

When age is not an obstacle: A case series of endoscopic transsphenoidal resection of pituitary macroadenomas in older patients

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Abstract. Due to the increase in life expectancy, the number of elderly patients suffering from a pituitary macroadenoma is expected to increase in the future. The endoscopic endonasal transsphenoidal (EET) approach tends to be the first choice for the treatment of pituitary macroadenomas in the general population. Notwithstanding, in the geriatric population, the goals of management for this condition remain unclear. The present study retrospectively evaluated and describes the cases of 6 patients >70 years of age with a pituitary macroadenoma who were treated by a skull base team, composed of one ENT surgeon and one neurosurgeon. All the patients experienced a notable improvement in their neurological deficit, while their hormonal status also improved or at least did not deteriorate after the surgery. The EET approach appears to be a safe and effective approach for the treatment of pituitary macroadenomas in the geriatric population.

Introduction

Pituitary macroadenomas (PM) are a common subtype of sellar tumors. Considering the gradual extension of human life

expectancy, in the near future, neurosurgeons would be expected to face an increasing number of PM cases among the elderly population. Any type of surgical treatment for patients of an advanced age is a debatable issue, as age is accompanied by significant comorbidities, and these patients are prone to developing systemic complications. Thus, a less invasive approach should be used if symptoms occurring due to PM necessitate surgical treatment. The endoscopic endonasal transsphenoidal (EET) approach for the resection of PMs is gradually gaining ground over the standard microscopic transsphenoidal approaches performed over the past decades. The better visualization during the surgery (1-3), the shorter duration of the surgery with fewer intraoperative complications (4-6), the more extensive tumor removal (7,8), and the shorter or equal hospitalization times of patients undergoing the EET approach compared to patients undergoing the microscopic transsphenoidal approach are some of the reasons behind the preference for the use of EET (9-11). It is also important to mention that the long learning curve of the EET approach (200 up to 500 cases) proposed in the past to achieve significantly lower morbidity and mortality (12) and for a number of years constituted an obstacle to the rapid advancement of the latter approach appears to be overestimated. Studies have demonstrated improved or at least comparable results of the EET vs. the microscopic approach after 17 or even fewer surgeries performed using the EET approach (11,13), if the former approach is performed in a multidisciplinary skull base center (11). The present study describes the cases of 6 elderly patients with PM who were treated with the EET approach at Nicosia General Hospital.

Patients and methods

Patients. The present study included patients >70 years who presented with pituitary macroadenomas that were treated

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surgically using an EET approach. All the patients with a PM that were either <70 years or treated with a different approach than the EET approach were excluded from the study. The patients' data were retrospectively collected and the data obtained included demographics, the extension of tumor removal, intraoperative and late complications, and endocrinology and neurological status pre- and post-operatively. The data were retrieved from the database of the hospital and accessed in an anonymous manner using unique code identifiers, while data were handled in accordance with the protocols of the ethics committee of Nicosia General Hospital (Nicosia, Cyprus). The patient demographics and clinical data, including surgical outcomes, are summarized in Table I.

The surgeries were performed between 2017 and 2022 by a team consisting of an attending ENT and a neurosurgeon. The nasal stages, including the anterior sphenoidectomy, as well as the final closure, were performed by the ENT surgeon, whereas the remainder of the surgery was performed by the neurosurgeon. For each procedure, a combination of 0°, 30° and 45° rigid endoscopes were utilized to achieve adequate exposure and visualization during tumor removal. Abdominal fat was placed in the tumor bed while water-tide closure was ensured using a triple layer of artificial dura, tissue glue and rhino-septal mucosal flaps (Hadad-Bassagasteguy flap). Neuronavigation was routinely utilized in all the cases. The mean duration of hospitalization was 1 week. The hormone levels that are considered 'normal' at our institution are the following: Growth hormone, 0-1 µg/l (males) and 0-10 µg/l (females); adrenocorticotrophic hormone, 4.7-48.8 ng/l; thyroid-stimulating hormone, 0.35-5.5 mU/l; prolactin, 2.1-17.7 µg/l (males), 2.8-29.2 µg/l (non-pregnant females), 9.7-208 µg/l (pregnant females) and 1.8-20.3 µg/l (menopausal women); follicle-stimulating hormone, 1.4-18.1 mU/l (males), 2.5-10.2 mU/l (females in the follicular phase), 3.4-33.4 mU/l (females in the ovulatory period), 1.5-9.1 mU/l (females in the luteal phase), and 23-116 mU/l (menopausal women); luteinizing hormone, 1.5-9.3 mU/l (males), 1.9-12.5 mU/l (females in the follicular phase), 8.7-76.3 mU/l (females in the ovulatory period), 0.5-16.9 mU/l (females in the luteal phase), and 15.9-54 mU/l (menopausal women).

