63	–	–	–	–	None	–	28%
McTyre	2017	Wake Forest School of Medicine	Winston-Salem, NC, USA	2013–2015	RS	Low	10	29%*	62*	–	–	–	–	–	–	–
Sadik	2017	Elisabeth-Tweesteden Hospital	Tilburg, Netherlands	2002–2015	RS	Low	50		57	0%	100%	26%	74%	None		–
Losa	2017	Istituto Scientifico San Raffaele, Vita-Salute University	Milan, Italy	1994–2014	RS	Low	272	51%	52	8%	92%	–	–	2%	–	–
Puataweepong	2016	Ramathibodi Hospital, Mahidol University	Bangkok, Thailand	2009–2012	RS	Low	27	40%*	50*	–	98%*	–	–	5%*	24	82%*
Hasegawa	2015	Komaki City Hospital	Komaki, Japan	1991–2001	RS	Low	16	50%	62	100%	0%	0%	0%	None	None	6%
Lee	2014	Multi-institutional	Multi-institutional	1988–2012	RS	Low	41	49%	69	100%	0%	0%	0%	None	None	37%
Liao	2013	Chang Gung Memorial Hospital at Linkou	Taoyuan, Taiwan	2006–2011	RS	Low	21	35%*	48*	0%	100%	47%*	53%*	6%*	–	–
Zeiler	2013	University of Manitoba	Winnipeg, Manitoba, Canada	2003–2011	RS	Low	47	43%*	56*	35%*	65%*	–	–	–	59.8*	–
Sheehan	2013	Multi-institutional	NAGKC	1988–2011	RS	Low	512	56%	53	6%	94%	–	–	7%	–	–
Chen	2013	Tri-Service General Hospital, National Defense Medical Center	Taipei, Taiwan	2007–2011	RS	Low	17	35%	58*	6%	94%	82%*	14%*	None	58	–
El-Shehaby	2012	Gamma Knife Center Cairo, Nasser Institute	Shobra, Egypt	2002–2008	RS	Low	21	62%	48	10%	90%	–	–	None	–	20%
Runge	2012	Department of Stereotaxy and Functional Neurosurgery, University Hospital	Cologne, Germany	1992–2008	RS	Low	61	59%	56	3%	97%	38%	59%	3%	–	43%

Table 1 Continued

Author	Year	Institution	Location	Years	Study Type	Evidence Quality	N	%Males	Age (y)	%Definitive	Prior Surgery	%Adjuvant	%Salvage	Prior RT	Time from Surgery to RT(mo)	% Hypopituitarism prior to RT
Wilson	2012	Wollongong Hospital	Wollongong, New South Wales, Australia	1971–2007	RS	Low	51	61%	53	2%	98%	96%	2%	None	–	–
Iwata	2011	Nagoya City University Graduate School of Medical Sciences	Nagoya, Japan	2000–2009	RS	Low	100	43%	59	6%	94%	–	–	None	11	26%
Park	2011	University of Pittsburgh	Pittsburgh, PA, USA	1987–2009	RS	Low	125	55%	54	12%	88%	20%	68%	14%	–	64%
Castro	2010	Institute of Neurological Radiosurgery	Sao Paulo, Brazil	1999–2009	RS	Low	14	48%*	43*	7%*	93%*	76%*	17%*	5%*	–	–
Hayashi	2010	Tokyo Women's Medical University	Tokyo, Japan	2003–2007	RS	Low	43	70%*	50*	0%	100%	95%	5%	None	–	–
Cho	2009	St. Mary's Hospital, The Catholic University of Korea	Seoul, Korea	2004–2008	RS	Low	17	47%	55	18%	82%	–	–	None	–	–
Killory	2008	Barrow Neurological Institute	Phoenix, AZ, USA	2004–2006	RS	Low	14	55%	47	0%	100%	45%*	55%*	5%	–	–
Hoybye	2009	Karolinska University Hospital	Stockholm, Sweden	1994–2004	RS	Low	23	56%	49	0%	100%	17%	83%	None	35	83%
Kobayashi	2009	Nagoya Kyoritsu Hospital	Nagoya, Japan	1996–2009	RS	Low	71	44%	50	8%	92%	–	–	17%	–	–
Pollock	2008	Mayo Clinic	Rochester, MN, USA	1992–2004	RS	Low	62	56%	53	5%	95%	24%	76%	5%	28	52%
Liscak	2007	Na Homolce Hospital	Prague, Czech Republic	1993–2003	RS	Low	79	56%	54	15%	85%	–	–	None	–	62%
Kajiwara	2005	Yamaguchi University School of Medicine	Ube, Japan	1999–2002	RS	Low	14	50%	68	0%	100%	–	–	14%	–	0%
Iwai	2005	Osaka City General Hospital	Osaka, Japan	1994–1999	RS	Low	31	29%	53	0%	100%	68%	32%	3%	–	35%
Muacevic	2004	German Gamma Knife Center Munich, Ludwig-Maximilians University	Munich, Germany	1994–2004	RS	Low	60		50	0%	100%	–	–	None	–	–
Petrovich	2002	University of Southern California	Los Angeles, CA, USA	1994–2002	RS	Low	56	59%*	53	5%	95%	17%	83%	5%	61	33%
Wowra	2002	Ludwig-Maximilians-Universität	München, Germany	1993–2002	RS	Low	30	47%	55	3%	97%	–	–	None	–	70%
Mokry	1999	University of Graz	Graz, Austria	1992–1998	RS	Low	31	49%*	46*	3%	97%	–	–	10%*	43*	–
Martinez	1998	Ruber International Hospital	Madrid, Spain	1992–1995	RS	Low	14	46%*	44*	50%	50%	–	–	7%	–	43%

