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REVIEW ARTICLE



Surgical approaches in pituitary neuroendocrine tumors

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ABSTRACT

Introduction. Pituitary neuroendocrine tumors account for 3.9-7.4/100.000 of central nervous system tumors in the Western world. They are particularly noteworthy, comprising 10-15% of all cases, with a higher prevalence in the 75-79 age group. In the Republic of Moldova, these tumors account for 34% of cases in postmortem examinations while remain an actual theme of discussion in the ENDO WHO congress and are regarded as a factor, which may influence the quality of life (QOL).

Material and methods. We have critically revised 66 literary sources, which were selected using the PubMed library after introducing the keywords “pituitary adenoma surgical approach”.

Results. The main surgical approaches were the transsphenoidal (transnasal, sublabial and endonasal) and transcranial (subfrontal unilateral/bilateral, fronto-lateral, fronto-temporal and median basilar) while the additional surgical approaches were designed for complicated and unusual pituitary neuroendocrine tumors and included combined versions, multiple surgeries or extended approaches. Numerous factors were influential for the selection of a surgical approach concerning the pituitary neuroendocrine tumors. They are not sensible for a type of pituitary neuroendocrine tumor according to the WHO classification while the size of a tumor may dictate its surgical approach.

Conclusion. Each surgical intervention requires a personalized approach and the critical thinking of the surgical team but most of them can be systematically considered before confronting the tumor in an intraoperative environment because most of the preoperative investigations are proven unreliable. There is no established superior surgical approach for each surgical intervention.

Keywords: pituitary neuroendocrine tumor; surgical approach, surgical complications.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

Unfortunately, there are no universal surgical approaches for each type of pituitary neuroendocrine tumors thus; a surgeon must be experienced in order to manage accurately such a surgical intervention.

The research hypothesis

There are a series of surgical approaches that may be efficient in different particular states of pituitary neuroendocrine tumors depending on their infiltration, size, and stage. The identification of these approaches is imperative.

The novelty added by the manuscript to the already published scientific literature

We have not found any studies in the literature that have integrated all the surgical approaches, both ordinary and unusual ones and have introduced a wider classification.

Introduction

Pituitary neuroendocrine tumors are a group of non-malignant tumors, which affects the central nervous system with a currently rising incidence in the Western world (3.9 to 7.4 cases per 100.000 in Belgium) [1]. They are being regarded as approximately 10-15% of the surgically treatable tumors of the central nervous system with a dominant incidence for the age group of 75-79 years [2]. The rate of this pathoanatomical structure was of 60% in Romania and of 34% in the Republic of Moldova in a study poll collected during necropsy [3]. The weight of a normal pituitary gland is approximately 0.5-1 g and its diameter of up to 1 cm [4].

The nomenclature of this pathological formation along with its classification have undergone significant changes over time. According to the ENDO3 WHO 2004, we could have differentiated the typical adenoma, atypical adenoma, and carcinoma. The ENDO4 WHO 2017 has come with an update on this matter considering only adenoma and carcinoma while the CNS5 WHO 2021 changed the nominal terminology of adenoma for pituitary neuroendocrine tumor remaining with the second type – carcinoma. Finally, the last known conference regarding this scientific question which is ENDO5 WHO 2022 and has agreed with the before mentioned, adopting the terminology of pituitary neuroendocrine tumor and carcinoma [5].

The main clinical classification that is indexed by the World Health Organization (WHO) in 2017 regards the growth factors and the hormones that reside in their target cells [6, 7].

The NR5A1 gene encodes the steroidogenic factor 1 (SF1) which regulates the differentiation of the cells which produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH), the POU1F1 gene encodes the pituitary transcription factor 1 (PIT1) which will induce the differentiation of the cells responsible for the growth hormone (GH), prolactin (PRL) and thyroid stimulating hormone (TSH) secretion and the TBX19 gene will encode the T-box transcription factor (TPIT) that will in turn induce the differentiation of the cells that will synthesize adrenocorticotropic hormone (ACTH) [6]. Estrogen receptor α (ER- α) and estrogen receptor β (ER- β) are key regulators of the lactotroph and gonadotroph tumor cells and are responsible for the hormone secretion and gonadotroph cell proliferation and apoptosis [8]. This receptor is notorious in breast cancer pathological mechanisms and has a major clinical value in its diagnosis [9]. Mutations of the transcription factor GATA2 are required for the development of the gonadotroph and thyrotroph pituitary neuroendocrine tumors [10, 11]. The estrogen receptors (ERs) and the GATA2 transcription factor have no tumoral type assigned but they may be involved indirectly in the clinical classification [8, 10].