Results

The clinical data of the 6 patients were as follows:

Patient 1. A 76-year-old female patient was admitted to the Nicosia General Hospital with an acute visual field deficit (significant bitemporal hemianopia). The levels of prolactin were increased, while the levels of other hormones were within normal limits. A macroadenoma with lateral extension to the right cavernous sinus (Knosp grade 3A) was identified in the MRI (Fig. 1), and it was gross-totally removed successfully using the EET approach (Fig. 2). The histological examination of the specimen revealed a prolactinoma. After the surgery, the patient experienced a notable improvement in bitemporal hemianopia (mild visual field restriction was observed in the last follow-up, 6 years after the surgery).

Patient 2. A 71-year-old female patient attended the neurosurgery outpatient clinic at Nicosia General Hospital due to a massive, Knosp grade 2 pituitary macroadenoma that was

found incidentally (Fig. 3). In the neurological evaluation, a mild bilateral hemianopia was discovered. The pituitary function was normal. The macroadenoma was endoscopically removed (Fig. 4) with no intra- or post-operative complications, while the histological result was a non-secreting adenoma. The patient's visual fields returned to almost normal levels post-operatively.

Patient 3. A 73-year-old female patient was referred to the neurosurgery outpatient clinic at Nicosia General Hospital by her endocrinologist due to resisting hypothyroidism and hypocortisolemia. The radiological evaluation revealed a Knosp grade 2 pituitary macroadenoma (Fig. 5), which was completely extracted using an EET approach (Fig. 6). The histological examination of the specimen revealed a non-secreting adenoma. The patient developed a post-operative cerebrospinal fluid (CSF) leak, which was successfully treated endoscopically. The patient was discharged with hormonal replacement therapy, even though in the long-term follow-up, her needs for replacement were reduced.

Patient 4. A 74-year-old male patient was urgently transferred to the ER at Nicosia General Hospital due to pituitary apoplexy. He experienced an acute unilateral visual loss, while the pituitary hormone levels were in the lower normal limits. The MRI revealed a Knosp grade 3A pituitary macroadenoma with internal bleeding (Fig. 7). The histological examination of the specimen revealed a non-secreting adenoma. The lesion was extracted successfully (Fig. 8), and the patient's neurological deficit gradually improved (he refers to moderate improvement in his vision shortly after the surgery and a 70% return in vision return 1 year after the surgery).

Patient 5. An 82-year-old male patient was transferred to the ER at Nicosia General Hospital due to an acute change of consciousness and unilateral blindness. The cortisone level was below the normal limit. The MRI revealed a large Knosp grade 2 PM, while signs of blood were also present (Fig. 9). Due to the clinically prominent pituitary apoplexy, the initial treatment plan was to partially remove the tumor, decompressing the optic chiasma; however, as the surgery was uneventful, it was decided to proceed with gross total resection (Fig. 10). The histological examination of the specimen revealed a non-secreting adenoma. The patient's vision gradually improved after the surgery (he refers to a 50% improvement in his vision at 6 months after the surgery); however, he still needs replacement therapy for cortisone.

Patient 6. A 71-year-old female patient presented to the outpatient clinic at Nicosia General Hospital due to headaches. The neurological evaluation did not reveal any notable findings, and the hormonal status was within normal limits. The radiological evaluation revealed a Knosp grade 3A PM with an extension to the right cavernous sinus (Fig. 11), which could not completely explain the patient's symptoms. The tumor was successfully removed (Fig. 12), while the headaches of the patients were reduced in frequency. The histological examination of the specimen revealed a non-secreting adenoma.

Outcomes. All patients experienced a notable improvement in their neurological deficits. Moreover, their endocrinology

Table I. Demographics and clinical data of the patients in the present case series.

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age, years	76	71	73	74	82	71
Sex	Female	Female	Female	Male	Male	Female
Clinical status	GCS14	GCS 15	GCS15	GCS 14	GCS12	GCS15
Pituitary hormonal status	Normal	Normal	Abnormal	Apoplexy	Apoplexy	Normal
Neurological deficit	Bilateral visual	Bilateral visual	None	Unilateral visual	Unilateral visual	None
Intraoperative complication	None	None	Dural tear	None	None	None
Late complication	None	None	CSF leak	None	None	None
Outcome	IMP	IMP	Stable (hormonal replacement)	IMP	IMP (hormonal replacement)	IMP

IMP, improvement; GCS, Glasgow Coma Scale; CSF, cerebrospinal fluid.

