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Original Article

Evaluation of endocrinological sequelae following particle therapy performed on anterior skull base lesions in the adult population

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ABSTRACT

Background: Radiotherapy has increasingly assumed a central role in the multidisciplinary treatment of skull base lesions. Unfortunately, it is often burdened by relevant radio-induced damage to the pituitary function and the surrounding structures and systems. Patients who were treated with radiotherapy around the sellar region especially have a high risk of developing radio-induced hypopituitarism. Particle therapy has the potential advantage of delivering a higher radiation dose to the target while potentially sparing the sellar region and pituitary function. The aim of this study is to evaluate the pituitary function in adult patients who have undergone hadron therapy for anterior skull base lesions involving or surrounding the pituitary gland.

Methods: This is a retrospective, observational, and noncontrolled study. We evaluated pituitary and peripheral hormone levels in all patients referring to National Center for Oncological Hadrontherapy, Pavia, Italy for anterior skull base tumors. Furthermore, we performed a magnetic resonance imaging for every follow-up to evaluate potential tumoral growth.

Results: We evaluated 32 patients with different tumoral lesions with a mean follow-up of 27.9 months. The mean hadron therapy (HT) dose was 60 ± 14 Gray, with a mean dose per fraction of 2.3 ± 2.1 Gray. Six patients were treated with carbon ions and 26 with protons. Pituitary hormone alteration of some kind was reported for six patients. No patient experienced unexpected severe adverse events related to particle therapy.

Conclusion: Particle radiotherapy performed on anterior skull base lesions has proved to cause limited damage to pituitary function in the adult population.

Keywords: Hadron therapy, Hormones, Particle therapy, Pituitary, Skull base

INTRODUCTION

Radiotherapy has increasingly assumed a central role in the multidisciplinary treatment of skull base lesions. However, when targeting anterior skull base lesions, it could cause relevant radio-

induced damage to the pituitary function and the surrounding structures.[5,6,9,12,17,22,26] The prevalence of any degree of hypopituitarism has shown to be between 37% and 77%.[3]

Particle radiotherapy (PT), on the other hand, has the potential advantage of delivering a higher radiation dose to the target while minimizing the damage toward the sellar region.[24,25]

Studies have also been carried out to identify a dosage tolerance threshold, beyond which more serious endocrinological complications arise – mostly in terms of pituitary function deficits.[13,18]

Patients referred for PT for anterior skull base lesions represent an ideal population to evaluate endocrinological toxicity on radio-induced pituitary dysfunction.

For this reason, the aim of this study is to evaluate the pituitary function in adult patients who have undergone PT for anterior skull base lesions involving or surrounding the pituitary gland.

The management of sellar lesions requires a multidisciplinary approach.[2,16,21,27] The institutional pituitary team of Fondazione IRCCS San Matteo in Pavia consists of neurosurgeons, otolaryngologists, and endocrinologists among others, who collaborate with radiation oncologists of National Center for Oncological Adrotherapy – the first structure in Italy to provide PT.[15] In a previous publication, we reported the preliminary results of a study conducted in a smaller cohort of patients with a shorter follow-up.[26] With the present study, more patients have been added to the cohort, while the previous patients continued with their follow-up visits.

MATERIALS AND METHODS

For this study, we enrolled 32 adult patients with different tumors involving the skull base and sellar region. The average follow-up time was 27.9 months.

Among these patients, 22 had already undergone neurosurgery, two had undergone conventional radiotherapy in addition to surgery, and eight had never approached the lesion with any treatment.

The treated tumors were the following: One pituitary macroadenoma, 16 meningiomas, two craniopharyngiomas, three carcinomas (two undifferentiated and 1 cystic), one mucosal melanoma, one glioma, two chondrosarcomas of the clivus, and six chordomas of the clivus.

All patients were treated with a multidisciplinary approach. Radiological, endocrinological, and neurosurgical evaluations found place both before and after the treatment, with preestablished follow-up times (at 3, 6, 9, 12, 18, and 24 months, then annually). For all patients, venous blood was collected to test for hormonal levels, together with urine samples. Blood hormone levels and 24-h urinary cortisol were re-evaluated during each follow-up.