*Entire patient cohort.
Abbreviations: RS, retrospective study; RT, radiotherapy; NAGKC, North American Gamma Knife Consortium; IGKRF, International Gamma Knife Research Foundation.

Table 2 Non-functioning pituitary adenoma SRS treatment outcomes and toxicities

Author	Year	N	Median Dose (Gy)	Median Fx	Median Follow-up (m)	Local Control (5 y)	Local Control (10 y)	Salvage Treatment	New Hypopituitarism	Maximum Dose to Optic Pathway (Gy)	Optic Neuropathy	CN Injury
Graffeo	2018	57	15	1	48*	100%	NR	Surgery + EBRT	31% at 5 years*	12 Gy	None	None
Narayan	2018	87	15	1	48	90% (crude)*	NR	GK or surgery	23%	10 Gy	None	3%
Pomeraniec	2017	222	15	1	69	NR	NR	NR	NR	13.7 Gy	NR	NR
Cohen-Inbar	2017	357	14	1	40	91% (crude)	NR	SRS, RT	10%	NR	NR	NR
ZibarTomsic	2017	18	20	1	71	NR	NR	NR	28%	NR	NR	NR
McTyre	2017	10	20	4	NR	100% (crude)	NR	NR	NR	NR	NR	NR
Sadik	2017	50	15	1	40	95% at 40 months	NR	Surgery ± EBRT	22%	9Gy	None	None
Losa	2017	272	15	1	79	95%	79%	Surgery, EBRT, GK, chemo	NR	10 Gy	NR	NR
Puataweepong	2016	27	25	5	39*	100% (crude)	NR	None	0%	32Gy/5 fx	None	None
Hasegawa	2015	16	15	1	86	100% (crude)	NR	None	0%	12.3 Gy	None	none
Lee	2014	41	12	1	48	94%	83%	Surgery	25%	11 Gy	None	2%
Liao	2013	21	21	3	37*	100% (crude)	NR	None	0%	21 Gy/3 fx	None	None
Zeiler	2013	47	14	1	35	98% (crude)	NR	NR	13%*	12.2 Gy	2%	2%
Sheehan	2013	512	16	1	36	95%	85%	Surgery and/or EBRT	21%	NR	7%	3%
Chen	2013	17	25	5	31	100%	NR	None	0%	17 Gy/5 fx	None	None
El-Shehaby	2012	21	12	1	44	95% (crude)	NR	None	0%	12.5 Gy	None	None
Runge	2012	61	13	1	83	98% (crude)	NR	NR	10%	9 Gy	None	None
Wilson	2012	51	14	1	50	100%	100%	None	NR	NR	None	None
Iwata	2011	100	21/25	3–5	33	98%	NR	NR	3%	25 Gy/5 fx	None	None
Park	2011	125	13	1	62	94%	NR	NR	23% at 5 years	11 Gy	2%	3%
Castro	2010	14	12.5	1	42*	100% (crude)	NR	None	3%	9 Gy	None	None
Hayashi	2010	43	18	1	36*	100% (crude)	NR	None	0%	10 Gy	None	None
Cho	2009	17	19	3	27	93% (crude)	NR	None	0%	NR	None	None
Killory	2008	14	25	5	27*	100% (crude)	NR	None	5%	25 Gy/5 fx	None	5%
Hoybye	2009	23	20	1	78	100% (crude)	NR	None	0%	11 Gy	None	4%
Kobayashi	2009	71	14	1	NR	97% (crude)	NR	None	8%	NR	NR	NR
Pollock	2008	62	16	1	64	95% at 7 years	NR	EBRT or SRS	32%	12 Gy	None	2%
Liscak	2007	79	20	1	60	100% (crude)	NR	None	14%	8 Gy	None	None

Table 2 Continued

Author	Year	N	Median Dose (Gy)	Median Fx	Median Follow-up (m)	Local Control (5 y)	Local Control (10 y)	Salvage Treatment	New Hypopituitarism	Maximum Dose to Optic Pathway (Gy)	Optic Neuropathy	CN Injury
Kajiwara	2005	14	13	3	35	93% (crude)	NR	NR	7%	NR	None	None
Iwai	2005	31	14	1	60	93%	NR	Surgery	7%	11 Gy	None	None
Muacevic	2004	60	17	1	22	90%	NR	GK	4%	NR	None	None
Petrovich	2002	56	15	1	36	100% (crude)	NR	None	4%	9 Gy	None	4%
Wowra	2002	30	16	1	58	93% (crude)	NR	GK	14% at 6 years	NR	None	None
Mokry	1999	31	14	1	21	98% (crude)	NR	Surgery	20%	9 Gy	None	None
Martinez	1998	14	14	1	36	100% (crude)	NR	None	0%	NR	None	7%