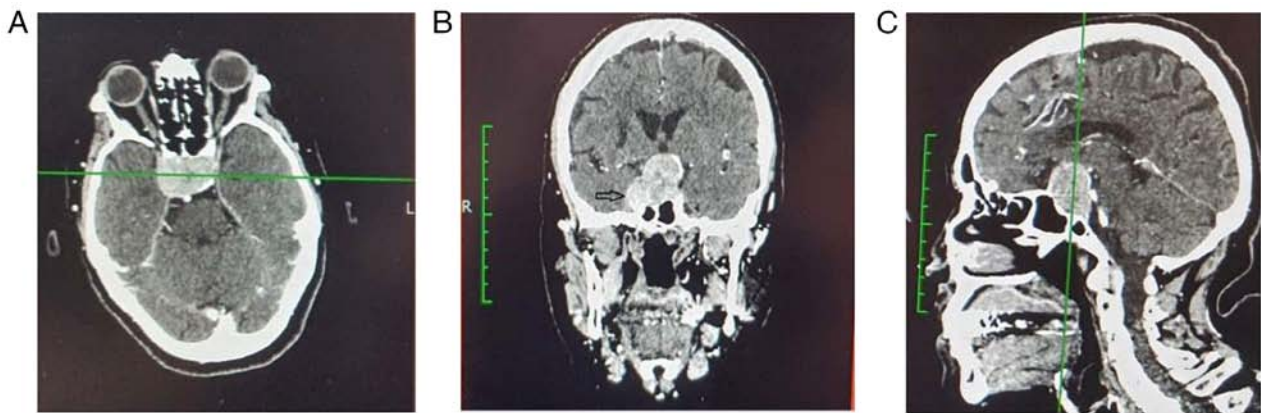


Figure 1. (A-C) Pre-operative contrast enhanced computed tomography scan of patient 1, depicting a large pituitary macroadenoma. Note the extension of the lesion to the right cavernous sinus (arrow).

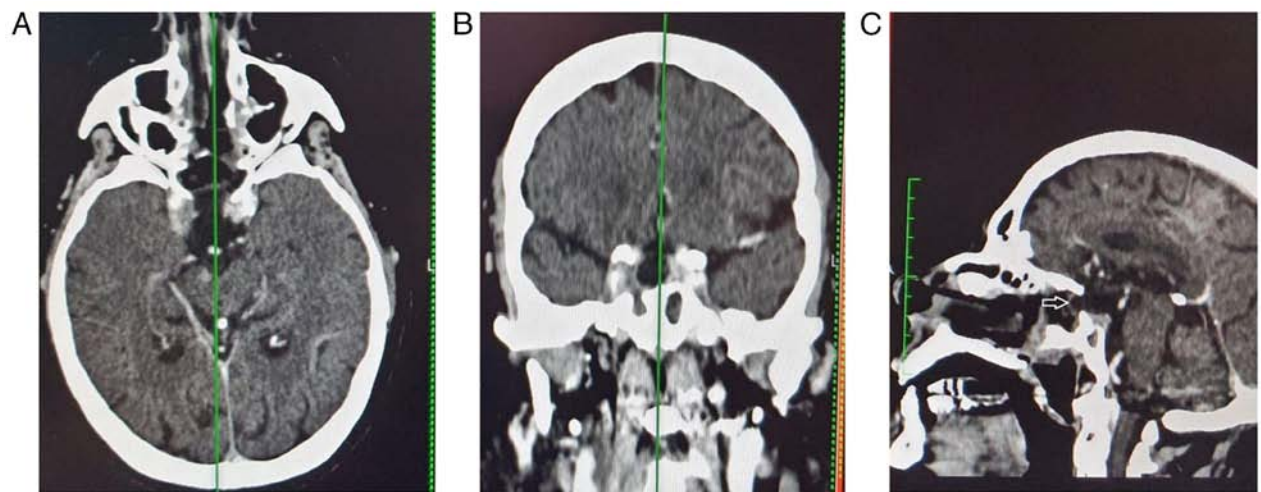


Figure 2. (A-C) Contrast enhanced computed tomography scan of patient 1 following the endonasal endoscopic gross total removal of the macroadenoma. Note the duroplasty materials (arrow).

status either normalized or remained stable. The patients were followed-up in the outpatient clinic after 1 month, 6 months,

and then annually post-operatively. An MRI was performed 3 months after the surgery and then annually.