Out of these patients, six were treated with carbon ions and 26 with protons [Table 1].

Hormonal alterations are reported in Table 2.

During each follow-up, a magnetic resonance imaging (MRI) was also performed to evaluate the lesion and the possible infiltration of surrounding structures.

In addition, patients were requested to fill in a questionnaire concerning potential side effects related to particle therapy (mucositis, skin reactions, deficit of cranial nerves V and VIII, and memory deficit) and irreversible side effects previously caused by the injury (visual impairment and headache). Toxicity levels were evaluated with Common Terminology Criteria for Adverse Events scale, version 5.0.[7]

Ophthalmological visits were also performed to assess pretreatment and posttreatment ophthalmological balance.[20]

All patients provided written informed consent to take part in the study.

Statistical analysis was performed using Student's *t*-test[14] and two-proportion z-test[11] to assess the development of hormonal alterations. All confidence intervals (CIs) were estimated at 95%. Statistical significance was considered achieved for $P < 0.05$.

RESULTS

Results in terms of quality of life and loss in terms of autonomy (according to Karnofsky Performance Scale [KPS] index), headache (assessed on the basis of Visual Analogue Scale pain scale), visual impairment, cranial nerve deficits (c.n. V and VIII), memory deficits, skin changes, toxicity detected during last follow-up, and hormonal changes are summarized in Tables 3 and 4.

The mean dose of administered particle therapy was 60 ± 14 Gray(RBE) (GyRBE), with a mean dose per fraction of 2.3 ± 2.1 Gy.

Out of 32 patients, 26 developed no hormonal alterations. Pituitary hormone alterations were reported for 6 patients (18.75%) [Table 1].

Patients with hormonal changes were patients 3, 5, 17, 18, 21, and 31.

Patient 3 already suffered from central hypothyroidism (presumably caused by the tumor) and were undergoing thyroid replacement therapy. Following the treatment, however, the patient was also diagnosed with central adrenal insufficiency and primary hypoparathyroidism.

Patient 5 had to undergo a levothyroxine and glucocorticoid replacement therapy due to central hypothyroidism and adrenal insufficiency. Central hypothyroidism was already

Table 1: Patients divided by histology, hormonal changes, sellar involvement, previous surgery or radiotherapy, and treatment type.

Patient	Histology	Hormone alterations	Sellar involvement	Previous surgery	Previous radiotherapy	Treatment
1	Pituitary nonfunctioning macroadenoma	No	Yes	Yes (2012)	No	Protons
2	Clivus meningioma	No	Yes	No	No	Protons
3	Poorly differentiated left orbital carcinoma (relapse)	Yes	No	Yes (1991, 1993, 2007)	Yes (1991)	Carbon
4	Left parasellar meningioma (relapse)	No	No	Yes (1992, 1995)	Yes (2005)	Protons
5	Progressing sphenopetroclival meningioma	Yes	Yes	Yes (2005)	No	Protons
6	Craniopharyngioma (relapse)	No	Yes	Yes (2013)	No	Protons
7	Left cavernous sinus meningioma	No	Yes	No	No	Protons
8	Meningothelial meningioma	No	Yes	Yes (2011, 2015)	No	Protons
9	Intracranic sphenoid wing meningioma	No	No	Yes (2001)	No	Protons
10	Parasellar meningioma	No	No	Yes (Biopsy in 2016)	No	Protons
11	Left optic nerve sheath meningioma	No	No	Yes (2016)	No	Protons
12	Undifferentiated sella turcica carcinoma	No	Yes	Yes (2017)	No	Protons
13	Meningothelial meningioma	No	Yes	Yes (2018, 2020)	No	Protons
14	Cavernous sinus meningioma	No	No	No	No	Protons
15	Clival chordoma	No	Yes	Yes (2018)	No	Carbon
16	Cranial base meningioma	No	No	No	No	Protons
17	Left clinoid and petrous bone meningioma	Yes	Yes	No	No	Protons
18	Craniopharyngioma	Yes	Yes	Yes (2014)	No	Protons
19	Clival chordoma	No	No	Yes (2019)	No	Protons
20	Left cerebellopontine angle meningioma	No	No	No	No	Protons
21	Chondrosarcoma of the sphenoethmoid complex	Yes	Yes	Yes (2011)	No	Protons
22	Clival chondroid chordoma	No	Yes	Yes (2019)	No	Carbon
23	Left cavernous sinus fibroblastic meningioma	No	No	Yes (2017)	No	Protons
24	Clival chordoma	No	No	Yes (2018)	No	Protons
25	Clival chordoma	No	Yes	Yes	No	Protons
26	Left pterygopalatine fossa adenoid cystic carcinoma	No	No	Yes (2018)	No	Carbon
27	Clival chondrosarcoma	No	No	Yes (2017)	No	Protons
28	Cavernous sinus meningioma	No	Yes	No	No	Protons
29	Primary mucosal melanoma of the sinonasal tract	No	No	Yes (2018)	No	Carbon
30	Right paraclival chondrosarcoma	No	Yes	Yes (2017)	No	Carbon
31	Low-grade glioma	Yes	No	Yes (2017)	No	Protons
32	Left cavernous sinus meningioma	No	Yes	No	No	Protons