The following pituitary neuroendocrine tumor types can be considered: somatotroph (PIT1 pathway), lactotroph (PIT1 and ER- α pathways), thyrotroph (PIT1 and GATA2 pathways), corticotroph (TPIT pathway), gonadotroph (SF1, GATA2, ER- α and ER- β pathways), null cell pituitary neuroendocrine tumor (no pathways), plurihormonal types

(usually somatotroph, lactotroph and thyrotroph: PIT1 pathway) and double pituitary neuroendocrine tumor (lactotroph and corticotroph: PIT1 and TPIT pathways) [2, 7, 8].

Most of the lactotroph tumors are managed using pharmacological methods while the rest of the tumors need surgical approach [2]. An exception for the aforementioned are the pituitary carcinomas which are metastatic tumors that have no protocols designed for their management and are usually resistant to pharmacologic treatment options [12].

Pituitary neuroendocrine tumors can be classified according to their size. Thus we may mention the microadenomas (<10 mm), macroadenomas (\geq 10 mm) and gigantic adenomas (\geq 40 mm) [13]. The proportion of these formations is 60% for microadenomas and 40% for macroadenomas [14].

Internationally, surgical strategies for pituitary neuroendocrine tumors are evaluated both historically and in terms of future perspectives. The aim is to provide neurosurgical patients with the most effective intervention, leading to an improved quality of life postoperatively.

Material and methods

A randomized literature study was conducted on 06.08.2023-22.08.2023 in order to identify randomized clinical trials, meta-analyses and review articles. The search was conducted using the PubMed library.

After introducing the keywords “pituitary adenoma surgical approach” we have selected the first 100 scientific articles from which we considered relevant to the topic only 45 sources. Additional 21 sources were studied independently without applying any search protocol, being collected manually. Overall, there were studied 66 literary sources.

We have studied all the known nomenclature considerations for the classical term of “pituitary adenoma” using the most recent publications in order to avoid a gap of terminology query [5].

The revised sources were selected using the principles that were described in the specialty literature.

Results and discussions

Historical aspects. The literature reports state that the first adenectomy was realized in 1889 but was reported only in 1906 using the transcranial subfrontal approach [15], while the first documented report of this intervention dates back to 1892 with a transcranial subtemporal approach [16]. Schloffer was the first to use the alternative transsphenoidal approach in order to manage a pituitary neuroendocrine tumor in 1907 and Hirsch extended this method by using a nasal speculum in 1910. Dandy still pioneered the transcranial method in 1918 [15], while Hardy has seen the progressive potential in augmenting the transsphenoidal route in 1960 by adding sophisticated technologies like illumination [17]. The most recent advances included the addition of technologies like intraoperative magnetic resonance imaging [18, 19], optical coherence tomography [20], fluoroscopy [21] and neuronavigation using preoperative CT or MRI findings [19, 22, 23].

Main surgical approaches. There are two surgical routes – the transcranial and transsphenoidal one (Table 1) [24]. Solari D. *et al* has elaborated in 2014 a more detailed classification of these two according to the instruments that were used or the incisions that has to be made. We differentiate the following transsphenoidal approaches: microsurgical and endoscopic which may have transnasal, sublabial or endonasal incisions. Transcranial approaches may be subfrontal (unilateral or bilateral interhemispheric), fronto-lateral, fronto-temporal [15] or median basilar [21]. The transsphenoidal routes were also considered by McEwen DR *et al.* in 1995 [4].

Table 1. Main surgical approaches in pituitary neuroendocrine tumors.

Transsphenoidal (microsurgical or endoscopic)	Transcranial
Transnasal	Subfrontal (unilateral or bilateral)
Sublabial	Fronto-lateral
Endonasal	Fronto-temporal
	Median basilar

Table 2. Additional surgical approaches in pituitary neuroendocrine tumors.

Combined	Multiple	Extended (transsphenoidal)	Extended (transcranial)
Transcranial / transcranial	Transcranial / transcranial	Anterior	Frontal
Transcranial / transsphenoidal	Transcranial / transsphenoidal	Posterior	Temporal
Transsphenoidal / transsphenoidal	Transsphenoidal / transsphenoidal	Lateral	Orbito-zygomatic
		Ethmoidal	Transcortical-transventricular
		Antero-posterior	

Practical considerations. The transnasal transeptal approach can be made bilaterally and is proven to have a better preservation of olfactory mucosa functionality [36] compared to the single-nostril endoscopic transnasal transsphenoidal approach [37]. Conditions like tobacco usage and prior naso-sinusal infections are factors, which may induce a diminished olfactory function in postoperative settings [37]. The transnasal route includes 3 phases: the endonasal / transsphenoidal, the resection phase, and the skull base reconstruction phase [38].