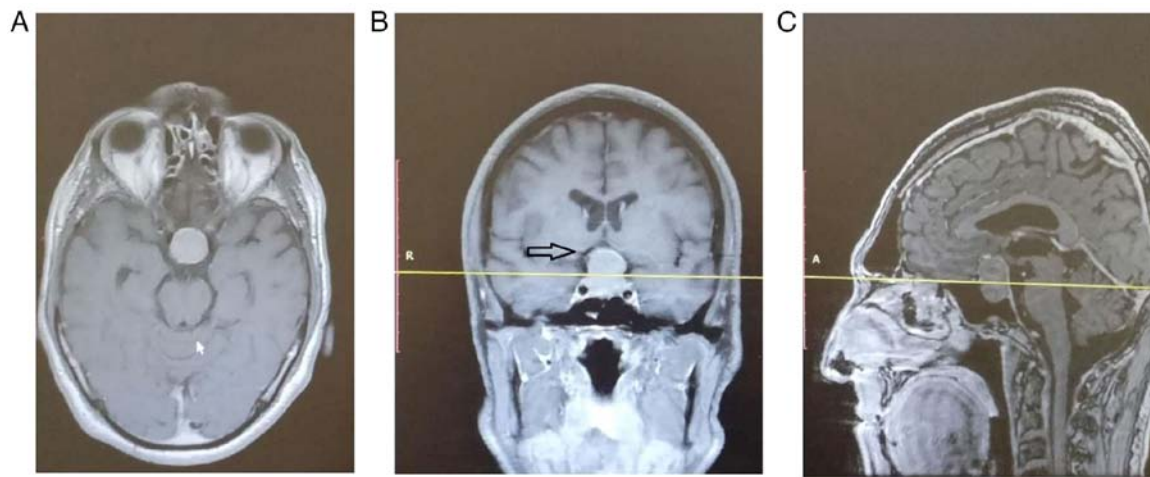


Figure 3. (A-C) Pre-operative contrast enhanced T1 MRI scan of patient 2, depicting a large pituitary macroadenoma that compress the optic chiasma (arrow).



Figure 4. (A-C) Post-operative contrast enhanced T1 MRI scan of patient 2. No tumor is depicted, while the pituitary stalk is decompressed (arrow).

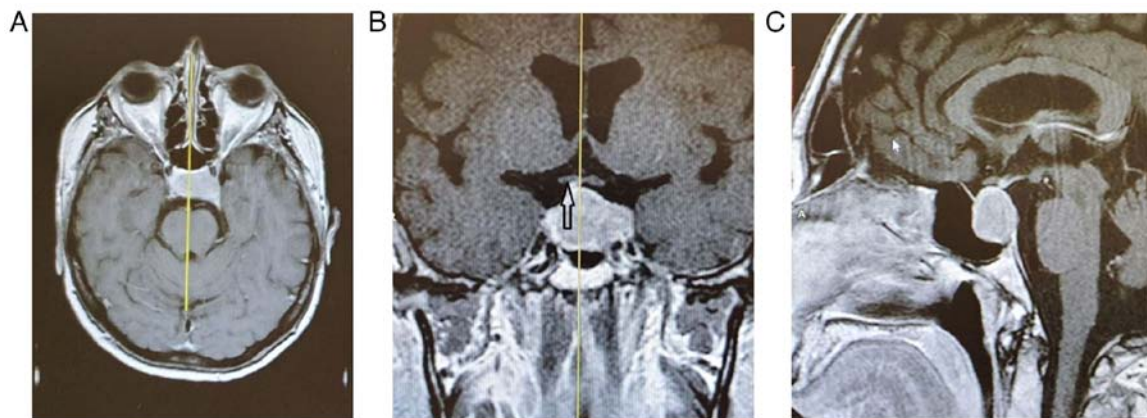


Figure 5. (A-C) Pre-operative contrast enhanced T1 MRI scan of patient 3, depicting a pituitary macroadenoma that comes into contact with, but does not compress the optic chiasma (arrow).

Discussion

The EET approach is gradually gaining ground in the treatment of PMs, compared with the standard microscopic approach. It offers a wider tumor removal, fewer complications and a shorter surgery duration (4,6,7). There is limited

literature available on the surgical treatment endpoints for elderly patients with PMs, and which approach has to be utilized in each case. Some previous studies have supported the microscopic transsphenoidal approach for PM resection in patients >65 years (14,15). Their conclusions were supported by a recent study by Azab *et al* (16), who stated

