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LINAC-radiosurgery for nonsecreting pituitary adenomas

Long-term results

Nonsecreting pituitary adenomas (NSA) become symptomatic by compression of surrounding structures causing visual or endocrinological dysfunction. Especially in cases of invasion of the cavernous sinus, complete microsurgical tumor removal might be associated with elevated surgery-related morbidity and, as a consequence, in many cases parasellar tumor remains [34]. For the management of residual tumor, therapeutic options consist of observation, external beam irradiation, fractionated stereotactic radiotherapy, and radiosurgery [1, 2, 3, 4, 5, 6, 8, 11, 14, 15, 18, 19, 21, 22, 23, 24, 25, 30, 31, 32, 33, 36, 37, 38, 39, 46, 47, 48, 51, 52]. The aim of this retrospective study was to investigate the value of linear accelerator-based radiosurgery (LINAC-RS) for the treatment of NSA, with regard to its long-term tumor control and safety.

Patients and methods

Patient selection and follow-up

Between 1992 and August 2008, 65 patients suffering from progressive NSA were treated with LINAC-RS. Patient treatment and follow-up were conducted according to a prospective protocol [48, 50]. Patients were included suffered from NSA, tumor recurrence, or progressive residual tumor, definable tumor, maximum dimension of 35 mm and a minimal distance of 1–2 mm to the anterior optic system.

Patients were followed with regard to their ophthalmological, endocrinological, and radiological (CT/MRI) course. The first complete follow-up examination was performed 6 months after LINAC-RS. Afterwards radiological follow-up was performed at 12-month intervals, whereas ophthalmological and endocrinological follow-up examinations were performed every 6 months.

Criteria for treatment-related ophthalmological side effects were impairment of vision or visual field. Every intake of new hormonal medication related to one of these axes as well as pathological hormone deficits were interpreted as radiation-induced hypothalamopituitary dysfunction.

Tumor size was determined by measuring the maximum tumor diameter in at least two dimensions. According to the greatest tumor dimension, we defined a "response" as a reduction of ≥ 25%, "progression" as an increase ≥ 25% compared to baseline diameter, and "stable disease" for all other cases. Complete response was documented if MRI studies no longer displayed a signal specific for tumor [1, 28].

For the assessment of radiation-induced hypothalamopituitary dysfunction, the calculation of radiation doses was performed using dose–volume histograms in cases with a definable pituitary gland and stalk and at least partial function of the anterior pituitary lobe before LINAC-RS. Peak doses in the tumor and the median dose were evaluated.

LINAC-RS

The detailed components of our treatment system are described elsewhere [26, 27, 41, 48, 50]. Before 1996, the tumor contour was outlined on stereotactic CT images. Since 1996, all patients received MRI 1–3 days prior to LINAC-RS, which was integrated into intraoperative stereotactic CT [13, 42]. Treatment planning was performed using specialized software (STP 3.3 and 3.5, Howmedica Leibinger, Freiburg, Germany).

On the day of treatment, the patient's head was fixated in a modified Riechert–Mundinger stereotactic frame [40]. To obtain contrast enhancement of the tumor and to visualize blood vessels for landmark correlation, 100 ml and 40–80 ml of contrast medium were applied approximately 30 min prior to and directly before CT scanning, respectively.

The dose applied to the anterior visual pathways was limited to 9 Gy and the volume of healthy brain tissue exposed to a minimum dose of 10 Gy has been restrict-