*Entire patient cohort.
Abbreviations: Fx, fraction; m, months; y, years; GK, GammaKnife; RT, radiotherapy; NR, not reported.

utilized for patients in the definitive setting, for residual disease after resection, and as salvage therapy in the setting of disease recurrence.[45] Several case series and institutional reports have described outcomes of patients with NFAs treated with SRS; however, there are clear limitations to the current literature. All of the studies, single or multi-institutional, are effectively retrospective case series providing low level IV evidence. Furthermore, a broad selection of patients within a case series were observed, including those with NFAs, functioning pituitary adenomas, and other base-of-skull tumors. This limited a clear identification of the key patient selection criteria and treatment outcomes relevant for this specific analysis.

Interestingly, of the 678 published reports screened for this systematic review, only 35 unique studies (5.2%) were included after review, 20 duplicate series or prior reports from the same institution were identified and excluded, and 142 articles in the medical literature provided only a summary, commentary, or other type of review without reporting new patient data, thereby creating an anomalous ratio of data versus opinion of 35:142 (~1:4). The objective of this systematic review was to provide a summary of the current data regarding the role of SRS for NFA and to provide key opinions for appropriate patient management.

Treatment Efficacy

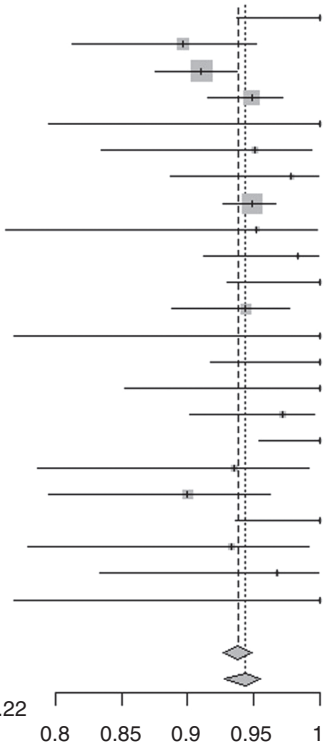
SRS was observed to be an effective treatment for patients with NFAs. The majority of patients identified in this review were treated in the adjuvant or recurrent setting. Treatment of patients definitively with SRS was often due to medical inoperability or patient refusal. It is important to note that a small proportion of patients were treated in the recurrent setting after prior conventional EBRT (0–17%), and treatment response and toxicity concerns may differ in this subset of patients. Although all studies were retrospective in nature and a minority reported actuarial outcomes, the pooled estimate of local control after 5 years following single fraction SRS was favorable at 94% (and similar to the value of non-actuarial studies). Since tumor control declines with longer follow-up, it is important to observe patients following treatment; in this meta-analysis, the pooled local control estimate at 10 years was 83%. Unfortunately, long-term tumor control was rarely reported, with only 4 studies in this meta-analysis describing 10-year clinical outcomes. It is important to note, however, that the few studies with long-term follow-up demonstrate interesting findings on recurrence patterns. For example, an Italian institutional series reported by Losa et al observed recurrences at a median of 8–9 years following treatment.[17] After examining these late recurrences, the authors surmised that there are 2 different pathophysiological mechanisms as well as prognostic significance to "in-field" and "out-of-field" late recurrences. This is especially important to identify, as practice trends are now changing to include the resection bed, and not only residual disease, in the treatment volume.[17,25]

In addition to the lack of time-dependent endpoint reporting, the lack of standardization of the definition of tumor control is clearly evident and may present a challenge to understanding late recurrence patterns of failure.

A

Study	Events	Total	Proportion	95%-CI	Weight (fixed)	Weight (random)
Graffeo, 2018	57	57	1.00	[0.94; 1.00]	0.5%	0.8%
Narayan, 2018	78	87	0.90	[0.81; 0.95]	7.8%	9.5%
Cohen-Inbar, 2017	325	357	0.91	[0.88; 0.94]	28.3%	19.0%
Losa, 2017	258	272	0.95	[0.92; 0.97]	12.9%	13.0%
Hasegawa, 2015	16	16	1.00	[0.79; 1.00]	0.5%	0.8%
Lee, 2014	39	41	0.95	[0.83; 0.99]	1.8%	2.9%
Zeiler, 2013	46	47	0.98	[0.89; 1.00]	0.9%	1.6%
Sheehan, 2013	486	512	0.95	[0.93; 0.97]	23.9%	17.7%
El-Shehaby, 2012	20	21	0.95	[0.76; 1.00]	0.9%	1.5%
Runge, 2012	60	61	0.98	[0.91; 1.00]	1.0%	1.6%
Wilson, 2012	51	51	1.00	[0.93; 1.00]	0.5%	0.8%
Park, 2011	118	125	0.94	[0.89; 0.98]	6.4%	8.3%
Castro, 2010	14	14	1.00	[0.77; 1.00]	0.5%	0.8%
Hayashi, 2010	43	43	1.00	[0.92; 1.00]	0.5%	0.8%
Hoybye, 2009	23	23	1.00	[0.85; 1.00]	0.5%	0.8%
Kobayashi, 2009	69	71	0.97	[0.90; 1.00]	1.9%	3.0%
Liscak, 2007	79	79	1.00	[0.95; 1.00]	0.5%	0.8%
Iwai, 2005	29	31	0.94	[0.79; 0.99]	1.8%	2.9%
Muacevic, 2004	54	60	0.90	[0.79; 0.99]	5.2%	7.1%
Petrovich, 2002	56	56	1.00	[0.94; 1.00]	0.5%	0.8%
Wowra, 2002	28	30	0.93	[0.78; 0.99]	1.8%	2.9%
Mokry, 1999	30	31	0.97	[0.83; 1.00]	0.8%	1.6%
Martinez, 1998	14	14	1.00	[0.77; 1.00]	0.5%	0.8%
Fixed effect model		**2099**	**0.94**	**[0.93; 0.95]**	**100.0%**	--
Random effects model			**0.94**	**[0.93; 0.96]**	--	**100.0%**