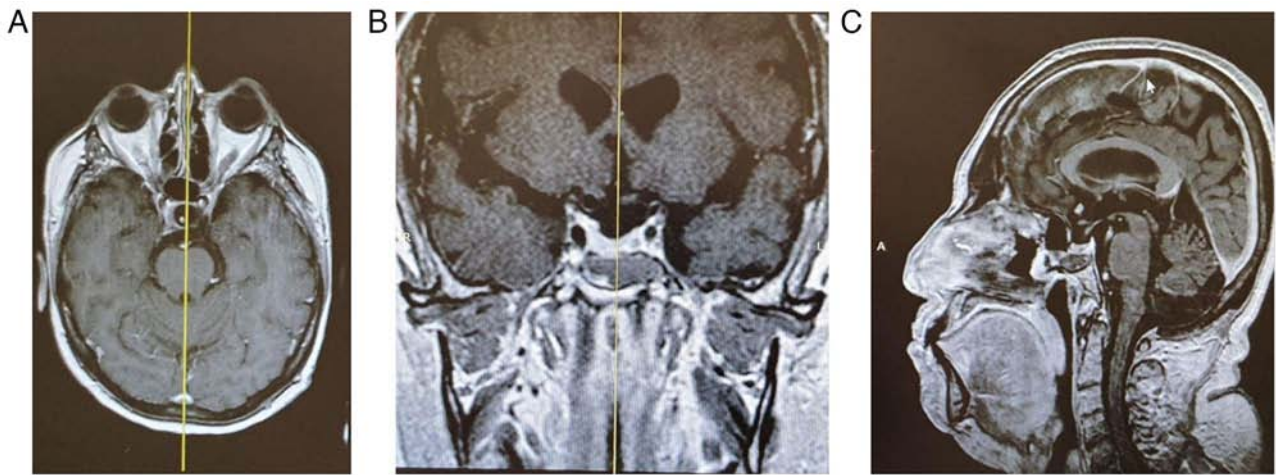


Figure 6. (A-C) Post-operative contrast enhanced T1 MRI scan of patient 3. No residual tumor is illustrated.

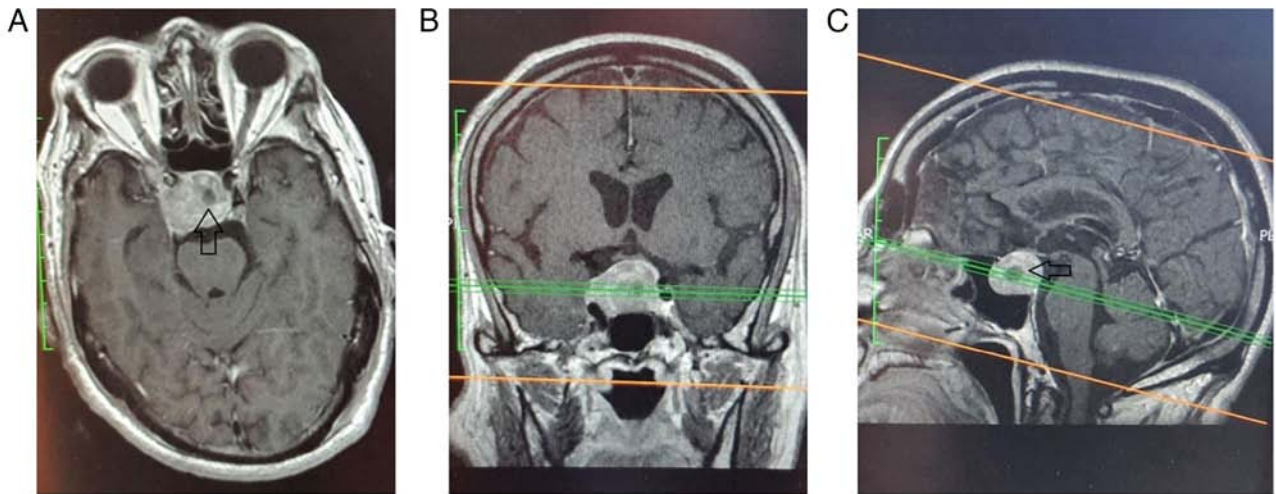


Figure 7. (A-C) Pre-operative contrast enhanced T1 MRI scan of patient 4, depicting a pituitary macroadenoma with internal bleeding (arrows). The patient presented with clinical signs of pituitary apoplexy.

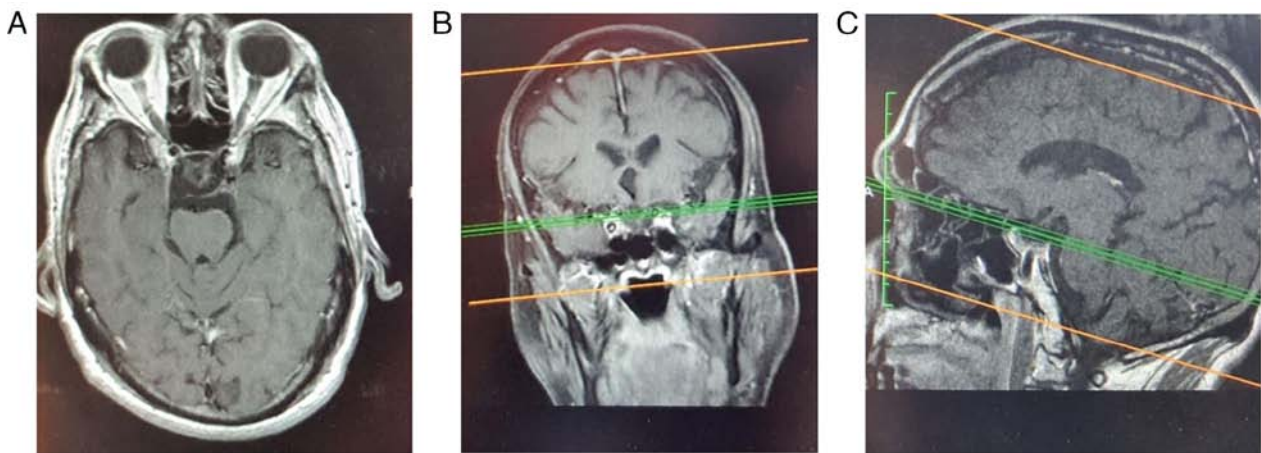


Figure 8. (A-C) Post-operative contrast enhanced T1 MRI scan of patient 4 illustrating complete tumor resection.