present before treatment, while adrenal insufficiency was discovered 6 months after the end of therapy.

Patient 17 was diagnosed with mild central adrenal insufficiency and hyperprolactinemia 6 months after completing of therapy, but no treatment was started. At the last follow-up, the values were back within range.

Patient 18 was diagnosed with central hypothyroidism and central adrenal insufficiency 2 years after completing therapy and started replacement therapy with cortisone acetate and levo-thyroxine.

Patient 21 showed a decrease in blood testosterone levels, together with an increase in prolactin, 5 years after the end of therapy (presumably a relapse). Furthermore, 6 years after the end of treatment, the patient was hospitalized for severe hypo-osmolar hyponatremia and diagnosed with severe central adrenal insufficiency. He then started replacement therapy with cortisone acetate.

Patient 31 showed a reduction in testosterone, as well as an increase in FSH and LH. For this reason, testosterone replacement therapy was started.

Table 2: Hormonal range values.

PRL	1.9–25 ng/mL
FSH	Men 0–5 mIU/mL (prepuberty), 0.3–10 mIU/mL (puberty), 1.5–12.4 mIU/mL (adulthood); Women 0–4 mIU/mL (prepuberty), 0.3–10 mIU/mL (puberty), 1.8–8 mIU/mL (follicular phase), 4–25 mIU/mL (ovulation), 1–5.1 mIU/mL (luteal phase), 25.8–134.8 mIU/mL (postmenopausal)
LH	Men 1.8–8.6 IU/L; Women 1.9–12.5 IU/L (follicular phase), 8.7–76.3 IU/L (ovulation), 0.5–16.9 IU/L (luteal phase), 15.9–54 IU/L (postmenopausal)
Testosterone	Men: 270–1070 mg/dL; Women: 9–30 ng/dL
TSH	0.4–4 mIU/L
fT4	8–19 pg/mL
GH	<8 ng/mL
IGF-1	87–238 ng/mL
ACTH	6–57 pg/mL
Cortisol (8 am measurement)	5–25 mcg/dL
24-hour(h) urinary cortisol	28–213 mcg/24 h

PRL: Prolactin, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone, fT4: Free thyroxine, GH: Growth hormone, IGF-1: Insulin-like growth factor 1, ACTH: Adenocorticotropic hormone

For the remaining 26 patients, no new hormonal alterations were detected and no replacement therapy was necessary (except for those who already showed hormonal alterations before PT).

Visual impairment (if present) remained stable compared to pretreatment, except in Patient 3, who experienced G4 – complete postactinic blindness.

Headache was reported as a side effect in six out of 32 patients (18.75%), with a maximum reported pain of 9/10 in Patient 7.