The sublabial transsphenoidal approach is highly traumatic and has great risks for postoperative complications or unneeded lesions of the nasal septum, gums, and lips along with a nose deformation [39]. The endoscopic endonasal transsphenoidal approach has a better outcome prediction than the endoscopic transnasal transsphenoidal one [40]. Contraindications for the transsphenoidal approach: anterior or medium cranial fossa extensions, lesions with intense vascularization, lesions extended above the sella turcica, recurrent tumors, and the anatomical variability of the internal carotid artery [4].

The Knosp and modified Knosp scale can have a good prognosis for the surgical approaches; while the Hardy-Wilson scale is not statistically significant, [41] and the Knosp scale along with the tumor dimension can be a good pre-

Additional surgical approaches. The following surgical approaches are essentially enhanced versions of the previously discussed methods thus making the interventions more complex, but with an increased rate of success (Table 2). Mehta GU *et al.* reported a mixed type that implied the usage of both microsurgical and endoscopic methods in 2017 [25]. Combined or multiple surgical interventions can be regarded as a separate entity because they are not routinely performed. We can differentiate the following combined approaches: transcranial / transcranial, transsphenoidal / transcranial and transsphenoidal / transsphenoidal while multiple surgical interventions are similar to the previous mentioned, but they are performed in multiple interventions [26]. Some incisions may be extended in order to give a larger view of the adjacent anatomical and anatomo-pathological structures. The transsphenoidal extensions are anterior (via tuberculum sellae and processus clinoides [27-29], posterior (subsellar via *diaphragma sellae*) [27, 30], lateral (transoculomotor triangle via sphenoidotomy) [31-33], ethmoidal [34] and combined (anterior and posterior) [32]. The transcranial extensions imply the frontal, temporal, orbito-zygomatic and transcortical transventricular ones [35].

diction factor for the surgical intervention complexity [42]. The only factor, which is reliable to determine recurrence risk, is the presence of the residual tumor after resection, while age, gender, infiltration, Knosp and Hardy-Wilson scales are not statistically adequate for that [16].

The microsurgical methods have a decreased rate of recurrence compared to the endoscopic ones (45% vs 70%) [26], while the invasive tumors require an endoscopic approach in order to have a favorable outcome [43]. If there is any aneurism surrounding the pituitary neuroendocrine tumor, then the combined endoscopic endonasal and bilateral transcranial subfrontal approaches may be of great use [44].

The transcranial approach is associated with significant pituitary dysfunction in the postoperative period and craniopharyngiomas result with diabetes insipidus more often than the pituitary neuroendocrine tumors [21]. Literature data state that this complication has an incidence of 2.5-20% [17]. An infiltration in the posterior cranial fossa is indicative for transcranial surgery [45].

The endoscopic endonasal approach is the most efficient in the excision of the calcium depositions on the capsule surrounding the pituitary neuroendocrine tumor [46] being also the first that is considered in any pituitary neuroendocrine tumor surgical intervention [45]. The tran-

scranial fronto-temporal approach can be dangerous for the lesion of the branches from the *plexus parotideus* [30]. An orbito-zygomatic extended approach may not be necessary when an orbital invasion is compatible [14].

The cerebrospinal fluid (CSF) leakage is diminished in the extended posterior transsphenoidal approach [27]. A nasoseptal flap (Hadad) can be made in order to preserve the tissues and to avoid the cerebrospinal fluid (CSF) leakage [17, 47] along with substitution using adipose tissue, connective tissue from fascia and osseous tissue [17].

In the pediatric population the most efficient approach was the transnasal transsphenoidal one with a marked decompression of the optic chiasm [48] and endoscopic methods are more preferred than the microsurgical ones [49]. The pediatric differential diagnosis is vital because most often they may be confounded with other pathological structures like craniopharyngiomas, Rathke cleft cysts, Langerhans cell histiocytosis, sarcoidosis and dermoid/epidermoid cysts [48, 49], while pituitary neuroendocrine tumors may be associated with more complex conditions like Carney complex, McCune Albright syndrome and multiple endocrine neoplasia type 1 [50]. The optical coherence tomography is a valuable tool for determination of the optic chiasm integrity after the resection of a pituitary neuroendocrine tumor [43]. Magnetic resonance imaging is not proven to be reliable for the determination of the pituitary neuroendocrine tumor consistency [51]. The “chop-sticks” method which implies a 3-instrument and 2-handed operatory technique is proven to reduce the postoperative morbidity [52].