that the microscopic transsphenoidal approach for elderly patients with PM was more efficacious compared with the EET approach. The latter findings are in conflict with those

of other studies (17-21), where the EET approach is strongly supported, as it provides a great panoramic view, the ability to perform meticulous and precise intra-operative maneuvers,

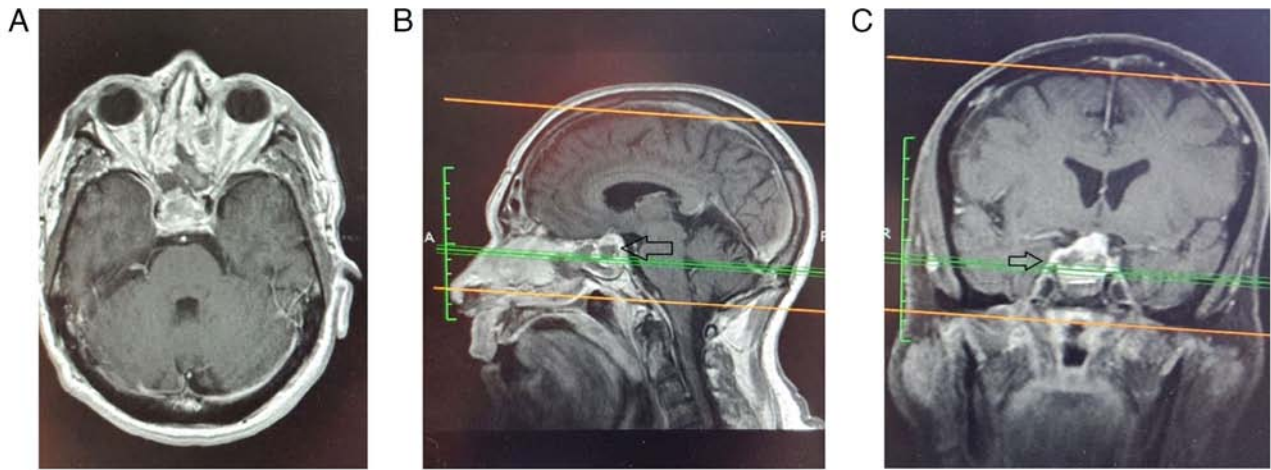


Figure 9. (A-C) Pre-operative contrast enhanced T1 MRI scan of patient 5, with pituitary apoplexy (arrows) due to a pituitary macroadenoma.

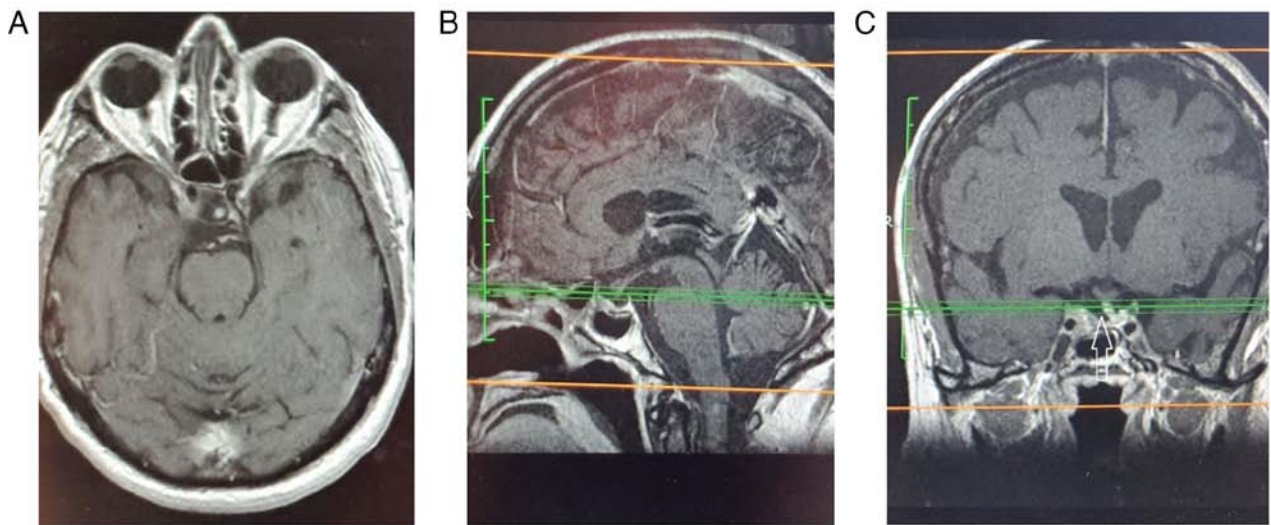


Figure 10. (A-C) Post-operative contrast enhanced T1 MRI scan of patient 5, following the endonasal endoscopic gross total removal of the macroadenoma. Note the pituitary stalk that is free of pressure (arrow).