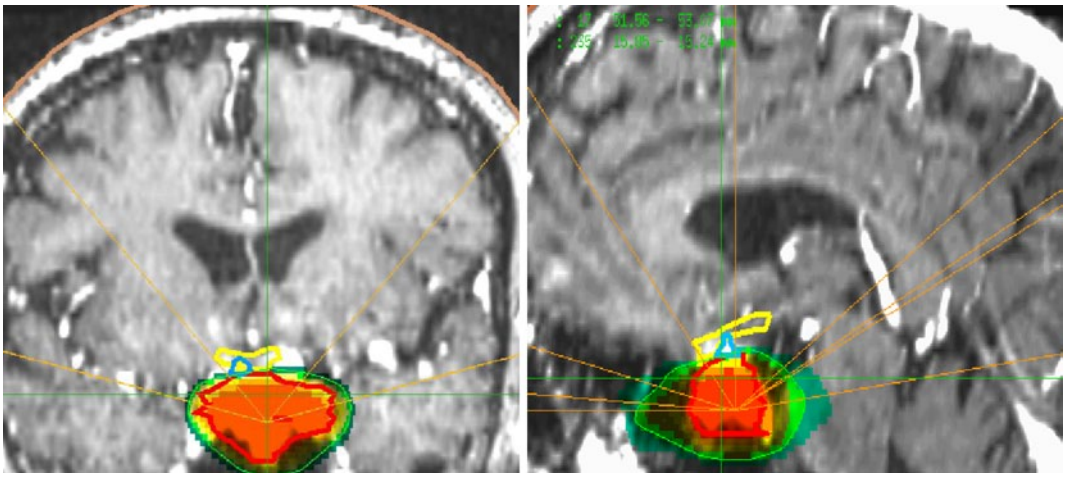

Fig. 1 ◀ Dose distribution for LINAC-RS using MMLC technique. *Yellow* chiasm and optic nerve, *blue* pituitary gland and stalk, *red* tumor, *greenline* 50% isodose consistent with 8 Gy in this case

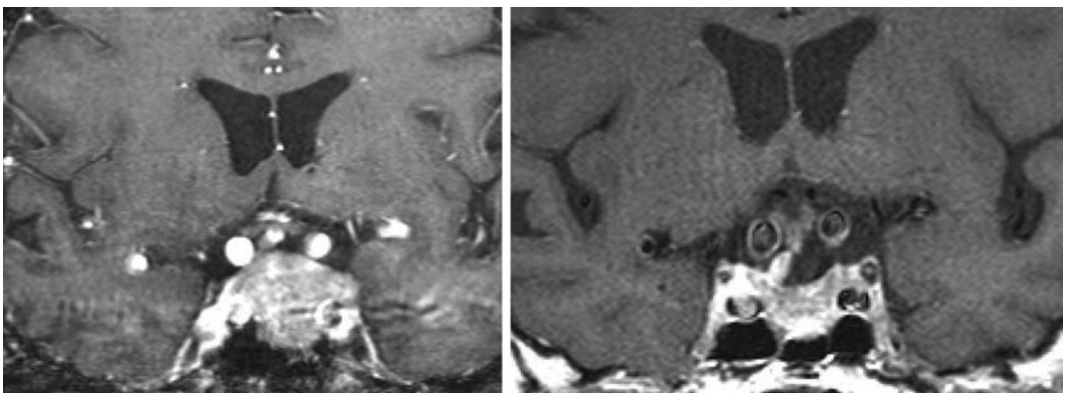

Fig. 2 ◀ Coronary T1-weighted MRI with contrast enhancement prior to (*left*) and 54 months after (*right*) LINAC-RS (radiation dose at tumor surface 12 Gy, maximum dose 16 Gy)

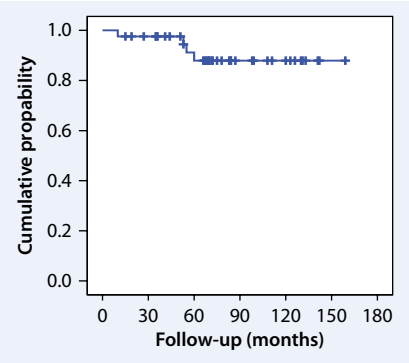

Fig. 3 ▲ Cumulative risk for radiation-induced damage of pituitary function according to Kaplan–Meier method. Ticks represent censored patients (n = 41, 90.2% censored, 4 events, cumulative probability 0.02 after 36 months, 0.12 after 142 months)

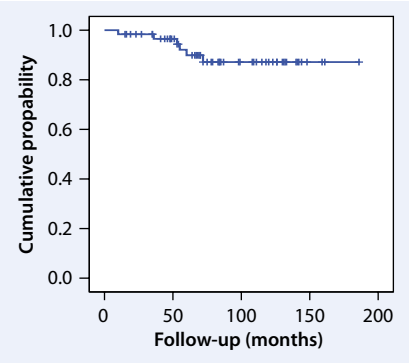

Fig. 4 ▲ Event-free survival after LINAC-RS for NSA. Cumulative risk for unfavorable events calculated with the Kaplan–Meier method. Ticks represent censored patients (n = 61, 90.2% censored, 6 events, cumulative probability 0.04 after 36 months and 0.13 after 161 months)

ed to 10 ml according to an in-house risk analysis introduced in 1996 [49].