Some patients reported nerve deficits, particularly cranial nerve V and VIII (trigeminal and vestibular-cochlear). In 10 patients a trigeminal deficit was reported (31.25%), while a vestibulo-cochlear deficit was detected in 8 patients (25%). The maximum reported grade for both deficits was G2.

During follow-up visits, a possible memory deficit was also investigated. This was reported in 6 patients (18.75%), with maximum grade G3. Five patients also reported postactinic skin changes (15.6%), with a maximum grade of G2.

Case illustration patient 14

To better understand the diagnostic and therapeutic process of the patients enrolled in this study, we report the case of a patient belonging to the cohort.

The patient was a previously healthy 30-year-old female in the third trimester of her first pregnancy. She suffered no pregnancy-related complications except for gestational hypothyroidism, which was treated with levo-thyroxine. The patient was brought to the Neurosurgeons' attention because of new-onset diplopia and left periorbital neuralgia. For this reason, she underwent an MRI and an eye examination. The MRI showed an expansive extra-axial lesion of the cavernous sinus (25 × 17 × 21 mm) that wrapped the carotid siphon, markedly reducing its caliber [Figure 1]. The lesion proved to be a cavernous sinus meningioma adjoining the left parasellar region, temporal-mesial convolutions, round foramen, and inferior orbital fissure. The optic chiasm showed no compression. No biopsy was performed.

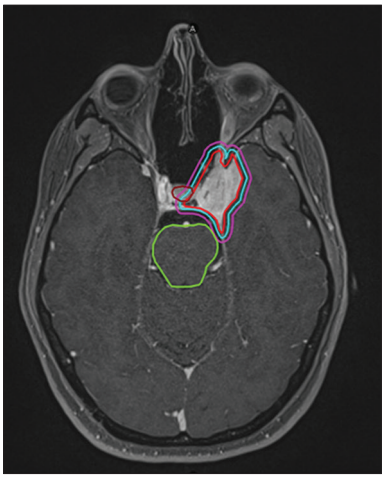


Figure 1: Pre-treatment magnetic resonance imaging (MRI). Colours only provide a visual representation of the cited area (pre-treatment masses).

Due to this finding, a cesarean section was performed at the 35 weeks of gestation. The patient was also referred for particle therapy treatment, since she was showing symptoms.

The proton treatment was carried out from February 27, 2017 to March 15, 2017, with a total dose of 55.8 GyRBE (1.8 GyRBE/fraction, 31 fractions, 5 fractions/week) and intensity-modulated proton therapy (IMPT) technique [Figure 2].

Table 3: Tumor histology, KPS, side effects, and toxicity.