excellent gross total tumor resection, and improved blood and CSF leak control. Additionally, patients who undergo an EET approach have been shown to achieve shorter hospitalization times (18) compared with patients who undergo a microscopic approach. Notwithstanding, there is a dispute, even in studies focusing on the EET approach. In detail, some researchers have found higher rates of complications in elderly groups (21,22) compared with groups of younger patients with PM who have been treated with an EET approach, while in another study, both young and aged patients had the same complication rates (17). A dispute exists in the duration of hospitalization as well; for example, Fujimoto *et al* (20) found a longer post-operative hospital duration in the elderly group, while others found the same duration of hospitalization (17,21,22).

In summary, the current trend in the literature is to treat patients of different age groups in a tailored manner. The clear indication for the surgery is either endocrinological, ophthalmological, or neurosurgical, due to the possible space-occupying nature of the tumor, although the endpoint of the treatment may differ. In younger patients with PM, the

goal is to perform aggressive tumor removal; hence, in elderly patients, more focus is paid to the improvement of any neurological (the visual deficit is the cardinal target) or hormonal deficit and the avoidance of any possible complications (18). The partial decompression at such advanced ages could translate into a reduced surgery duration and a shorter hospitalization period, with all the complications the latter carries, even if there is a remnant of the tumor (19). The lower rate of recurrence that is observed in elderly patients compared with their younger counterparts supports subtotal tumor removal if it is accompanied by the decompression of the adjacent structures (17), while the choice of a partial decompression of the neural structures with a massive PM remnant is not a viable possibility in younger patients, as the regrowth of the remaining tumor is highly possible.

The management algorithm in the patients described herein did not differ. The original aim was a subtotal extraction of the PM to alleviate the symptoms; notwithstanding, gross total removal was performed as the procedures were uneventful. The outcomes of the patients in the present study are also in

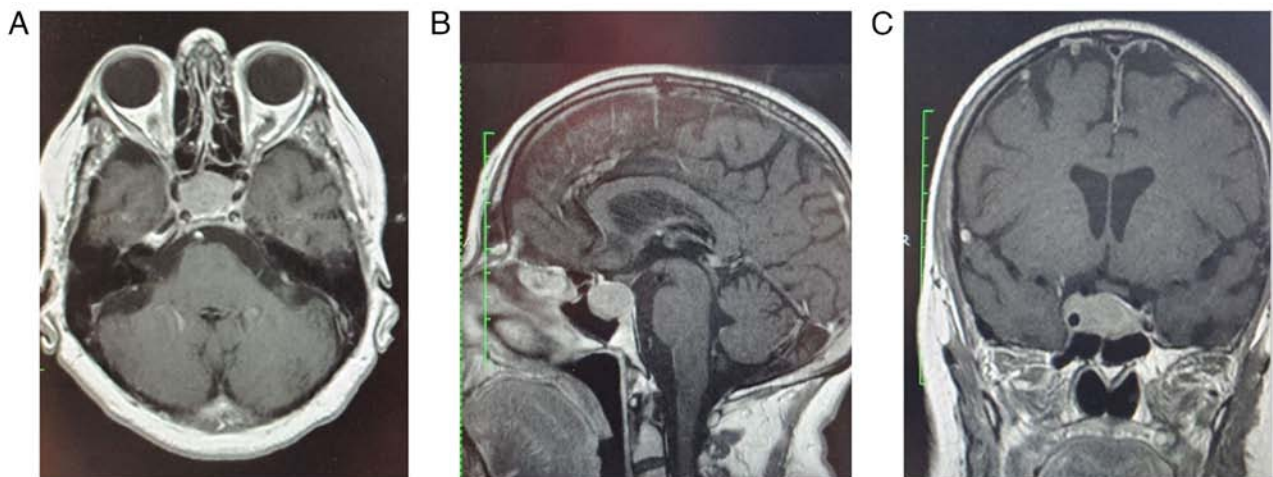


Figure 11. (A-C) Pre-operative contrast enhanced T1 MRI scan of patient 6, depicting a pituitary macroadenoma.

