Original article

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Ultrasound Doppler examination in the surgical treatment of pituitary adenomas with cavernous sinus extension

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Objective: To determine the effectiveness of intraoperative Doppler ultrasound in the surgical treatment of pituitary adenomas with invasive parasellar growth into the cavernous sinus Knosp 3 and Knosp 4.

Material and Methods. During 2009–2017, 71 patients with pituitary adenomas (PA) with extension into the cavernous sinus Knosp 3 and Knosp 4 were retrospectively reviewed. According to the size PA were divided into pituitary macroadenomas, (from 10 to 40 mm) in 45 (63.4%) patients, and giant PA (over 40 mm) – in 26 (36.6%) patients. Cavernous sinus invasion Knosp 3 and 4 was identified in 47 (66.2%) and 24 (33.8%) patients respectively. Non-secreting PA - 43 (60.5%) patients and hormone-secreting PA - 28 patients (39.4%). Endoscopic endonasal trassphenoidal (EET) approach was used in all cases. Laterally expanded EET (LEEET) approach was used in 29 cases. Intraoperative Doppler ultrasound (IDUS) was used in 36 (51%) cases.

Results. Intraoperative Doppler ultrasound was used in cases of Knosp 3 extension in 23 (32.4%) cases and in Knosp 4 - in 13 (18.3%) cases. Gross total resection, including extension into the cavernous sinus using IDUS was achieved in 22 (62.7%) patients. In cases where IDUS was not used, gross total resection was achieved in 19 (52.7%) cases. In cases where the IDUS was not used, recurrence rate was 7.3%, with IDUS - 5%. Biochemical remission was achieved in 22 (78.6%) cases. Liquorrhea nasalis after surgery was observed in 6 (8.4%) cases, meningoencephalitis - in 1 (1.4%) case, oculomotor palsy -3 (4.2%) cases.

Conclusions. Intraoperative Doppler ultrasound is an informative method that provides safe resection of pituitary adenomas with cavernous sinus extension with a low level of possible postoperative complications.

Parasellar extension of Pituitary adenomas into the cavernous sinus Knosp 4 significantly reduces the possibility of gross total resection. However, the use of intraoperative ultrasound makes it possible to determine safe boundaries for manipulation both medially and laterally from the internal carotid artery, increasing the level of radicality and the duration of clinical remission.

Intraoperative Doppler ultrasound during endoscopic endonasal transsphenoidal surgery of pituitary adenomas with parasellar extension allows to identify the internal carotid artery in the tumor stroma with the existing changed skull base anatomy. Dura incision under intraoperative Doppler ultrasound reduces the risk of internal carotid artery injury.

Key words: *cavernous sinus; pituitary adenoma surgery; endoscopic surgery; intraoperative ultrasound*

Introduction

Cavernous sinus invasion in pituitary adenomas (PA) complicates surgical manipulations, increases the frequency of internal carotid artery (ICA) trauma and the risk of intraoperative CSF leakage, which involves to partial tumor removal. Therefore, cavernous sinus invasion affects the further management and prognosis of PA [1,2]. Considering the absence of bone side walls in the pituitary fossa, macro- and giant PA occurs mainly in the parasellar direction (6–10% of cases).

The development and integration of modern navigation systems have contributed to their use in cases of invasive tumor growth and loss of anatomical structures in the surgical field [3–5]. The use of modern neuronavigation techniques is becoming an integral part of surgery of PA with parasellar spread. However, most operations over PA are performed without using of portable navigation systems, based on the surgeon's experience and orientation in anatomical structures.

