Comparison of the endoscopic endonasal to microscopic sublabial transsphenoidal approach in a case series of pituitary macroadenomas

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Abstract. For a number of years, the microscopic sublabial transsphenoidal (MST) approach was considered the gold standard approach for the treatment of pituitary macroadenomas. Nonetheless, the trend is currently shifting away from the MST to the endonasal transsphenoidal (EET) approach. The aim of the present study was to examine the post-operative outcomes of the first cases operated by a team of two young surgeons using the EET approach, compared to the cases operated by a team of senior neurosurgeons with extensive experience with the MST approach. For this purpose, data from 20 patients with pituitary adenoma were retrospectively collected from a single center who were operated by the current and previous pituitary-surgery teams. All the patients who presented with visual impairment in the EET group recovered completely (5/5), whereas 4/5 patients in the MST group recovered completely. Primary hospitalization duration was similar in the two groups. Gross tumor removal was achieved in 90% of patients in the EET group compared to 70% of the patients operated with the MST technique. Intraoperative complications were comparable between the two groups. The first cases operated at the center with EET proved to have better visual outcomes and a larger tumor removal when compared to the MST group. A greater experience in using this technique could exponentiate the differences in the post-operative outcomes, such as a lower hospitalization duration and fewer intraoperative complications. On the whole, colleagues who have yet to familiarize themselves with the EET approach could perhaps be encouraged to learn to utilize this technique, provided that their center is staffed with an experienced team of skull base surgeons to intervene in an intraoperative complication.

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Introduction

The novel concept of rapid access to the sellar region was first highlighted by Davide Giordano, an Italian anatomist, in 1897 (1), while Hermann Schloffer, an Austrian neurosurgeon, was the first to introduce transsphenoidal pituitary surgery in 1907 by the superolateral nasoethmoidal approach (2). In 1909, H. Cushing took the approach a step further, demonstrating the superiority of the sublabial, transseptal and transsphenoidal approaches; subsequently, in the

1960s, J. Hardy was the pioneer who routinely combined the use of televised radiofluoroscopy, optical magnification with the surgical microscope, and the use of microsurgical techniques in his approach (3-6). At the beginning of the 2000s, the post-operative outcomes of certain hospitals created a trend towards the use of the transnasal transsphenoidal approach as it is currently known, with credit given to E. Laws, who demonstrated a series of >6,000 patients who were operated on using that approach (3-7).

The microsurgical transsphenoidal (MST) technique (either sublabial or transnasal) was the gold standard approach for pituitary surgery. Each approach has its advantages and disadvantages. In the 1990s, the introduction of rigid endoscopes gave rise to the endonasal endoscopic transsphenoidal (EET) approach (8-13). The EET approach was not instantly adopted by the majority of neurosurgeons. Notwithstanding, the endoscopic systems evolved and, along with the introduction of extended endoscopic approaches and improved methods of anterior cranial base reconstruction, such as the Hadad-Bassagasteguy flap, led to the utilization of the EET approach by more neurosurgeons (14-16).

The currently available literature includes a plethora of meta-analyses and actual studies providing strong evidence that supports the superiority of the ETT over the MST approach (17-21). Pioneers of the EET approach, such as Jho and Carrau (22,23) in their early reports, emphasized the advantages of their methods, such as the greater panoramic view during the surgery, a more rapid post-operative recovery, and the avoidance of nasal packing.

The study by Gao *et al* also underlined the better view inside the sellar region and the lesser trauma to the tissues, while they demonstrated similar results compared to the widely utilized sublabial approach (17).

The learning curve of the EET technique was one of the main reasons why many neurosurgeons treated this technique as an adjunct and did not use this as a replacement of the MST approach in the late 1990s (24). Furthermore, with the exception of the double-blind randomized controlled trial by Jain *et al* (24), to the best of our knowledge, there is only a small number of studies directly comparing the two techniques (25), which does not allow for a confident verdict. Thus, it could be argued that there is no clear superiority of one of the methods to the other.

The aim of the present study was to compare the outcomes of pituitary macroadenomas operated using the EET approach by a team comprised of two young consultants with those operated by a team of senior neurosurgeons with extensive experience in using sublabial MST pituitary surgery.