Patient	Histology	KPS pre-HAT	Δ KPS last FU	Headache max VAS	Visual deficit	V c.n. deficit	VIII c.n. deficit	Memory deficit	Skin disorder	Toxicity at last FU
1	Pituitary nonfunctioning macroadenoma	100	0	7/10	Stable	G0	G0	G0	G0	G0
2	Clivus meningioma	90	−20	0/10		G0	G2	G0	G0	G0
3	Poorly differentiated left orbital carcinoma (relapse)	90	−50	6/10	Complete blindness, G4	G2	G2	G0	G0	G4
4	Left parasellar meningioma (relapse)	80	0	0/10	Stable	G1	G0	G2	G2	G2
5	Progressing sphenopetroclival meningioma	90	−10	0/10	G1	G2	G0	G2	G0	G2
6	Craniopharyngioma (relapse)	100	0	0/10	G0	G0	G0	G0	G0	G0
7	Left cavernous sinus meningioma	90	0	9/10	G0	G2	G1	G0	G0	G1
8	Meningothelial meningioma	90	0	0/10	Stable since surgery	G0	G0	G0	G0	G0
9	Intracranic sphenoid wing meningioma	90	0	0/10	Stable	G0	G1	G0	G0	G1
10	Parasellar meningioma	90	0	0/10		G0	G0	G0	G0	G0
11	Left optic nerve sheath meningioma	90	0	0/10	Stable	G2	G0	G1	G0	G2
12	Undifferentiated sella turcica carcinoma	80	−10	0/10		G0	G0	G0	G0	G0
13	Meningothelial meningioma	90	0	0/10	Absent	G0	G0	G0	G1	G1
14	Cavernous sinus meningioma	100	0	0/10	Absent	G0	G0	G0	G0	G0
15	Clival chordoma	100	0	0/10	Absent	G0	G0	G0	G1	G1
16	Cranial base meningioma	100	−20	3/10	Worse	G0	G0	G0	G0	G0
17	Left clinoid and petrous bone meningioma	90	−10	0/10	Stable	G1	G0	G0	G0	G1
18	Craniopharyngioma	50	0	0/11		G0	G0	G3	G0	G0
19	Clival chordoma	80	0	0/10	Stable	G2	G0	G0	G0	G2
20	Left cerebellopontine angle meningioma	90	0	0/10	Absent	G0	G0	G0	G0	G0
21	Chondrosarcoma of the sphenoethmoid complex	100	−10	0/10		G0	G0	G0	G0	G2
22	Clival chondroid chordoma	90	0	0/10	Better	G0	G0	G0	G0	G0
23	Left cavernous sinus fibroblastic meningioma	100	0	0/10	Absent	G0	G0	G0	G0	G1
24	Clival chordoma	50	−30	0/10		G0	G0	G0	G0	G0
25	Clival chordoma	100	0	3/10	Absent	G0	G0	G0	G0	G0
26	Left pterygopalatine fossa adenoid cystic carcinoma	90	0	0/10	Stable	G0	G1	G0	G0	G1
27	Clival chondrosarcoma	90	0	0/10		G1	G0	G0	G0	G0
28	Cavernous sinus meningioma	100	0	0/10	Stable	G0	G2	G1	G0	G2
29	Primary mucosal melanoma of the sinonasal tract	90	0	0/10	Absent	G1	G0	G0	G1	G1
30	Right paraclival chondrosarcoma	90	0	0/10	Stable	G1	G1	G0	G0	G1
31	Low-grade glioma	90	0	0/10		G0	G1	G1	G1	G2
32	Left cavernous sinus meningioma	100	−10	7/10	Stable	G0	G0	G0	G0	G0

VAS: Visual Analog Scale, c.n.: Cranial nerve, KPS: Karnofsky Performance Scale, FU: Follow-Up, VIII c.n.: VIII cranial nerve, V c.n.: V cranial nerve, G0: Grade 0, G1: Grade 1, G2: Grade 2, max VAS: Maximum pain according to VAS pain scale, pre-HAT: Pre-HT (hadron therapy), ΔKPS: KPS difference

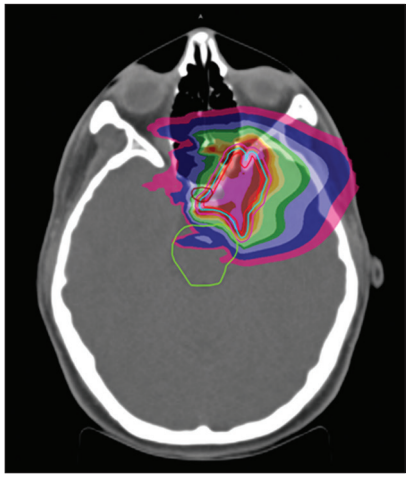


Figure 2: Pre-treatment magnetic resonance imaging (MRI) with therapy plan. Colours only provide a visual representation of the cited area (therapy plan).

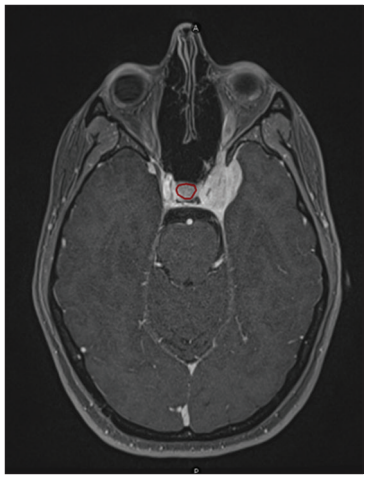


Figure 3: Post-treatment magnetic resonance imaging (MRI). Colour only provides a visual representation of the cited area (residual mass).