A large number of studies have shown the relationship between a decrease in the volume removal of PA and the extension of the tumor into the cavernous sinus [7–10]. The degree of invasion into the cavernous sinus is a factor that affects the radical removal of the tumor [11], another criterion is the intraoperative determination of critical anatomic

landmarks, which allows for safe removal of lateral extension of PA [13]. ICA injury remains one of the serious and fatal complications in transsphenoidal surgery (both microsurgery and endoscopy) [14,15]. The use of intraoperative Doppler ultrasound (IDUS) allows to detect the artery timely and prevent its injury during tumor removal [16]. Existing anatomical landmarks (nasal septum, choanae, sella turcica, paraclival ICA and opto-carotid resess) are usually sufficient for a properly oriented and safe approach to the tumor. However, in some cases, these landmarks can not be detected, especially in reoperated cases with significant infrasselar tumor growth [14,17]. Various navigation systems can be used to reduce the risk of ICA injury to determine safe access trajectory for standard and laterally extended transsphenoidal endoscopic approach (TEA). However, according to some researchers, IDUS is more effective method for intraoperative navigation and allows in real-time determine ICA position, to assess clear and safe boundaries of the dura mater incision [18–20].

Objective: To determine the effectiveness of intraoperative Doppler ultrasound in the surgical treatment of pituitary adenomas with invasive parasellar growth into the cavernous sinus Knosp 3 and Knosp 4.

Materials and methods

A multicenter retrospective study was conducted. The case history of 208 patients for the period from 2009 to 2017 with a diagnosis of PA was analyzed. The study involved 71 patients.

Patient acquisition criteria:

1. Patients with PA of any sex and age who underwent inpatient treatment at the Romodanov Neurosurgery Institute of National Academy of Medical Sciences of Ukraine, Institute of Otolaryngology named after Prof. O.S. Kolomiichenko of National Academy of Medical Sciences of Ukraine and Odessa Regional Clinical Hospital in the period from 2009 to 2017.

2. Invasive parasellar spread of the tumor into the cavernous sinus Knosp 3 and 4.

3. The diagnosis is verified histologically and / or with the help of neurovisual technologies.

Study design

Magnetic resonance imaging of the brain with targeted visualisation of the pituitary gland was performed in all patients, in 67 (94.3%) cases - MRI with intravenous paramagnetic contrast with gadolinium, if necessary - spiral computed tomography.

The size of PA was divided into macro-adenomas (10 to 40 mm) and giant pituitary adenomas (> 40 mm). To determine the extension of PA into the cavernous sinus the classification of E. Knosp et al. was used [6].

There were two study groups: with the use of IDUS - 36 (51%) cases and without the use of IDUS - 35 (49%). Intraoperative Doppler ultrasound was performed using Mizuho sensor 20 Hz. The effectiveness of IDUS for PA was evaluated. The choice of TEA type and the use of IDUS depended on the extension of PA into the cavernous sinus. In all observations TEA was used, in 29 - laterally extended TEA. Operations were performed using an endoscopy tower based on the HD-endoscope «Image-1HD» (Karl Storz, Germany). Rigid 4 mm Karl Storz endoscopes with viewing angles of 0 and 35° were used.

Follow-up of 71 patients was from 12 to 60 months, at average –25.4 months (2.1 years).

Characteristics of the study group

There were 42 men (59.2%) and 29 women (40.8%). Age of patients - from 18 to 72 years, average age - (48.24 ± 13.9) years.

In 71 patients there was the spread of PA into the cavernous sinus Knosp 3 and 4.

Macro-adenomas were diagnosed in 45 (63.4%) patients, giant PA in 26 (36.6%).

Medical history of the disease ranged from 3 to 240 months.

According to hormonal activity groups of hormonally inactive PA (43 (60.5%) patients) and hormonally active PA (HAPA) (28 (39.4%)) were identified. Somatomamotropinomas predominated (12 (42.8%)), there were slightly less PA with somatotropin (11 (39.3%)), the third place was occupied by prolactinomas -3 (10.7%), and 1 (3.6%) case - thyrotropic and adrenocorticotropic PA.

All patients gave written consent to the examination and use in research data from the medical history.

The study was approved by the Commission on Ethics and Bioethics of the Romodanov Neurosurgery Institute (Meeting Minutes No 3 of 06 June 2016).