Heterogeneity: $I^2 = 18\%$, $\tau^2 = 0.0559$, $p = 0.22$



B

Study	Events	Total	Proportion	95%-CI	Weight (fixed)	Weight (random)
McTyre, 2017	10	10	1.00	[0.69; 1.00]	7.6%	7.6%
Puataweepong, 2016	27	27	1.00	[0.87; 1.00]	7.8%	7.8%
Liao, 2013	21	21	1.00	[0.84; 1.00]	7.8%	7.8%
Chen, 2013	17	17	1.00	[0.80; 1.00]	7.8%	7.8%
Iwata, 2011	98	100	0.98	[0.93; 1.00]	31.3%	31.3%
Cho, 2009	16	17	0.94	[0.71; 1.00]	15.0%	15.0%
Killory, 2008	14	14	1.00	[0.77; 1.00]	7.7%	7.7%
Kajiwara, 2005	13	14	0.93	[0.66; 1.00]	14.8%	14.8%
Fixed effect model		**220**	**0.97**	**[0.93; 0.98]**	**100.0%**	--
Random effects model			**0.97**	**[0.93; 0.98]**	--	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.97$

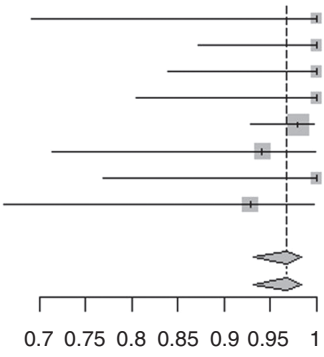


Fig. 1 Forest plot of 5-year local control following treatment of non-functioning pituitary adenomas with (A) single fraction stereotactic radiosurgery (SRS) and (B) hypofractionated stereotactic radiotherapy (HSRT). Squares indicate the proportions from individual studies and horizontal lines indicate the 95% confidence interval. The size of the data marker corresponds to the relative weight assigned in the pooled analysis using the random effects model. Diamond indicates the pooled proportion with 95% CI. Both the fixed effect and random effects models pooled estimates are presented and heterogeneity analysis is included.

Most institutions report tumor control either as a percentage of tumors which reduce in size or are stable on imaging or with a volumetric cutoff, such as 15% or 25%, for tumor response and tumor progression. For a benign tumor, stabilization is typically the goal of treatment, but given that patients do experience reduction of tumor volume, this is also an important endpoint to describe, although its clinical value could be debatable in small NFAs. Reduction in tumor volume may be important in terms of improving CN dysfunction from tumor compression or other neurologic symptomatology, for larger tumors. Losa and colleagues described different dose thresholds for

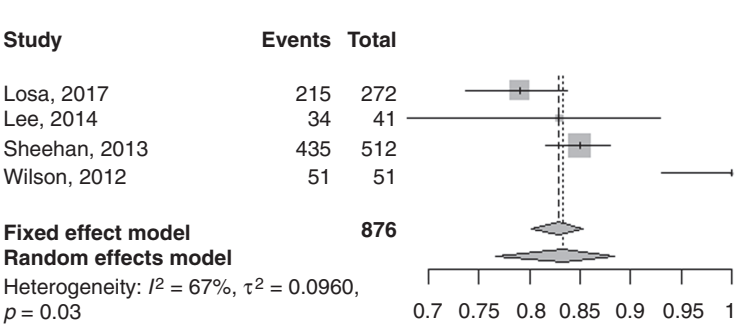


Fig. 2 Forest plot of 10-year local control following treatment of non-functioning pituitary adenomas with single fraction SRS. Squares indicate the proportions from individual studies and horizontal lines indicate the 95% CI. The size of the data marker corresponds to the relative weight assigned in the pooled analysis using the random effects model. Diamond indicates the pooled proportion with 95% CI. Both the fixed effect and random effects models pooled estimates are presented and heterogeneity analysis is included.