In 45 of 61 (73.7%) patients, dose application was performed with circular collimators fitted to an adapted linear accelerator (Philips SL 75/20 at 9 MV or Elekta Sli25 at 6 MV) using STP 3.5 (until February 1996 STP2, Leibinger, Freiburg, Germany) [45]. An arching beam technique was used with 10 table positions. For individual treatment planning, this standard technique can be modified in terms of diameter, table position, number of table angles, ranges of gantry rotation, beam weight, irradiation dose, and number of isocenters [44].

In 16 of 61 (26.2%) patients, a micro-multileaf collimator (MMLC) with 1.5 mm leaf width (Siemens, Heidelberg, Germany) was used. Because the MMLC technique is able to treat complex-shaped tumors, this technique has been used predominantly since in 2001. A focal irradiation technique with 14–20 static fields was applied. Each beam was shaped according to the beam's eye view of the tumor and structures at risk. Treatment planning was performed using Virtuoso 3.0.3 software (Howmedica Leibinger, Freiburg, Germany). A representative treatment plan is illustrated in ◘ **Fig. 1**.

Statistical analysis

For statistical analysis SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA) was used. Actuarial local tumor control rate, rate of neurological deficits and new deficits in hypothalamopituitary function as well as actuarial survival were determined using the Kaplan–Meier method [20].

The log-rank test was performed to compare patient groups comprising censored patients in order to determine prognostic factors for endocrinological func-

tion. For evaluation of the course of endocrinological function, patients with complete insufficiency of the anterior lobe and with diabetes insipidus were excluded. Patients were compared concerning pre-existing conditions (age, sex, microsurgical operations, tumor volume, tumor location, hypothalamopituitary deficits) and treatment-associated factors (dose, radiation application technique, dose to pituitary gland and stalk). A p value ≤ 0.05 was considered statistically significant.

Results

Four patients were lost to follow-up. Sixty-one individuals with a minimum follow-up of 12 months were included in this retrospective analysis. For details of patients' characteristics see **Tab. 1**.

The median therapeutic dose applied to the tumor margin was 13.0 Gy, minimum 10 Gy, and maximum 20 Gy. The dosage characteristics referring to the two collimation techniques used are displayed in **Tab. 2**.

Follow-up

Mean follow-up after LINAC-RS was 90 months (median 83, range 15–186 months); 36 months after LINAC-RS 1 patient (female, 60 years) died of reasons unrelated to pituitary disease and treatment. None of the patients developed radiation induced tumors during the follow-up period.

Tumor

At the end of follow-up, 60 patients (98.3%) showed local tumor control on MRI, including 24 patients (40.0%) with partial tumor remission (**Fig. 2**). Tumor progression was observed in 1 male patient treated on the basis of CT in 1995 suffering from an invasively growing adenoma with intra-, para-, supra-, and retrosellar extension. After LINAC-RS, none of the patients experienced tumor bleeding, necrosis, ischemia or pituitary apoplexy.

Hypothalamopituitary function

Four (9.8%) of 41 patients at risk experienced new endocrinological deficits

Zusammenfassung · Abstract

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LINAC-radiosurgery for nonsecreting pituitary adenomas. Long-term results

Abstract

Background and purpose. Stereotactic linear accelerator-based radiosurgery (LINAC-RS) is increasingly used for microsurgically inaccessible or recurrent pituitary adenomas. This single-center study evaluates the long-term follow-up after LINAC-RS of nonsecreting pituitary adenomas (NSA).

Patients and methods . Between 1992 and August 2008, 65 patients with NSA were treated. Patient treatment and follow-up were conducted according to a prospective protocol. Indications for LINAC-RS were (1) tumor recurrence or (2) residual tumor. Three patients were treated primarily. For analysis of prognostic factors, patients were grouped according to epidemiological or treatment-associated characteristics.