Statistical analysis

Statistical data processing was performed using the statistical software package Statistica 10.0 StatSoft Inc. USA. All material was standardized, databased and subjected to statistical processing using methods of descriptive and non-parametric statistic. Pearson's criterion $\chi 2$ was used to compare the frequencies of independent categorical features in conjugation tables. Nonparametric criteria were used. The results were considered statistically significant when reaching the p-level of the criterion <0.05.

Results and discussion

In 36 (51%) cases, IDUS was used to determine ICA position in cases of cavernous sinus invasion Knosp 3 in 23 (32.4%) and Knosp 4 13 (18.3%) cases. Identification of ICA position is an important point in transnasal endoscopic surgery over PA with cavernous sinus extension ***(Fig. 1).*** Once the ICA has been identified, safe manipulations can be performed both medially and laterally from the ICA, preventing its possible injury.

M. Rutkowski and G. Zada [21] reported their experience in the treatment of 86 patients with HAPA, who underwent PA surgery using TEA, in 21% of cases cavernous sinus invasion was observed. Of these invasive PA, the total removal was achieved in 33.3%. A. Ajlan et al. [22] studied a cohort of patients with 176 PA, mostly treated with TEA, and found that 23% of patients had cavernous sinus invasion, which reduced the number of complete tumor removed to 47%. Among our observations, the invasion of the cavernous sinus Knosp 3 and 4 was detected in 47 (66.2%) and 24 (33.8%) patients, respectively.

MA. De Paiva Neto et al. [23] reported that giant PA with cavernous sinus invasion Knosp 3 and 4 are almost impossible to remove completely. The number of radically removed PA was 9.6%. With the use of IDUS radical tumor removal in PA with cavernous sinus extension was achieved in 23 (63.9%) patients. In the group of patients without the use of IDUS, the number of totally removed PA was 18 (51.4%).

The use of IDUS ensures the safety of manipulations in the removal of PA infra- and parasellarly, increases the rate of radically removed tumors ***(Table 1)*** and increases the recurrence-free period. In cases where IDUS was not used, the recurrence rate was 7.3%, using IDUS - 5% (McNemar Chi-square (B / C) = 7.56; p = .005) ***(Fig. 2).***

The use of IDUS in PA surgery with parasellar spread was 55.6% (36). This allowed to increase the proportion of patients with radical removal to 57.8%. The onset of recurrence of PA without the use of IDUS was 0.24 (odds ratio - 2.24 [0.36–13.78], relative cumulative risk - 2, AUC = 0.6). When using this technique, the chance of recurrence is 0.05 (see ***Fig. 2***).

Among patients with HAPA, there is a tendency to cavernous sinus invasion in PA with mixed secretion: Knosp 3 - 7 (15%) patients, Knosp 4 - 5 (21%). Somatotropic PA with cavernous sinus extension Knosp 3 and 4 occurred in 8 (72.7%) and 3 (27.3%) patients, respectively. The least invasive HAPA were prolactinomas, thyrotropic and adrenocorticotropic PA in which the cavernous sinus extension was observed in 8, 4 and 2% of patients ***(Fig. 3).***

Biochemical remission (BCR) in invasive HAPA with extension into the cavernous sinus is difficult to achieve. Thus, V. Briceno et al. [20] in a large meta-analysis of 14 studies examined the possibility of achieving BCR in 972 patients with HAPA who underwent surgical removal. They found that only 48% of cases could obtain BCR. M. Rutkowski and G. Zada reported the achievement of BCR in invasive PA in 39% of patients [21].

In our series BCR was achieved in 22 (78.6%) cases ***(Table 2***), in particular with Knosp 3 - in 15 (83.3%) patients, and Knosp 4 - in 7 (70%) cases.

The achievement of BCR is influenced by PA extension into the parasellar region, namely cavernous sinus extension, suprasellar extension and into the the 3rd ventricle. The extension of HAPA into the 3rd ventricle was observed in 3 (9.4%) patients, of which only 1 achieved BCR.