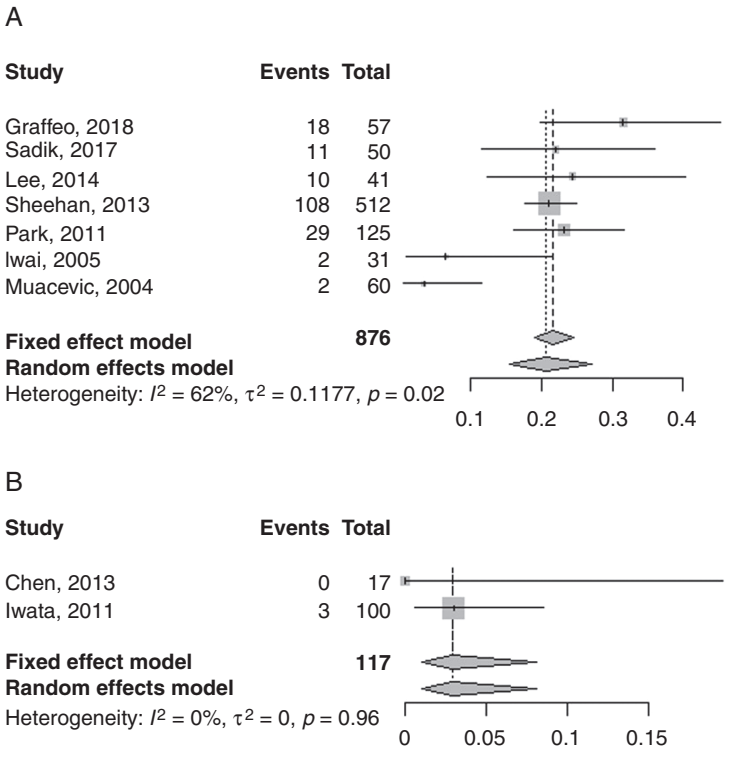


Fig. 3 Forest plot of new hypopituitarism following treatment of non-functioning pituitary adenomas with (A) single fraction SRS and (B) HSRT. Squares indicate the proportions from individual studies and horizontal lines indicate the 95% CI. The size of the data marker corresponds to the relative weight assigned in the pooled analysis using the random effects model. Diamond indicates the pooled proportion with 95% CI. Both the fixed effect and random effects models pooled estimates are presented and heterogeneity analysis is included.

tumor volume reduction (~17 Gy) versus tumor volume stabilization (~15 Gy)[46]; however, other reports demonstrated similar rates of tumor volume reduction with doses as low as 12 Gy.[25] Standardized response criteria for solid tumors such as the Response Evaluation Criteria in Solid Tumors (RECIST 1.1)[47] should be included in future studies.

Dose and Fractionation Schedules

A majority of patients reported herein were treated with a median peripheral dose of 15 Gy. Prescription doses at each institution varied considerably and are typically based on the maximum dose delivered to the optic apparatus—in

other words, the practice of "restriction-guided dosing." The largest multi-institutional study reporting this described 512 patients with NFAs, 94% of whom had undergone prior resection and 7% of whom had received prior EBRT; the median SRS peripheral dose of 16 Gy resulted in excellent tumor control rates of 95% at 5 years and 85% at 10 years.[23] However, the minimally effective dose remains controversial given the wide dose variation utilized in practice. Mingione and colleagues reported a minimal effective SRS dose of 12 Gy and suggested that doses greater than 20 Gy did not provide increased tumor control.[48] El-Shehaby and colleagues reviewed the outcomes of 21 patients (median tumor volume 4.8 cc; 44 mo follow-up) treated with 12 Gy, with tumor reduction observed in 52% and disease stabilization in another 9 patients (43%).[25] Additional long-term studies with clear objective response criteria are needed to determine a potential dose threshold to balance the rate of tumor control with toxicities such as new hypopituitarism, a risk which appears to increase significantly beyond a marginal dose of 18 Gy.[20] Dose escalation may be considered for patients at higher risk for local recurrence, such as those with larger adenomas or those with more aggressive subtypes, such as silent corticotroph staining pituitary adenomas[13,49]; however, firm data to make recommendations are lacking. Based on the available literature, we recommend a dose of 14–16 Gy for single fraction SRS.

Hypofractionated schedules identified in this analysis included 21 Gy in 3 fractions,[21] 20 Gy in 4 fractions,[15] and 25 Gy in 5 fractions,[28] with a pooled 5-year tumor control estimate of 97%. Each of these schedules yields a biologically equivalent single fraction dose of approximately 11–13 Gy (assuming an α/β ratio of 3 Gy), although in vitro studies suggest that these may translate to a higher effective single fraction dose.[50] Although the median follow-up periods for these reports are typically shorter than 5 years, the reported local control rates are high, with low rates of treatment-related toxicity. Given the heterogeneity in treatment selection, however, there was no observed difference in local control between fractionation schedules. Given the lack of association between tumor control and dose as a function of tumor volume in our meta-regression analyses, it is likely that dose and fractionation are most important for reducing the risk of toxicity, such as optic pathway dysfunction, rather than tumor control. Therefore, hypofractionated schedules can be considered for tumors that are in close proximity to the optic pathways, or in previously irradiated situations, but limited long-term data prevent this from becoming a routine fractionation schedule. Given the lack of long-term (>10 y) tumor control data, patients should be consented appropriately.