At the end of proton therapy, the patient's conditions were good, except for slight skin erythema (G1 toxicity) with initial alopecia. She reported no visual disturbances or headaches. At discharge, pain according to Numeric Pain Rating scale was 0/10. No hormone replacement therapy was necessary.

During follow-up visits, the patient's MRIs showed a clear reduction (27 × 10 × 21 mm) and subsequent stability of the mass [Figure 3]. The only reported side effects were occasional mild left trigeminal paresthesia (which disappeared 18 months after treatment). The patient's blood chemistry showed no hormonal changes except for mild breastfeeding-related hyperprolactinemia. Three years after treatment, the patient was pregnant with her second child. Gynecologists carried out regular ultrasound checks, which showed regular fetal growth and no ultrasound abnormalities. After completing the second pregnancy, the thyroid replacement therapy was stopped and thyroid hormone levels returned within range. Prolactin levels went back to normal after the patient stopped breastfeeding her first child, but raised again when the breastfeeding of the second child began.

Therefore, we can state that the patient's hormonal alterations were not caused by radiation therapy as hyperprolactinemia and hyperthyroidism were linked, respectively, to breastfeeding and pregnancy.

Table 4: Patients' details and endocrinological complications.

Patient	Sex	Age	Endocrinological complications
1	F	58	No
2	F	82	No
3	F	66	Yes: Hypoadrenalism, hypoparathyroidism
4	F	69	No
5	F	62	Yes: Hypothyroidism, hypoadrenalism
6	M	27	No
7	F	63	No
8	M	76	No
9	F	74	No
10	M	70	No
11	F	72	No
12	F	81	No
13	F	60	No
14	F	33	No
15	M	63	No
16	F	51	No
17	F	46	Yes: Hypoadrenalism, hyperprolactinemia
18	F	73	Yes: Hypothyroidism, hypoadrenalism
19	F	67	No
20	F	69	No
21	M	59	Yes: Hypoadrenalism, hyperprolactinemia, low testosterone
22	F	57	No
23	F	64	No
24	M	67	No
25	M	32	No
26	F	60	No
27	M	22	No
28	F	81	No
29	M	83	No
30	F	58	No
31	M	38	Yes: Low testosterone and growth hormone
32	F	48	No

F: Female, M: Male

DISCUSSION

Various studies have proven that hormonal deficits following radiotherapy cause significant losses in terms of quality of life.[1,3,8]

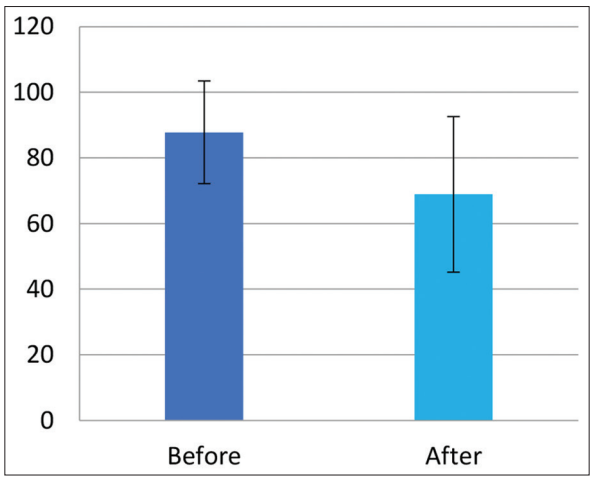
Postactinic hypopituitarism has been reported in 37–77% of patients with anterior skull base lesions treated with conventional radiotherapy.[3,10]

Furthermore, radiotherapy in the anterior skull base has also proven to be burdened by several other side effects, including memory loss,[23] mucositis, and osteoradionecrosis.[19]