Results. A total of 61 patients with a follow-up ≥ 12 months (median 83 months, range 15–186 months, longest follow-up of published radiosurgery series) were evaluated with regard to their clinical, radiological, and endocrinological course. The median tumor volume was 3.5 ml (± 4.3 ml, range 0.3–17.3 ml) treated with a median surface and maximum dose of 13.0 Gy and 29.7 Gy, respectively. Local tumor control was achieved in 98%. One patient died of unrelated cause after 36 months and 1 patient developed a radiation-induced seizure disorder. Visual complications did not occur. In 37 of 41 patients (90.2%), pituitary function remained stable. Maximum dose to the pituitary ≤ 16 Gy and female gender were positive prognostic factors for the preservation of pituitary function.

Conclusion. LINAC-RS is a minimally invasive, safe, and effective treatment for recurrent NSA or microsurgically inaccessible residual tumor. LINAC-RS yielded a high rate of local long-term tumor control with a small number of radiation-induced side effects.

Keywords

Radiosurgery LINAC · Nonsecreting pituitary adenoma · Pituitary function tests · Treatment outcome · Prognosis

LINAC-Radiochirurgie zur Behandlung nicht hormonaktiver Hypophysenadenome. Langzeit-Ergebnisse

Zusammenfassung

Hintergrund und Ziel. Die stereotaktische, Linearbeschleuniger-gestützte Radiochirurgie (LINAC-RS) wird zunehmend zur Behandlung mikrochirurgisch nicht zugänglicher oder rezidivierter Hypophysenadenome angewandt. Die vorliegende Studie evaluiert den Langzeitverlauf nach LINAC-RS von hormoninaktiven Hypophysenadenomen (NSA).

Patienten und Methoden. Zwischen 1992 und August 2008 wurden 65 Patienten mit NSA behandelt. Die Therapie und die Nachsorge wurden entsprechend einem prospektiven Protokoll durchgeführt. Indikationen für LINAC-RS waren (1) Tumorrezidiv oder (2) postoperativer Tumorrest. Drei Patienten wurden primär radiochirurgisch behandelt. Zur Ermittlung prognostischer Faktoren wurden die Patienten entsprechend epidemiologischer und behandlungsabhängiger Eigenschaften gruppiert.

Ergebnisse. 61 Patienten mit einem Follow-up ≥ 12 Monaten (Median 83 Monate, 15–185 Monate; längster Nachbeobachtungszeitraum publizierter Radiochirurgie-Serien) wurden im Hinblick auf den klinischen, den radiologischen und den endokrinologischen Verlauf ausgewertet. Das mediane Tumorvolumen betrug 3,5 ml (± 4,3 ml; 0,3–17,3 ml), welches mit einer medianen Oberflächen-/Maximaldosis von 13,0 Gy/29,7 Gy behandelt wurde (**Tab. 2**). Bei 98% gelang die lokale Tumorkontrolle (**Fig. 2**). Eine Patientin verstarb nach 36 Monaten aus einem nicht-assoziierten Grund; ein Patient entwickelte ein strahleninduziertes Anfallsleiden. Therapieassoziierte Sehstörungen traten nicht auf. Bei 37 von 41 Patienten (90,2%) blieb die hypophysäre Funktion unbeeinträchtigt (**Fig. 3**). Eine Strahlenbelastung der Hypophyse ≤ 16 Gy und weibliches Geschlecht waren positive prognostische Faktoren für den Erhalt der hypophysären Funktionen (**Tab. 3**).

Schlussfolgerung. LINAC-RS stellt eine minimal-invasive, sichere und effektive Behandlung für rezidivierte NSA oder mikrochirurgisch nicht zugängliche Tumorreste dar. LINAC-RS erzielte eine hohe Rate lokaler Tumorkontrolle bei einer geringen Zahl radiogener Nebenwirkungen.