Subgroups at Increased Risk for Local Recurrence

A number of factors have been evaluated for increased risk of tumor recurrence following SRS. Given that the articles in this meta-analysis were restricted to an SRS cohort, there is an initial bias in the types of tumors treated (typically well-delineated targets in the upfront or recurrent setting), without inclusion of the resection cavity, and smaller treatment volumes. Moreover, the small sample sizes and relatively short follow-up of single institution reports prevent detailed analysis of patient, disease, and treatment-related factors associated with clinical outcome. Across the studies, the median tumor volume was 3.5 cc (effectively the volumetric rendition of an 18.8 mm diameter spheroid), and the majority of patients were treated with single fraction SRS. There have been a number of variables evaluated for increased risk of tumor recurrence, including age, sex, tumor volume, presence of suprasellar extension, cavernous sinus extension, timing of radiosurgery (intact vs postoperative and adjuvant vs salvage), and dose. When evaluating most SRS series individually, tumor size itself is not often a factor associated with treatment outcome, but that may be biased by the cases preselected for SRS as well as sample sizes (median of 31 patients per report). For example, in one of the largest studies with the longest follow-up included in this review, tumor volume was not associated with disease control.[17] However, the median tumor volume in that series was only 1.5 cc (effectively the volumetric rendition of a 14.2 mm diameter spheroid) with a maximum of 2.6 cc—well below the median in this meta-analysis. Tumor volume >5 cc (effectively the volumetric rendition of a 21.3 mm diameter spheroid) was an important factor associated with disease control reported in a study by Narayan et al of 58 NFAs (median PFS 98.4 mo > 5 cc compared with 136.5 mo < 5 cc, $P = 0.05$),[11] and a similar volume threshold of 4.5 cc (5-year PFS 86% vs 97%) by Park and colleagues.[51] A similar finding was not observed in this meta-analysis as volumes and tumor control rates were summarized by abstracting only the medians and a larger patient-level study would be needed to investigate this further.

Upfront vs Delayed Radiosurgery

The rate of tumor recurrence after subtotal resection of NFAs varies widely in the literature from approximately 20–80% by 10 years following initial resection. In this meta-analysis, only 35% of studies reported on the proportion of patients treated adjuvantly versus those treated in the salvage setting with SRS—with half of patients treated in either setting. Multiple studies in the literature support the role of immediate fractionated EBRT compared with observation and salvage therapy in patients with residual NFAs.[51,52] However, there is little consensus in the literature on the appropriate timing of SRS in patients who have undergone resection and have residual disease, because although upfront SRS might yield superior local control, it remains unclear whether close follow-up and salvage as necessary might yield similar outcomes. More recently, Pomeraniec et al reported on the clinical outcomes of 64 patients (32 treated in the early setting defined as ≤6 mo from resection, and 32 treated in the late setting defined as >6 mo from resection) treated with SRS for NFAs.[53] The authors observed a reduction in risk of radiographic and symptomatic progression in patients treated in the early group. This finding was later corroborated by a 9-center multi-institutional study of an expanded cohort of 222 patients, suggesting that earlier treatment results in more favorable outcomes than expectant management. Caveats to this management strategy include lack of clear data on

early salvage as described above (radiological progression) versus delayed salvage (symptomatic progression), as other reports stratifying patients by adjuvant treatment (within 6 mo) or delayed salvage (radiological progression) have not demonstrated benefit with early treatment.[16] Selection of patients with high risk for tumor recurrence after resection is complex as prediction models remain limited in scope at this time and further studies are clearly needed.

Toxicities Associated with Treatment

SRS was associated with low rates of permanent treatment-related toxicities. However, transient side effects do occur and it is important to counsel patients about these risks. For example, in the report by Zeiler et al, 31 of the 76 patients (34%) in their series experienced transient side effects as a result of treatment; however, approximately 75% of these toxicities were related to the stereotactic frame placement (including pin site swelling, infection, dysesthesias). Other acute toxicities included visual blurring, short-term memory loss, and ataxia.[22]

Cranial neuropathies, injury to the carotid artery or subsequent risk of CVA as a result of irradiation, and radiation necrosis were rarely encountered in this analysis. Narayan et al observed visual field deficits (n = 9, 8%), isolated CN palsies (n = 9, 8%), hydrocephalus (n = 3, 3%), and radiation necrosis (n = 2, 2%) in a series of patients treated over a 17-year period without specific dosimetric or patient-related variables associated with development of toxicity.[11] In an experience of 89 patients treated with SRS for pituitary adenomas invading the cavernous sinus, Hayashi and colleagues reported on 2 patients who developed transient abducens nerve palsy and oculomotor nerve palsy; however, the latter patients received less than the prescription dose of 24 Gy. Therefore, peritumoral edema and resulting compression of an adjacent nerve may also be a factor to consider. With the lower dosing for NFAs, cranial neuropathies are rarely reported; however, in the setting of cavernous sinus invasion or extrasellar extension, it is important to carefully delineate the adjacent cranial nerves to ensure they do not fall in a high-dose region.[31,41] Fractionated EBRT is associated with a 1.5- to 2-fold increased risk of CVA incidence and mortality, but once again whether this is technique or patient/disease specific remains unclear.[54] Fewer than 5 cases in this literature reported on CVAs after SRS,[55–57] of which 2 of the 3 series reported on patients with functioning adenomas treated to higher doses than NFAs. Currently no dose threshold exists for carotid artery stenosis, but for patients with significant baseline risk factors and comorbidities, this should be considered at the time of SRS planning.