Patients and methods

The present study examined a series of 20 patients who underwent pituitary macroadenoma resection at the Nicosia General Hospital (Nicosia, Cyprus) between May, 2004 to January, 2021. The patients were separated into two groups as follows: The first group included the 10 last patients operated by the former neurosurgical team, composed of neurosurgeons with 20 to 30 years of experience in using the MST approach. The second group, included the first 10 patients that were operated by the current pituitary-surgery team, comprised of an otolaryngologist and a neurosurgeon with 6 and 4 years of experience in endoscopic pituitary surgery, respectively.

Data for patient demographics, the date of the surgery, the surgeon and surgical approach (sublabial microscopic or endonasal endoscopic), late cerebrospinal fluid (CSF) leak, tumor recurrence, the duration of hospitalization or re-hospitalization in the case of redo, vision status pre- and post-operative, intra-operative complications, miscellaneous complications, lumbar drainage insertion or not post-operatively, and peri-operative mortality were all collected retrospectively. Pituitary hormones were assessed pre- and post-operatively using clinical and biochemical data. The abnormal function of the axis was defined as biochemical data outside reference values for the respective hormone or in the case of patients that were already on substitution therapy. The intact function was defined in the case of hormone levels within the normal range. The patients in the MST approach group underwent the standard Hardy method (Fig. 1). An incision was performed, the vomer was removed, and the sphenoid sinus was accessed. Entering the sphenoid sinus, the floor of the sellar region was opened, revealing the hypophysis. The post-operative radiological evaluation is depicted in Fig 2.

For the EET approach group (Fig. 3), a combination of 0˚, 30˚ and 45˚ rigid endoscopes were utilized to ensure adequate exposure and visualization during tumor removal. The tumor bed was filled with abdominal fat, the anterior wall of the sphenoid sinus was reconstructed, and the watertight closure was ensured using a triple layer of artificial dura, tissue glue, and rhino-septal mucosal flaps. The follow-up of the patients with a magnetic resonance imaging (MRI) and evaluation in the outpatient clinic was similar in both groups at 1 month post-operatively, 6 months post-operatively and once annually (Fig. 4).

All surgical records were retrieved from the database of the hospital and accessed in an anonymous manner using unique code identifiers. The Institutional Review Board (IRB) of Nicosia General Hospital, Cyprus approved the study (IRB no. ΕΕΒΚ ΕΠ 2019.02.158). The study was in line with the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000).

Results

The patient demographics and clinical data, including surgical outcomes, are summarized in Table I. The first group of surgeries were performed between 2004 and 2015, and the patients were followed-up post-operatively for 1 month, 6 months, and annually for 5 years post-operatively. The male to female ratio sex ratio in the MST group was 7:3, while the mean age was 59.9±13.1 years.

The macroadenomas in the MST group were two prolactinomas, one growth hormone (GH)-secreting adenoma causing acromegaly, and two tumors that caused panhypopituitarism, while four patients had normal hormone levels. Finally, 1 patient had pituitary apoplexy. The patients with prolactinomas required surgery due to an acute loss of vision. In total, 3 patients required post-operative hormone replacement; specifically, the patient with apoplexy at presentation and the ones with panhypopituitarism.