Schlüsselwörter

LINAC-Radiochirurgie · Nicht hormonaktives Hypophysenadenom · Behandlungserfolg · Hypophysenfunktionstest · Prognose

Tab. 1 Patients' characteristics and treatments before LINAC-RS

Patient characteristics	
Patients	61
Male/female (%)	36/25 (59%/41%)
Age Median (range)	56 years (18–75)
Microsurgical operations Yes/no 1 2 3 3 + 30 Gy EBRT 4	Number of patients 59/2 19 24 13 1 2
Pituitary function Normal (%) Partial insufficiency (%)	 15 (25%) 26 (43%)
Tumor volume Median, range Mean, SD	 3.5 ml, 0.3–17.3 ml 5.3 ml, ± 4.3ml
Tumor location Suprasellar (%) Retrosellar (%) Parasellar (%)	 21 (34%) 15 (25%) 48 (79%)
Indication Progressive tumor Tumor remnant Primary LINAC-RS	 36 (59%) 23 (38%) 2 (3%)

EBRT conventional external beam radiation therapy, **SD** standard deviation.

Tab. 2 Dosage characteristics for therapeutic dose (***TD***) and maximum dose (***MD***) of the tumor

Radiation dose characteristics		
	Median (range)	Mean (± SD)
TD		
Overall	13.0 Gy (10–20 Gy)	13.1 Gy (± 1.9 Gy)
Circular collimators	13.0 Gy (10–20 Gy)	13.2 Gy (± 2.1 Gy)
MMLC	12.5 Gy (11–16 Gy)	12.9 Gy (± 1.6 Gy)
MD		
Overall	29.7 Gy(15–57 Gy)	28.8 Gy (± 10.2 Gy)
Circular collimators	**33.4 Gy (15–57 Gy)** [a]	**32.6 Gy (± 9.0 Gy)** [a]
MMLC	**17.1 Gy (15–27 Gy)** [a]	**18.1 Gy (± 3.1 Gy)** [a]

[a] The numbers indicate the striking difference of the applied maximum doses that were necessary to obtain comparable therapeutic doses. **MMLC** micro-multileaf collimator.

Tab. 3 Prognostic factors for endocrinological function for NSA after LINAC-RS

Prognostic factors for hypothalamopituitary function	
	p
Age	n. s.
Sex (see text)	**0.043***
Number of operations (≤ 1 vs. > 1 op; ≤ 2 vs. > 2 ops)	n. s.
Microsurgical approach (frontal vs. transsphenoidal)	n. s.
Insufficiency prior to RS or not	n. s., p = 0.107
Intrasellar tumor	n. s.
Extrasellar tumor	n. s., p = 0.064
Parasellar tumor	n. s.
Suprasellar tumor	n. s.
Retrosellar tumor	n. s.
RS technique (circular collimators vs. MMLC)	n. s.
Tumor volume ≤ 3.5 ml/5 ml vs. > 3.5 ml/5ml	n. s.
Therapeutic dose ≤ vs. > 13 Gy/14 Gy/15 Gy	n. s.
Maximum dose ≤ vs. > 17 Gy/20 Gy/25 Gy/30 Gy	n. s.
Maximum dose to pituitary gland (≤ 16 vs. > 16 Gy)	**0.035***
Maximum dose to pituitary stalk	n. s.
Median dose pituitary gland/stalk	n. s.

* value considered significantop operation, **RS** radiosurgery, **MMLC** micro-multileaf collimator.

after a mean of 44.5 months (median 54 months, range 10–60 months). The cumulative risk for radiation-induced hypothalamopituitary dysfunction was 12.1% after 60 and 120 months (**Fig. 3**).

Except for female gender (p = 0.043) and maximum dose to the pituitary gland less than 16 Gy (p = 0.035), there were no favorable prognostic factors for preservation of endocrinological function. Extrasellar tumor extension showed a tendency towards a positive prognostic factor (p = 0.064) for preservation of endocrinological function as well as no patient without pituitary deficiency prior to LINAC-RS suffered radiation-induced hormonal deficit (p = 0.107; **Tab. 3**).

Neurology

Cranial nerves

None of the patients developed a new deficit of visual field or vision after application of a maximum of punctually 9 Gy to the anterior optic system.