Given the smaller treatment volumes and stereotactic techniques, the risk is likely to be lower than that of secondary tumors following EBRT for patients with pituitary tumors, which was approximately 2% at 10 years and 2.4% at 20 years, translating to a relative risk of secondary brain tumor development of 10.5 compared with the incidence in the normal population.[58] This risk is substantially lower in the SRS population,[59] and no studies evaluated in this meta-analysis reported secondary cancer events.

Visual Pathway Tolerance

Optimal consideration for single fraction SRS (vs HSRT or EBRT) is the location of the tumor in relation to the optic pathways. In patients with NFAs, a dose of 10–12 Gy to the anterior visual pathway is usually achievable and is in line with the dose tolerance reported by many institutional series (Table 2).[60] Leavitt and colleagues reported a retrospective review of 222 patients treated with single fraction SRS to benign tumors in close proximity to the visual pathways and reported a neuropathy risk of 9% with maximum doses ≤12 Gy and 10% for those >12 Gy.[61] However, it is important to note the tolerance of the visual pathways in the setting of prior radiotherapy, as cases of vision loss in the re-irradiation setting have been observed.[22] Nevertheless, cases of visual deterioration have been observed even with doses of less than 8 Gy.[29] Although the risk for visual dysfunction remains low, formal visual acuity and visual field testing should be performed at initial diagnosis, following resection, and at the time of SRS to ensure accurate assessment of pretreatment visual function.

New Onset Hypopituitarism

The most common delayed effects of radiotherapy for NFAs is the risk of new onset hypopituitarism. There are multiple factors associated with this risk, including patient age, pituitary function prior to resection, prior surgery and extent of disease resected, duration of follow-up, adenoma size and disease extension, and radiotherapy technique. This is a concern given the long natural history of patients with NFAs and the increased risk of death in those who develop secondary hypopituitarism compared with otherwise healthy patients.[62] EBRT has been associated with a 30% risk of clinical hypopituitarism at 10 years, and 50% at 20 years.[63] The pooled estimate of new hypopituitarism was 21% following single fraction SRS in this meta-analysis; however, a clear time point to compare this could not be established. Tumor volume has been associated with hypopituitarism in some studies,[29,64,65] whereas others have not observed this relationship,[65] as was the finding in this study.

There are multiple factors associated with post-SRS hypopituitarism, including visualization of the normal pituitary gland at the time of SRS target volume delineation, tumor extension outside of the cavernous sinus and sella, marginal prescription dose, and dose to the pituitary gland or infundibulum. Marek and colleagues reported the effect of marginal dose, with a 2% risk of hypopituitarism in 45 patients treated to a mean pituitary dose <15 Gy compared with 73% in those with a dose >15 Gy.[66] In this series, the dose to the distal infundibulum was also associated with hypopituitarism with a maximum recommended dose of 17 Gy. Graffeo et al specifically evaluated dosimetric factors on 97 patients (57 of whom were diagnosed with NFAs) treated with single fraction SRS, and of the 27 patients (28%) in their series who developed posttreatment endocrine deficits, multivariable analysis found that male sex (hazard ratio [HR]: 2.38, P = 0.04), a smaller pituitary gland volume (HR: 0.99, P = 0.01), and increased mean gland dose (HR: 1.31, P < 0.001) were associated with

Table 3 Key opinions for treatment and management of non-functioning pituitary adenomas