According to the literature, complications in PA surgery with invasive parasellar extension and invasion into the cavernous sinus occur in 10% of cases. Hypopituitary syndrome is observed in less than 10% of cases, CSF leak - 13.9%, oculomotor disorders - in 6%, ICA injury - in 2% of cases [21,24–26].

CSF leak is one of common complications after TEA over PA. In our series CSF leak occurred in 5.8% of cases. Overall cases (71 patients) with macro- and giant PA with extension into the cavernous sinus, the frequency of postoperative CSF leak was 8.4%. Previously, these patients underwent sella reconstruction using multilayer technique with a fragment of fascia lata and naso-septal

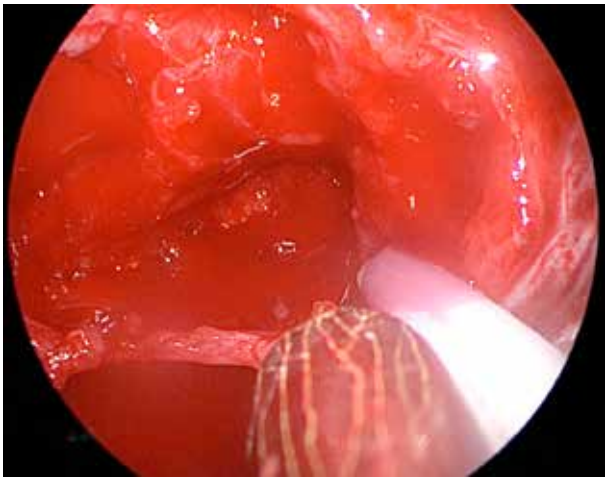

Fig. 1 IDUS: 1 - intracavernous portion of ICA; 2 - diaphragm of the Turkish saddle

Table 2. The results of surgical treatment of pituitary adenoma with extension into the cavernous sinus depending on the use of IDUS

Indicator	with IDUS (n=36)		without IDUS (n=35)	
	Abs.	%	Abs.	%
Extension into the cavernous sinus:				
• Knosp 3	23	63,9	24	68,6
• Knosp 4	13	36,1	11	31,4
Radicality:				
• total	23	63,9	18	51,4
• subtotal	8	22,2	13	37,1
• partial	6	16,6	4	11,4
Recurrence of PA in total removal	1	4,3	4	22,2
The type of TEA:				
• standard	20	55,6	22	62,9
• extended	16	44,4	13	37,1
Complications:				
• liquorrhea nasalis and meningitis	6	16,7	1	2,9
• oculomotor disorders	3	8,3	–	–