Seizures

In one early case (1.7%) of those patients included in this study in 1995, a seizure disorder occurred 11 months after treatment. The therapeutic isodose was 18 Gy with a maximum dose of 57 Gy (maximum peak dose in study) leading to radiation-induced temporary contrast enhancement with edema in the right temporal lobe. Under anticonvulsant medication, seizures ceased and further follow-up revealed resolution of the radiation-induced changes. Since the limitation of the volume of peritumoral brain tissue exposed to 10 Gy to 10 ml, no seizure disorder has occurred [49].

Overall outcome

After a mean follow-up time of 90 months (median 83 months, range 15–186 months) treatment success with local tumor control and absent radiation-induced side effects could be demonstrated in 90.2% of cases. Six patients (9.8%) suffered aversive events (4 hypothalamopituitary dysfunction, 1 tumor progression, 1 seizure disorder). The Kaplan–Meier method revealed a cumulative probability for absence of aversive events of 87% after 141 months (**Fig. 4**).

Tab. 4 Results of GKRS, LINAC-RS, CRS, stereotactically guided fractionated radiotherapy, and conventional radiotherapy in series with follow-up of at least 48 months and comparable studies

	Dose application	Number	Mean FU (months)	TD (Gy)	Tumor control (%)	Side effects	
						N. II	Pituitary
LINAC-RS, GKRS							
Yoon 1998 [52]	LINAC-RS	8	49	17	96	n.s.	?
Feigl 2002 [15]	GKRS	61	55	15	94	n.s.	?
Wowra 2002 [51]	GKRS	45	55	16	93	None	14%
Iwai 2005 [18]	GKRS	31	60	14	93	None	6%
Liscak 2007 [25]	GKRS	79	60	20	100	None	2%
Pollock 2008 [38]	GKRS	62	Median 64	Median 16	97	None	32%
Park 2011 [36]	GKRS	125	Median 103, n=41 36, n=84	Median 15 13	90	3%	17%
Present series	LINAC-RS	61	90	13	98	None	10%
CRS							
Kajiwara 2010 [19]	CRS	14	32	13	93	None	n.s.
Cho 2009 [7]	CRS	17	30	19[d]	88	None	None
Killory 2009 [22]	CRS	14	29	5×5 Gy	100	None	None
Fractionated stereotactically guided radiotherapy							
Milker-Z 2001 [30]	LINAC	42	39[c]	52.2/1.8	98	n.s.	
Colin 2005 [8]	LINAC	110	Median 82[a]	50.4/1.8	99	None[b]	37%
Conventional radiotherapy							
Becker 2002 [3]	LINAC	825	n. s.	n. s.	89	n.s.	13–56%

FU follow-up time, **N II** radiation-induced optic neuropathy, **pituitary** radiation-induced endocrinological deficit, **n.s.** not specified, **TD** therapeutic dose, **LINAC-RS** linear accelerator-based radiosurgery, **GKRS** gamma knife radiosurgery, **CRS** CyberKnife radiosurgery [a]75 patients with persistent macroscopic tumor after microsurgical operation. [b]2 patients developed disturbances in visual acuity. After evaluation of radiation doses they were finally diagnosed not to suffer radiation-induced toxicity. [c]All types of pituitary adenomas. [d]2 patients received a single dose, 15 patients 3 fractions, 5 after 5 years.

Discussion

In the present study with the longest overall follow-up of a radiosurgery series, local tumor control was achieved in 98% of patients comparable to other radiosurgery series using relatively low therapeutic and maximum doses (**Tab. 4**). The only patient experiencing tumor progression after LINAC-RS had been treated in the pre-MRI era with a reduced dose (therapeutic dose 10 Gy) due to a large atypical adenoma [36, 38]. With today's microsurgical options and imaging, a comparable patient would surely not be treated radiosurgically.

Remarkably, in this series there was no correlation between tumor size and local control, which is in contrast to the findings of other centers [36, 38]. This is not easy to comprehend as those centers used higher therapeutic doses. We presume that there are additional factors affecting biological impact that currently cannot be quantified. In addition, every patient receiving a therapeutic dose of 12 Gy exhibited local tumor control in our series.