Recommendations for Treatment and Management of Non-Functioning Pituitary Adenomas (NFAs)
Patient Selection
1. Patients with NFAs who are medically inoperable or refuse resection can be considered for SRS as the primary definitive treatment.
2. After resection, patients with residual disease should be presented in a multidisciplinary setting where the risks and benefits of immediate adjuvant SRS, or observation with salvage SRS, should be reviewed in light of patient characteristics, disease extent, pathology for high-risk features, and imaging findings.
3. Prior to SRS, patients should undergo comprehensive neurological, neuro-ophthalmologic, and neuroendocrine evaluations.
4. For patients who have received prior external beam radiotherapy, a thorough review of the prior treatment records and doses received to nearby critical structures at risk should be evaluated by the treatment team.
Treatment
1. A high-resolution volumetric treatment planning MRI, with at least a T1 post-gadolinium and axial T2 sequence, should be performed at the time of SRS to ensure accurate target volume delineation.
2. Key at-risk structures important for consideration at the time of treatment include the hypothalamus, infundibulum, residual pituitary, optic pathway, and brainstem.
3. Single fraction SRS is preferred to HSRT if constraints to nearby structures at risk can be met given the long-term control and toxicity data.
a. A prescription dose of 14–16 Gy is recommended for patients treated in the definitive setting.
b. A prescription dose of 14–16 Gy is recommended for patients with residual or recurrent disease.
c. HSRT (21 Gy in 3 fractions, 20 Gy in 4 fractions, or 25 Gy in 5 fractions) can be considered for patients with larger adenomas (>2–3 cm) or close to the optic apparatus; however, the lack of long-term (>10 year) tumor control data is acknowledged and patients must be consented appropriately in this context.
Treatment Outcomes
1. Patients treated with SRS should undergo routine clinical follow-up, including neuro-ophthalmology and neuroendocrine visits, and imaging surveillance for at least 5 years. A schedule of every 6 months for the first year, annually for up to 5 years, and every 2 years thereafter is reasonable. Earlier follow-up can be considered based upon clinical events.
a. Tumor dimensions or volumetric assessments should be performed at each follow-up imaging time point using standardized response criteria.
b. Recurrent disease following SRS should be categorized as "in-field" or "out-of-field" recurrences and subsequent salvage treatments should be comprehensively recorded in the shared medical record.
2. Treatment-related toxicities should be recorded and graded using standardized reporting criteria.
a. The development of new or worsening hypopituitarism should be defined as "biochemical" or "clinically significant."

posttreatment hypopituitarism.[10] Given the various factors described in the literature, it is likely that the mean dose most closely approximates the dose received by most of the organ and, therefore, correlates best with long-term risk of hypopituitarism. On the other hand, the maximum dose to the infundibulum, either because of its function as a serial structure connecting hormonal secretion pathways between the hypothalamus and the pituitary or because of its small size, may be the most important variable to monitor.[67] Suprasellar extension, which has been observed in some series to correlate with posttreatment hypopituitarism,[68] likely leads to higher doses to the infundibulum and hypothalamus, and these structures should be delineated and monitored at the time of SRS planning. Baseline hormone levels should be obtained prior to surgery and prior to radiotherapy for comparison to post-SRS values.

One of the key limitations of the present review is that it comprises primarily retrospective cohort studies spanning long time intervals with limited long-term follow-up beyond 10 years. As patients were not treated on prospective observational study protocols, length of follow-up and posttreatment imaging and neuroendocrine evaluation was performed at varying intervals across studies. This limits evaluation of key variables, especially with lack of time-dependent analyses. Also, every effort was made to prevent overlap of data across studies, and if multi-institutional patient level data were available, these were given preference over individual studies as they would incorporate data from centers which did not always publish individual outcomes. However, given the multi-institutional nature of the data collection and analysis, fewer variables were reported on. Also, different multi-institutional reports had overlapping time periods of data collection and therefore were included in order to evaluate the maximum number of patients, with partial but unknown quantity of overlap with subsequent studies.

Given the key interest of the neuro-oncology community in the management of patients with NFAs, as highlighted by the vast number of commentaries, summaries, and reviews of the literature, it was felt timely and necessary to perform a meta-analysis and high-level overview of the role of SRS in the management of these tumors. Despite the aforementioned limitations of this study, key differences are important to highlight from prior works. First, approximately 25% of the reports included in this meta-analysis (9/35 manuscripts) were newly published since the last guidelines.[69] Second, this report focused on SRS, instead of all types of radiation therapy, and provided a

more detailed analysis of key variables regarding SRS-specific practice, study details, procedure details (dose/fractionation), and outcome variables. For example, in this report, we specifically reviewed each study in great detail to describe key variables not addressed in prior reports, such as the proportions of patients treated in the definitive versus adjuvant versus salvage setting, incidence of prior radiotherapy, description of individual technique details (dose/fractionation), tumor volume ranges, etc, which are important to consider in evaluating patients for SRS and are different for patients receiving conventionally fractionated radiotherapy. Third, the current study provides pooled estimates for both local control and hypopituitarism and, new to published literature, separated these outcomes by type of SRS, a specific and unique focus. Finally, this study analyzed SRS-specific toxicities and described them in detail throughout the report. Together, these key features of this study make this report the most recent study on the role of SRS for patients with NFAs with the most updated data on published outcomes.

Conclusion

From this meta-analysis and detailed review of the literature for NFAs, the ISRS provides key management and key treatment opinions for patients with NFAs (Table 3). To recapitulate, SRS is an effective treatment with 10-year outcome results for patients treated to doses of 14–16 Gy and promising 5-year results for radiobiologically equivalent HSRT schedules, with the long-term risks of new hypopituitarism and rare risk of CN or vascular injury and extremely low risk for radiation-induced malignancy.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

KeyWords

consensus | ISRS | non-functioning | pituitary adenomas | radiation therapy | radiosurgery

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Authorship statement. Conception and design: RK, AS, JS, SY, JS. Analysis: RK, MR, JS, SY. Critical review of manuscript: RK, AS, MR, ADS, LF, BP, ML, LM, IP, JR, JS, SY, JS.
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