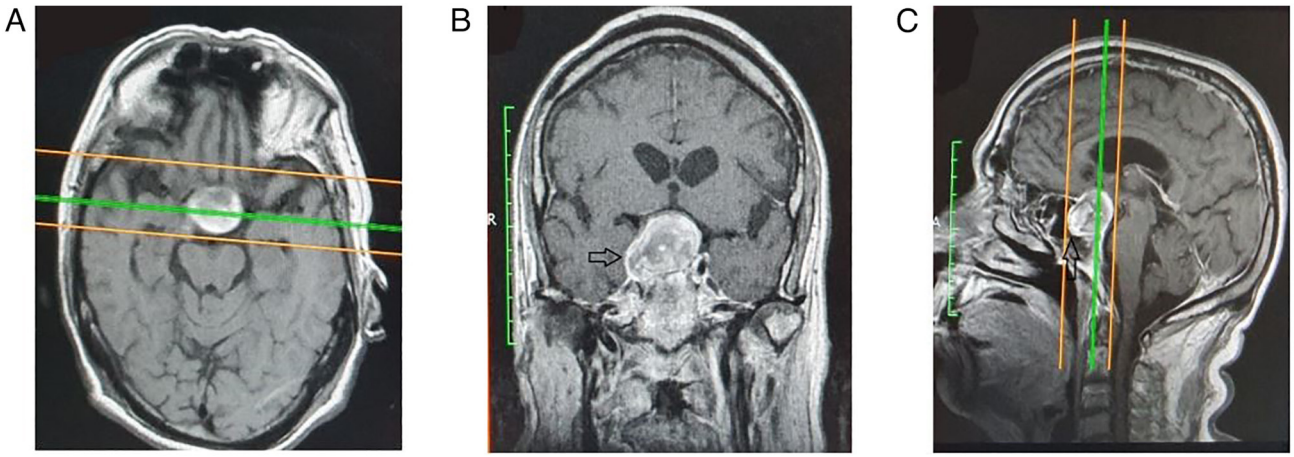

Figure 1. Pre-operative (MST approach) contrast enhanced T1 magnetic resonance image. (A) A large pituitary adenoma is depicted in the axial cut. (B) Coronal cut in the same patient. Note the lateral extension to the Rt cavernous sinus (arrow). (C) In the sagittal cut, the erosion/expansion in the sphenoid sinus (arrow) can be seen.

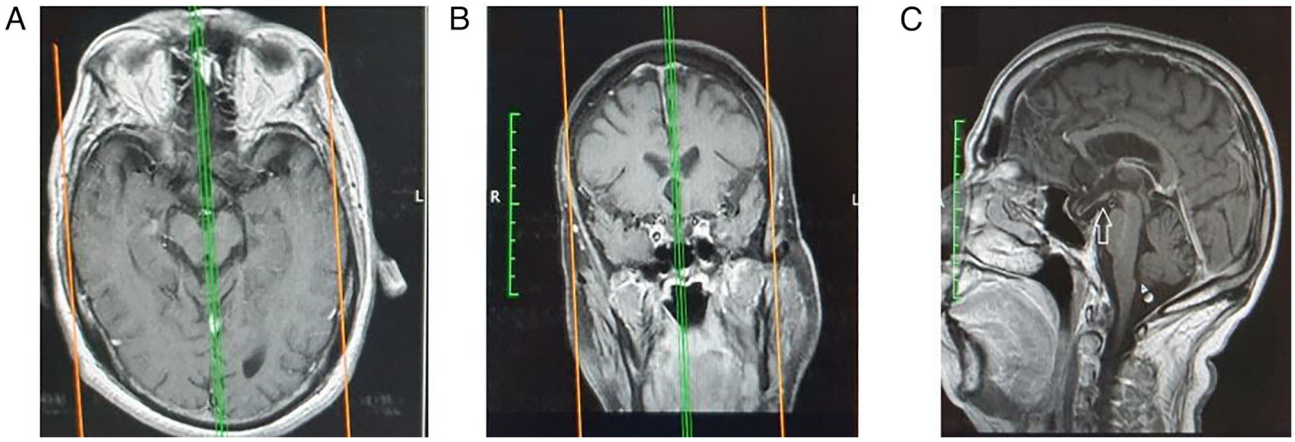

Figure 2. Post-operative (MST approach) contrast enhanced T1 magnetic resonance image following the microscopic sublabial approach. (A) There are no tumor remnants. (B) The part of the tumor inside the Rt cavernous sinus is removed. (C) The pituitary stalk (arrow) was decomposed during the surgery.

At presentation, visual deficits were reported in half of the patients. Of these 5 patients, 4 patients recovered completely, while 1 patient remained with a stable visual deficit (bitemporal hemianopia, which was initiated 2 days prior to his arrival at the hospital). Intra-operative complications included two cases of CSF leak and one case of intra-operative bleeding.

The mean duration of hospitalization in the MST group was 12.6±13.1 days (range, 5-48 days). In this group, 1 patient had an extensive intra-operative cavernous sinus hemorrhage, which led to the termination of tumor removal by the surgeons. The patient required 48 days of hospitalization; the hematoma was subsequently resolved, while he did not undergo a re-operation for the residual tissue. Additionally, 2 patients required secondary hospitalization. The first patient required a further 9 days of hospitalization and was the only one that required lumbar drainage. The other patient remained in the hospital for a total of 22 days. The latter patient also required a redo operation 14 years later for a recurrence, which was performed using a transcranial approach. Total tumor removal was achieved in 7 patients (70%), and in the remaining 30% of patients, a subtotal resection was performed. No deaths were reported in the MST group. In the EET group, the surgeries were performed between 2017 and 2021. The sex male to female ratio was equal (5:5), and the mean patient age was 54.6±12.0 years. The macroadenomas in this group were two prolactinomas and two GH-secreting adenomas. In total, 3 patients from the latter group had normal hormone levels, while 2 patients presented with pituitary apoplexy. The patients with prolactinomas, similarly to the patients of the MST group, were operated on due to acute vision disturbance at presentation. In addition, 2 patients required permanent hormone replacements post-operatively.