It is worth mentioning that all NSA treated with the MMLC technique using low therapeutic and maximum doses (**Fig. 2**) showed local tumor control at the end of follow-up. The MMLC technique provides conformal dose distribution and seems to be a useful tool in lesions with an irregular configuration like NSA. The use of the MMLC since 2001 is an additional step towards lower peak doses and more conformal and homogenous irradiation, which is desirable in benign lesions like pituitary adenomas.

In one series, 11 out of 41 patients (27%) developed new endocrinological deficits [38]. The actuarial risk after 5 years was 32% compared to 12% in this study. At least partially, this may be a consequence of the higher applied therapeutic and maximum doses of 16.3 Gy and 34.0 Gy (compared to 13.1 Gy and 28.8 Gy). On the other hand, another evaluation [25] kept the rate of new endocrinological deficits as low as 2% after applying a relatively high therapeutic mean dose of 20 Gy. The reasons for such inconsistent results will hopefully be identified on the basis of future evaluations.

A maximum of 16 Gy applied to the pituitary gland was a significant prognostic factor for preservation of endocrinological function in this series. This is reasonably consistent with the results of three GKRS series [15, 23, 47]. Vladyka et al. [47] found a mean dose of more than 17 Gy and 20 Gy to be a risk factor for impairment of the gonadotrophic and corticotrophic/thyrotrophic function, respectively. Because the critical doses are approximately in the same range, they strongly support efforts for dose reduction in recognizable pituitary tissue [23].

In this study, extrasellar tumor location had a tendency to be a favorable prognostic factor for preservation of pituitary function (**Tab. 3**). None of the patients with extrasellar tumor developed a new endocrinological deficit. Generally, one would expect that tumors with no intrasellar portion could be treated radiosurgically with a lower risk for endocrinological function because of radiation sparing and easier recognition of the pituitary gland and stalk, which the present evaluation could not confirm. Data remains inconclusive in this regard at the moment.

Generally, after macroscopic complete tumor removal additional treatment is required in up to 6% of NSA patients and in even 20–26% after incomplete removal with or without conventional radiotherapy [12, 16, 29]. In the light of several radiation-based treatment options and individual tumor location and size, tailored adjuvant treatment strategies are necessary.

In a prospective study [8], fractionated stereotactic radiation therapy led to hypopituitarism in 28.5% of 110 patients after 4 years. Another series [30] revealed impairment of visual acuity in 4 out of 60 patients (6.7%) and hypopituitarism in 3 of 63 patients (4.6%). After 5 years, tumor control was achieved in 93% [30]. Although the results for NSA are not reported separately, LINAC-RS seems to yield more desirable results especially concerning the visual system. Treatment results after radiosurgery, CyberKnife radiosurgery, stereotactically guided radiotherapy, and conventional fractionated radiotherapy of NSA are presented in **Tab. 4**. The first reports of CyberKnife treatment of pituitary adenomas are available [7, 19, 22]. Despite the few cases with short follow-up, it can be recognized that optimal radiation dose and application mode have to be elaborated.

Because of the higher rate of local tumor control and lower rate of hypopituitarism compared to conventional radiotherapy, LINAC-RS should be preferred in selectable tumors, although it has to be kept in mind that for the review of results of conventional radiation therapy, data of the last few decades were included [3] with many cases suffering tumors not selectable for radiosurgery. Radiation-induced hypopituitarism occurred in of 13–56% after conventional radiotherapy [3].

Conclusion

Our series regarding radiosurgical treatment for NSA is the one with the longest overall follow-up studies presented so far. We could demonstrate that LINAC-RS is a minimally invasive, safe, and effective treatment option for recurrent NSA or microsurgically inaccessible residual tumor. The present study shows that extrasellar growth, which in case of parasellar tumor is a serious problem for operation planning, is even a favorable growth pattern for safe LINAC-RS and preservation of pituitary function.
In cases where 12 Gy can be applied to the tumor surface with maximally punctual application of 9 Gy to the optic system and a dose to the pituitary gland not exceeding 16 Gy LINAC-RS is superior to external beam irradiation and fractionated stereotactic radiation therapy and therefore should be preferred.
The main focuses for the future should certainly be avoidance of visual complications and further reduction of hypopituitarism.

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Conflict of interest. The corresponding author states that there are no conflicts of interest.

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