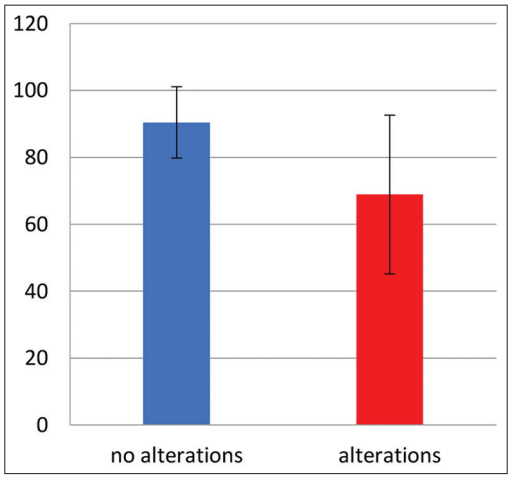
In our sample, 18.75% of patients reported hormonal alterations.

The patients who developed hormonal deficits, as predicted, showed a significant reduction ($P = 0.027$) in terms of quality of life when compared to patients who did not develop hormonal deficits [Graph 1].

The mean radiation dose received by patients who reported hormonal alterations was 57.6 GyRBE, lower than the mean radiation dose in the sample of patients who did not show hormonal alterations (60.6 GyRBE). Analyzing the collected data, evidence shows that there is no statistically significant correlation ($P = 0.34$) between the dose of administered radiation and incidence of postactinic hypopituitarism. The main reason for this result is that different doses of particle therapy are standardized within protocols specifically designed to avoid iatrogenic damage of this type [Graph 2].



Graph 1: Karnofsky performance scale alterations before and after treatment.



Graph 2: Posttreatment Karnofsky performance scale difference.

The losses in terms of quality of life and post-PT performance status were not statistically significant ($P = 0.066$) in the patient sample, but there was a trend toward worsening of overall health status (according to KPS) in patients with postactinic hypopituitarism when compared to patients with no postactinic hormonal alterations.

By comparing the data collected in this study with the meta-analysis performed by Appelman-Dijkstra *et al.*,[3] we can note the difference between particle therapy and conventional radiotherapy in terms of incidence of postactinic hypopituitarism. The data speak in favor of particle therapy, which shows a lower incidence of damage to the hormonal axis ($z = 5.47$).

We also compared the data collected in this study with other studies carried out in the past 10 years. The two studies that we mainly considered were: *Pituitary dysfunction following cranial radiotherapy for adult-onset nonpituitary brain tumors* by Kyriakakis *et al.*,[12] and *Pituitary dysfunction in adult patients after cranial irradiation for head and nasopharyngeal tumors* written by Appelman-Dijkstra *et al.*[4]

The results showed by both studies strengthen our argument. Specifically, the first publication shows that a significant number of patients developed hypopituitarism following conventional radiotherapy (88.8%), while the second shows an increase in the incidence of hypopituitarism in time (from 47% 2 years after treatment to 89% 15 years after treatment). These findings further stress the importance of long-term follow-up visits in patients who have undergone some radiotherapy targeted to the sellar region.

Our study, however, does show some limitations. First of all, this is a retrospective analysis.

Moreover, the sample size is small and inhomogeneous in terms of tumor histology and previous treatment.

Given the different anatomy and radiosensitivity patterns in every patient, it is impossible to assess the exact dose of radiation received by the pituitary gland in a standard fashion (although the isodoses were collected for each patient). Furthermore, even though all patients were adults, radiosensitivity may vary with age. Local invasion, previous surgery, and comorbidities may also play a role, especially in the microvascular pattern of both portal and arterial pituitary vasculature.

The study is also limited by the fact that blood samples and MRIs were carried out in different laboratories and centers.

CONCLUSION

Particle therapy appears to be burdened by a lower incidence of side effects when compared to conventional radiotherapy, especially with regard to alterations in pituitary function.

For this reason, particle therapy could represent a new frontier in the treatment of tumors involving the sellar region. Further studies are needed to confirm a potential long-term advantage of PT over conventional radiotherapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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