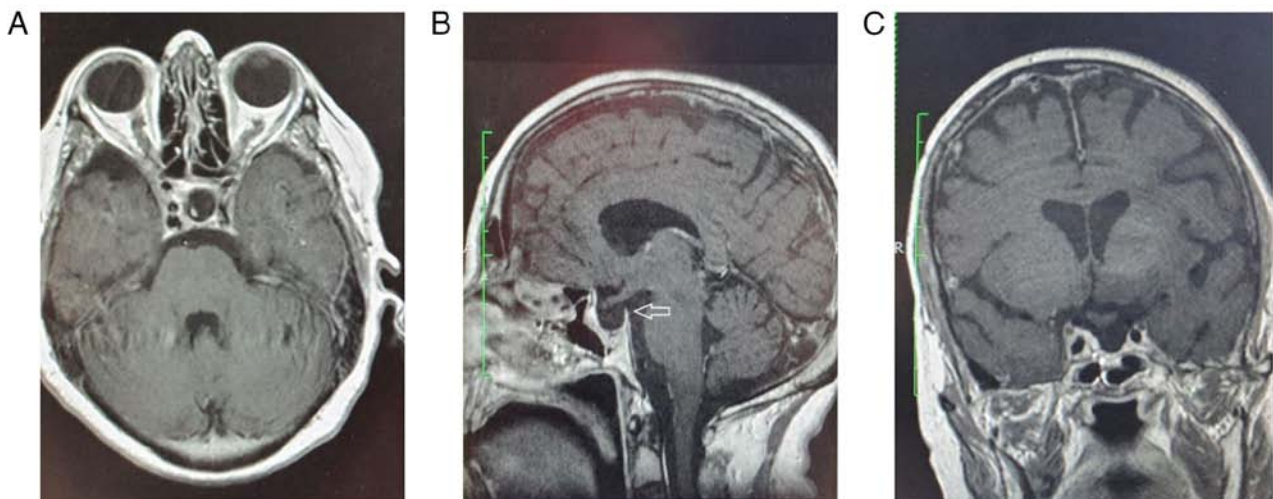


Figure 12. (A-C) Post-operative contrast enhanced T1 MRI scan of patient 6. No tumor is depicted, while the sella is empty (arrow).

parallel with those of the literature, as all the patients with a pre-operation neurological deficit experienced a notable improvement in their deficit (4 out of 4 patients, or 100%), their hormonal status normalized (2 out of 3 patients or 66.6% with pre-operative abnormal hormonal status were discharged with a better hormonal status), and the only complication that was encountered was a post-operative CSF leak (1 out of 6 patients or 16.6%), which was successfully treated endoscopically. Finally, the surgeries were undertaken in a low-volume hospital. Even if the literature suggests that a long learning curve is required to master the EET approach, it is considered that if the surgery is performed by a multidisciplinary skull base team consisting of ENTs and neurosurgeons, the outcome could be excellent for the patient.

Some limitations of present study should be mentioned. The present study was retrospective in nature, which makes it prone to reporting and selection bias. Notwithstanding, all the patients with a PM >70 years of age that were treated with the EET approach in the given period were included. In addition, the group was not uniform, as it was composed of patients with different macroadenoma histologies and clinical presentations. Finally, the small sample size of the series did not allow for a

solid statistical analysis. Further studies with a greater number of cases are required the near future in order to allow for a proper analysis and to extract clearer results.

In conclusion, when a physician manages elderly patients with PMs, factors such as life expectancy, comorbidity, neurological deficits and tumor recurrence rate should be taken into consideration. Hence, the goals of treatment are not the same as those in younger patients, where the aim is to perform a complete tumor resection. Considering the low recurrence rate of a remnant in the geriatric population with PMs and the comorbidity that is met at such an age, the partial removal of the tumor with decompression of the neural structures and the normalization of the hormone status is an acceptable choice. The small case series in the present study parallels that of the international literature, supporting EET as an ideal approach for treating PM in patients of an advanced age. That approach can be applied even in centers with a low PM-patient influx, as long as these centers are staffed with a multidisciplinary skull base team. Larger multicenter studies in the future will provide more cases in order to perform a proper statistical analysis which will further support the current findings.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

GF and KF conceptualized the study. KF, GF, AA and IG advised on patient care and medical treatment, and wrote and prepared the draft of the manuscript. GF, KF, IGL, AA, IG, VEG, NT, IT, PP and DAS analyzed the patients' data and provided critical revisions. GF and KF confirm the authenticity of all the data. All authors contributed to manuscript revision and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The data were retrieved from the database of the hospital and accessed in an anonymous manner using unique code identifiers, while data were handled in accordance with the protocols of the ethics committee of the hospital at Nicosia General Hospital.

Patient consent for publication

Written informed was obtained from the patients for the publication of their data and any accompanying images.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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