Anatomical and anatomo-pathological considerations. The bones that are involved in the transnasal transsphenoidal approach may be variable in their positions and dimensions. Thus, the nasal septum may have a deviation on the left side in 23.1% cases, bilateral middle turbinate pneumatization in 19.2% cases, bilateral middle turbinate curvature in 7.7% cases, supraposition of the ethmoid sinus above the sphenoid sinus in 3.8% cases, vertical sphenoid fissure in 3.8% cases and internal carotid artery defects in 3.7% cases [53]. One study conducted by researchers from the Republic of Moldova observed a 30% anatomical variability of the Willis circle [54].

The pituitary neuroendocrine tumor may have a capsule that surrounds it from healthy glandular tissue. These capsules can be unique or can be patched in groups. Small tumors usually do not have capsules thus making them more difficult to spot using radiological methods [55]. Cerebral abscesses may coexist with the pituitary neuroendocrine tumors thus requiring their excision and placement of a drainage system [56]. Hemorrhage is not unusual in setting and will require extended versions of the surgical approaches [57]. An aneurysm may be present associated with the arterial branches surrounding the pituitary neuroendocrine tumor [44].

Double pituitary neuroendocrine tumors can require critical thinking in intraoperative settings [58]. The calcifications always adhere to the pituitary neuroendocrine tumor capsule [59].

A mutation in the BRAF gene (V600E) determines the development of a special state of tumor that is intermediary between the pituitary neuroendocrine tumor and craniopharyngioma [60]. Tumors which invade the cavernous sinus can be operated with an extended transsphenoidal approach with posterior ethmoidectomy but will determine transitory postoperative double-vision [34].

The gigantic pituitary neuroendocrine tumors have blood vessels originating from the infraclinoid portion of the internal carotid artery thus making an extended anterior approach risky and determining the necessity to use the transcranial approach [61, 62], while it has been proven that the transnasal transsphenoidal approach is efficient for most of these tumors [63] and they were also usually managed using endoscopic endonasal transsphenoidal approach. An infiltration in the 3rd ventricle was proven to be difficult in surgical management no matter the approach (transcranial or transsphenoidal) [45]. Schwannoma can be misdiagnosed as a pituitary neuroendocrine tumor if it is located adjacent to the sella turcica [64].

Predictions scales. The Knosp scale constitute 5 severity degrees. Grade 0: the tumor is medial to the medial tangential line; Grade 1: the tumor is between the medial tangential line and the intercarotid line; Grade 2: the tumor is between the intercarotid line and the lateral tangential line; Grade 3: the tumor is lateral to the lateral tangential line and Grade 4: the intracavernous portion of the internal carotid artery is completely covered in tumoral tissue. The modified Knosp scale includes Grade 3A: the tumor is above the intracavernous internal carotid artery and Grade 3B: the tumor is below the intracavernous portion of the internal carotid artery [41].

The Hardy-Wilson scale has the A-E severity degrees. Type A: suprasellar mass of <10 mm; type B: the tumoral mass reaches the 3rd ventricle and is 10-20 mm; type C: the tumoral mass is inside the 3rd ventricle and is 20-30 mm; type D: the tumoral mass extends above the Monro foramen and is >30 mm and type E: the tumoral mass is extending laterally [38].

Conclusions

The surgical approaches in pituitary neuroendocrine tumors have a historical continuity with regard of the constant improvements that are made in this field. Different conditions require a personalized approach and the skills of a trained neurosurgeon in order to choose the right surgical strategy. Preoperative clinical instruments are not always reliable thus requiring decisions that are made intraoperatively according to the previous experiences of the neurosurgical team. Most of the complications can be avoided if preventive measures are taken adequately. There is no proven superior surgical approach for each surgical intervention.

Competing interests

None declared.

Contribution of authors

DC drafted the manuscript and realized the literature search, VA designed the study and revised the manuscript

critically, SV drafted the manuscript and revised the manuscript critically, AD revised the manuscript critically.

Ethical statement

No approval was required for this study.

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