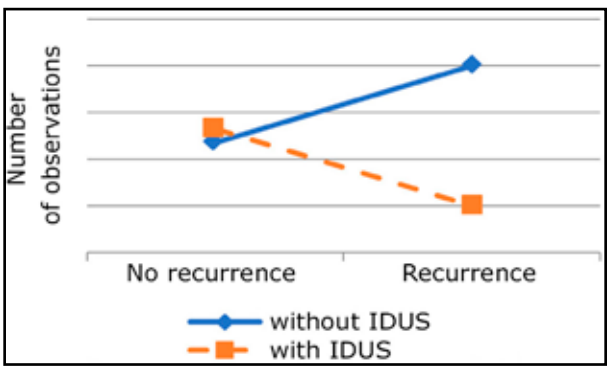

Fig. 2. The effect of using IDUS on the radical removal of pituitary adenomas

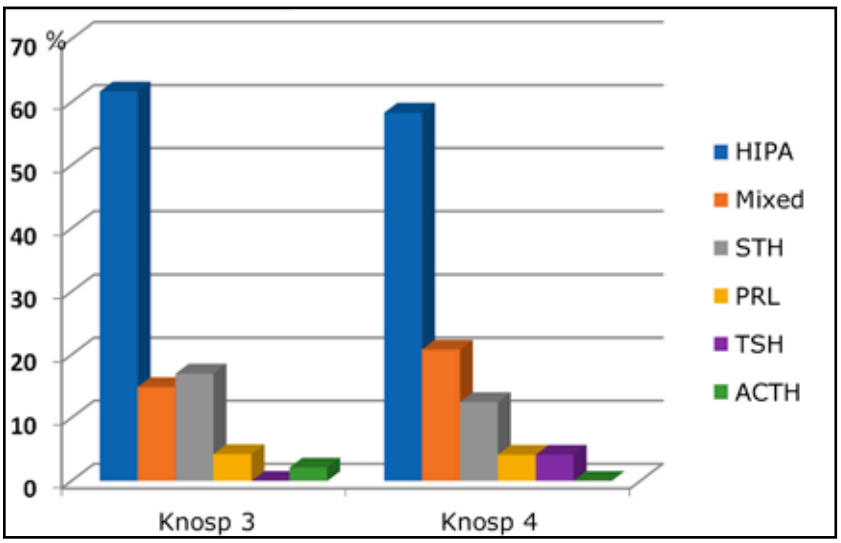

Fig. 3. Distribution of observations of hormonal activity of pituitary adenomas depending on the degree of extension into the cavernous sinus: HIPA - hormonally inactive adenomas; PRL - prolactinoma; STH - somatotropic hormone; TSH - thyroid-stimulating hormone; ACTH -adenocorticotropic hormone

Table 2. The results of surgical treatment of hormonally active pituitary adenomas

Type of HAPA	CRR			
	achieved		not achieved	
	Abs.	%	Abs.	%
PRL (n=3)	0	–	3	100
STH (n=12)	11	100	0	–
ACTH (n=1)	1	100	0	–
TSH (n=1)	1	100	0	–
Mixed (n =12)	9	75	3	25
Total	22	78,6	6	21,4

Note: PRL - prolactinoma; STH - somatotropic hormone; TSH - thyroid stimulating hormone; ACTH - adenocorticotropic hormone.

flap. Treatment of CSF leak was surgical in 5 patients. Endoscopic endonasal revision was performed, the location of the CSF leakage was detected, and the fluid fistula was repaired by fascia lata and naso-septal flap reposition. In one case of postoperative CSF leak was treated by lumbar drainage during for 7 days. Meningoencephalitis developed in one patient. The treatment was with medications (antibacterial therapy).

Oculomotor disorders after surgery were mostly observed in patients with cavernous sinus extension Knosp 4 (2 cases). In the group of patients where IDUS was not used, oculomotor disorders were not observed after surgery ($p < 0.05$). In our opinion, this is due to more aggressive approach during the surgery, manipulations in cavernous sinus in cases of tumors that were invasive and had a fibrous structure. In addition, these complications were observed in cases of HAPA, which have a more invasive type of growth than hormonally inactive. ICA injuries were not observed in our study.

Conclusions

1. Intraoperative Doppler ultrasound is an informative method that provides safe removal of pituitary adenomas with cavernous sinus extension with a low level of possible postoperative complications.

2. Cavernous sinus extension Knosp 4 significantly reduces the possibility of radical tumor removal, but the use of Doppler ultrasound allows to determine safe limits for manipulation both medially and laterally from the internal carotid artery, increasing the level of radicality and clinical remission length.

3. Ultrasound intraoperative Doppler imaging during transsphenoidal endoscopic surgery over pituitary adenomas with paracellular extension allows to identify the internal carotid artery in the tumor stroma with changed skull base anatomy. Dura incision under Doppler control reduces the risk of internal carotid artery injury.

Disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical norms

All procedures performed on the patient during the study meet the ethical standards of the Romodanov Neurosurgery Institute of National Academy of Medical Sciences of Ukraine, National Ethics Committee and Helsinki Declaration of 1964 and its later amendments or similar ethical standards. The study was approved by the Commission on Ethics and Bioethics of the Romodanov Neurosurgery Institute (Meeting Minutes No 3 of 06 June 2016).

Informed consent

Informed consent was obtained from each of the patients.

Financing

The study was performed without sponsorship.

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