Half of the patients reported visual deficits at presentation, although their vision significantly improved after the surgery. A small residual tumor was observed in 1 patient in the EET group and this patient has remained stable during the follow-up period. The mean duration of hospitalization was 12.4±7.9 days (minimum, 7 days; maximum, 33 days).

The complications in the EET group included 3 patients who had CSF leak intra-operatively. The intra-operative meningoplasty was sufficient in one of the patients, while the other 2 patients exhibited a late CSF leak. These patients under-

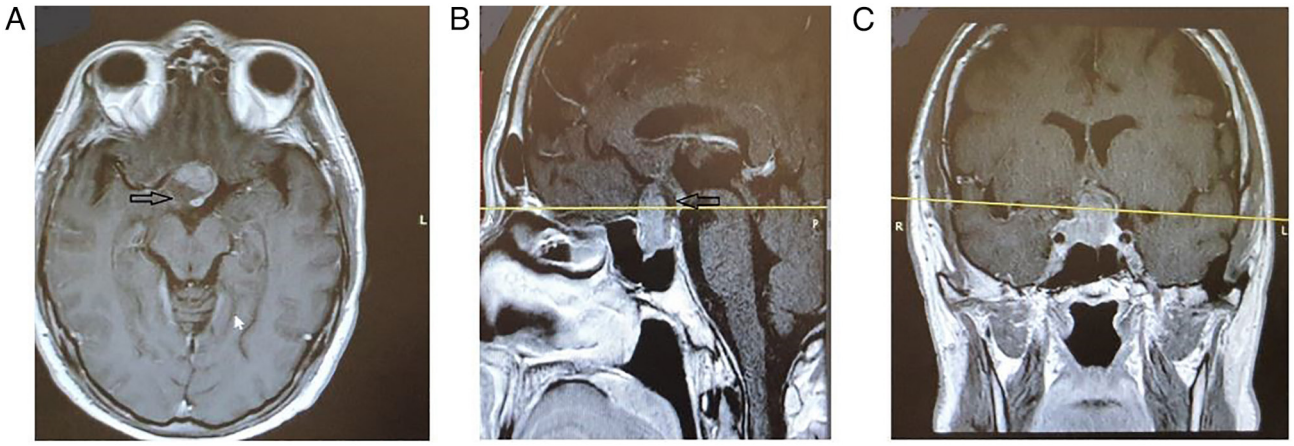

Figure 3. Pre-operative (EET approach) contrast enhanced T1 magnetic resonance image. (A) In the axial cut the tumor was enhanced following gadolinium infusion. Note the low magnetic signal area (arrow), representing hemorrhage due to apoplexy. (B) Sagittal cut in the same patient. The low magnetic signal area in the dorsal part of the tumor (arrow) was caused due to hemorrhage inside the tumor. (C) In the coronal cut, the cranial supra-sellar extension of the tumor compress significantly the optic chiasma.

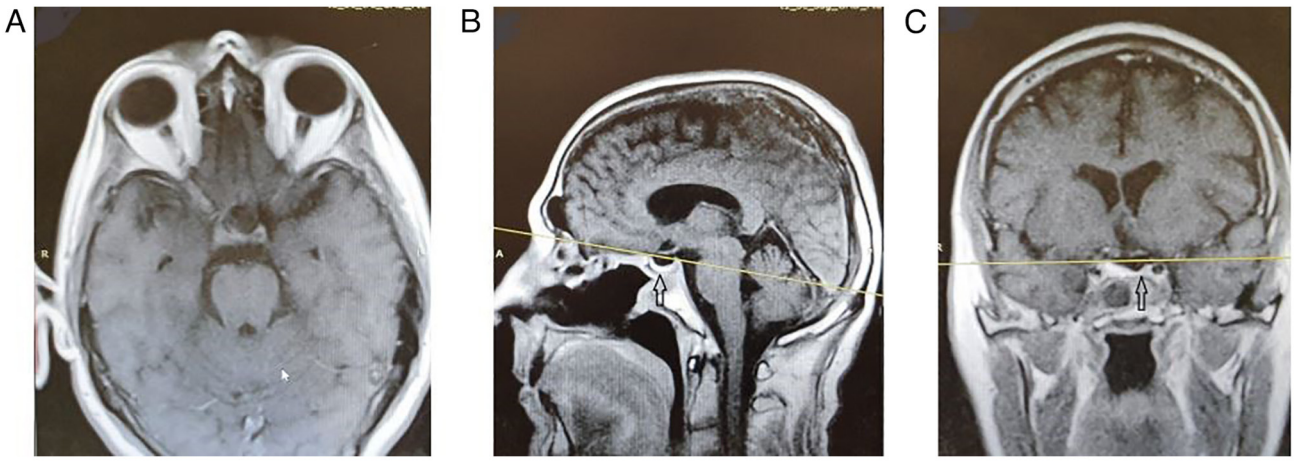

Figure 4. Post-operative (EET approach) contrast enhanced T1 magnetic resonance image following the endoscopic endonasal approach. (A) No residual tumor is depicted. (B and C) Note the meningoplasty grafts in the skull base (arrows). (C) The optic chiasma is free of compression.

went an endoscopic meningoplasty, while in one of the latter cases, the use of a lumbar drain was necessary. Ultimately, the CSF leak was resolved. Ultimately, the CSF leak was resolved. In the EET group, one death was reported; however, this was not associated with the procedure per se. This patient was admitted with an acute visual deficit. The macroadenoma was identified; however, due to a respiratory infection, the surgery was postponed. When the patient recovered, the surgery was performed using an EET approach. On the 5th day post-operatively, the patient developed a recurrence of the respiratory infection, followed by sepsis, admission to the intensive care unit, and ultimately death.

The follow-up of the patients with an MRI and evaluation in the outpatient clinic was similar in both groups, namely 1 month post-operatively, 6 months post-operatively, and once annually.

Discussion

In the past, only a small number of studies that compared the efficacy of EET vs. MST were available. In these studies, no clear recommendation for which approach should be used was made (21,25,26).

The systematic review and meta-analysis by Goudakos *et al* (26) 10 years ago concluded that due to the subjectivity of the outcomes, the lack of standardized protocols, the short follow-up period of the patients and the retrospective nature of the studies, no clear verdict upon whether the EET approach was superior to MST could be stated. The latest meta-analysis promotes the superiority of EET compared to MST in terms of fewer complications, larger tumor removal, and less operative time (18,21,25-29). Other studies promote the superiority of EET compared to MST in terms of fewer complications, improved tumor removal and a decreased operative time (18,28,29).

The present study, using a case series of 20 patients, demonstrated that EET could provide equal surgical outcomes when applied by surgeons with a relatively brief experience compared to extensively experienced neurosurgeons who use the MST approach for treating a long list of microadenomas and numerous macroadenomas.

Table I. Demographic and clinical data of the patients in the sublabial and endonasal groups.

Parameters	MST group	EET group
No. of patients	10	10
Mean age, years	59.5±13.1	54.6±12.0
Sex		
Male	7 (70%)	5 (50%)
Female	3 (30%)	5 (50%)
Pituitary function pre-operatively		
Normal	4 (40%)	3 (30%)
Prolactinoma	2 (20%)	2 (20%)
Apoplexy	1 (10%)	2 (20%)
Acromegaly	1 (10%)	2 (20%)
Panhypopituitarism	2 (20%)	0
Hypocortisolism and hypothyroidism	0	1 (10%)
Hormone Replacement Post-operative	3 (30%)	2 (20%)
Vision Status		
Normal	5 (50%)	5 (50%)
Deficit pre-operative	5 (50%)	5 (50%)
Improvement post-operative	4 (80%)	5 (100%)
Recurrence and redo	1 (10%)	0
Late leak	2 (20%)	2 (20%)
Primary hospitalization (days)	12.6±13.1	12.4±7.9
Secondary hospitalization	2 (20%)	0
Intra-operative complications	3 (30%)	3 (30%)
Miscellaneous complications		
None	10 (100%)	8 (80%)
Pneumonia	0	1 (10%)
Sepsis	0	1 (10%)
Gross tumor removal		
Residual	3 (30%)	1 (10%)
Total	7 (70%)	9 (90%)
Lumbar drain	1 (10%)	1 (10%)
Mortality	0	1 (10%)

MST, microscopic sublabial transsphenoidal; EET, endoscopic endonasal transsphenoidal.

Additionally, using EET, a 90 vs. 70% gross tumor removal was achieved compared with the MST group. The superior results of EET over MST are in agreement with the current literature (27,30-34).

Furthermore, the literature demonstrates that the duration of hospitalization is shorter or at least not longer in patients treated with EET compared to MST (26,32,34-37). The study by Razak *et al* (29) is one of the exceptions, in that it reports a more extended duration of hospitalization by EET vs. MST when it comes to non-functioning adenomas. In the series in the present study, there was a longer mean hospitalization duration, than that described in the meta-analysis by Gao *et al* (17). 12.4±7.9 vs. 5.1±0.7, respectively This can be explained by the fact that in the series in the present study, nasal packing was used in all patients post-operatively. This may violate the post-operative algorithm proposed by a number of authors (19,20,26); however, none of the patients in the EET group in the present study exhibited post-operative epistaxis, a common complication of the procedure (17).

The comparison of the present EET and MST series revealed similar intra- and post-operative characteristics, as presented in Table I, even though the EET group was operated by two young, yet well-trained surgeons. However, the literature frequently notes that the EET approach has a long learning curve (17,33,38). In the late 1990s, Ciric *et al* (39) mentioned that the significantly lower rate of morbidity and mortality of the EET approach compared to the MST approach could be achieved once a surgeon has performed 200 or up to 500 endoscopic endonasal pituitary surgeries. In the study by O'Malley *et al* (33), previously non-experienced neurosurgeons in endoscopic approaches demonstrated improved surgical outcomes after 17 surgeries using the EET approach. Additionally, in multidisciplinary skull base teams, the long experience of ENT surgeons in endonasal endoscopic surgery

offers an additional advantage; it may contribute to the more rapid mastering of the endoscopic approach (40). In the present study, the EET group demonstrated an improved post-operative visual improvement, and an improved post-operative hormonal status, while none of the patients required a re-do for persistent tumor or relapse. According to the study by Zaidi *et al* (41), the results were comparable between surgeons with 1 year of EET experience and highly experienced surgeons with 30 years of MST pituitary surgeries (41).

Several limitations of the presented study should be mentioned. The present study was retrospective in nature, which renders it prone to reporting and selection bias. The study presented all the cases that have been operated with the endonasal endoscopic approach and the last 10 patients operated with the MST technique by the previous team of neurosurgeons in the hospital. The follow-up in the EET group (maximum of 2 years) was shorter than that of the MST cases, as the MST group included older cases, while the EET group included recent cases, which is the reason for the difference in the follow-up period. Thus, a possible tumor relapse or long-term post-operative complications may not have been manifested in that time frame in the EET group. In addition, another limitation of the present study is that the population included in the two groups was not homogenous, as the sex ratio was not the same between the two groups, and the mean age in MST group was 59.5±13.1 and that in the EET group was 54.6±12.0. Finally, the small sample size of the series does not allow for a proper statistical analysis. A greater number of cases would allow for the presentation of more solid data.

In conclusion, the endonasal endoscopic approach for pituitary tumors tends to be established as the gold standard technique, as it is steadily gaining ground over the traditional microscopic approach. The learning curve is known to be long; however, in the case series in the present study, the new skull base team demonstrated equal or even better results than those of the past neurosurgical team of the same department. Colleagues who have yet to familiarize themselves with the endonasal endoscopic approach may thus be encouraged to learn and utilize this technique, provided that their center is staffed with an experienced team of skull base surgeons to intervene in an intraoperative complication.

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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

SC, AA, KF and GF conceptualized the study. KF and AA performed the surgeries in the EET group. VEG, AAF, KT, NT, PS, DAS, NM and PP made a substantial contribution to data analysis and interpretation, and wrote and prepared the draft of the manuscript. GF and KF analyzed the 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 Institutional Review Board (IRB) of Nicosia General Hospital, Cyprus approved the study (IRB no. ΕΕΒΚ ΕΠ 2019.02.158). The study was in line with the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000).

Patient consent for publication

Written informed was obtained from the patients for publication of the data and associated images.

Competing interests

The authors declare that they have no competing interests.

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