Tampereen yliopisto

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SURGICAL OUTCOMES IN PATIENTS WITH PITUITARY ADENOMAS OPERATED TRANSCRANIALLY IN TAMPERE UNIVERSITY HOSPITAL BETWEEN 1996-2015

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TIIVISTELMÄ

Aino Virkamäki: Kraniotomiateitse leikattujen aivolisäkekasvainpotilaiden leikkaustulokset Tampereen yliopistollisessa sairaalassa vuosina 1996—2015
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Noin 90 % kaikista aivolisäkkeen kasvaimista on hyvänlaatuisia. Suurin osa aivolisäkekasvaimista leikataan nenän kautta eli transsfenoidaalisesti, mutta osa vaatii kallonavauksella eli kraniotomiateitse tehdyn leikkauksen. Suuret, invasoivat kasvaimet aiheuttavat aivolisäkkeen toiminnan häiriöitä ja painavat näköhermoa vaarantaen näön. Tutkimuksemme tavoitteena oli tutkia leikkaustuloksia kraniotomiateitse leikatuilla potilailla, ja arvioida syitä tämän leikkaustekniikan valitsemiselle aikana, jolloin transsfenoidaalinen leikkaustapa on aivolisäkekasvainten hoidon kultainen standardi.

Tutkimuksemme on retrospektiivinen tutkimus Tampereen yliopistollisessa sairaalassa vuosina 1996–2015 aivolisäkekasvaimen vuoksi leikatuista potilaista. Aineisto kerättiin Tampereen yliopistollisen sairaalan potilasrekistereistä. Demografiset ja radiologiset tiedot kerättiin. Lisäksi tiedot leikkausten tuloksista sisältäen näkötutkimukset, aivolisäkkeen toiminta ja leikkauskomplikaatiot arvioitiin.

Aineistomme koostui 27 potilaasta. Heistä 63,0 % (n = 17) oli miehiä. Miesten keski-ikä oli 45 vuotta ja naisten 53 vuotta. Aivolisäkekasvainten maksimimitan keskiarvo oli 39,5 mm (20–80 mm). Makroadenomien osuus kasvaimista oli 60,9 % (n = 14), ja 39,1 % (n = 9) kasvaimista oli jättiadenomia. Leikkaustavan valitsemiseen vaikuttivat kasvaimen sijainti ja suuri koko 59,3 % (n = 16) tapauksista. Näön heikkenemistä esiintyi 56,6 % (n = 15) potilaista ennen leikkausta ja aivolisäkkeen vajaatoimintaa 37,0 % (n = 10) potilaista. Vain 14 potilaalla oli tietoja näöstä leikkauksen jälkeen. Heistä 92,9 %:lla (n = 13) oli heikentynyt näkö leikkauksen jälkeisessä arviossa. Yhdellä potilaalla, jolla oli ennen leikkausta normaali näkö, oli normaali näkö vielä leikkauksen jälkeen. Aivolisäkkeen vajaatoimintaa esiintyi 11,1 %:lla (n = 3) leikkauksen jälkeen.

Kraniotomia on leikkaustapana turvallinen matalan kuolleisuuden takia. Tutkimuksemme mukaan leikkaus ei paranna aivolisäkkeen toimintaa tai palauta jo menetettyä näköä. Lisää tutkimuksia tarvitaan ymmärtääksemme paremmin niitä riskejä, joita tähän leikkausmenetelmään liittyy.

Avainsanat: Aivolisäkekasvain, kraniotomia, aivolisäkkeen vajaatoiminta, näköpuutos, makroadenoma, jättiadenoma

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ABBREVIATIONS

ACTH = corticotrophin

CSF = cerebrospinal fluid

CT = computer tomography

FT4 = free thyroxin

DA = dopamine agonist

DI = diabetes insipidus

E2 = estradiol

FSH = follicle stimulating hormone

GH = growth hormone

IGF-1 = insulin-like growth factor 1

LH = luteinizing hormone

MRI = magnetic resonance image

PRL = prolactin

SSA = somatostatin analogs

TSH = thyreotropin hormone

TSS = transsphenoidal surgery

1 INTRODUCTION

1.1 Definition and grading

Pituitary adenomas are common among general population accounting for 10-20% of all intracranial tumors (1,2). About 90% of all pituitary tumors are benign adenomas (2,3). The incidence of clinically relevant pituitary adenomas is 2-4 cases in a year / 100 000 persons. Adenomas can be classified according their size to microadenomas (<10 mm), macroadenomas (=/>10 mm) or giant adenomas (>40 mm). (4–6) Adenomas can also be classified by their hormonal activity and immunohistochemistry. The most common adenoma type is prolactinoma followed in order by non-secreting adenoma, growth hormone secreting adenoma and corticotrophin secreting adenoma (3). Hormonally active adenomas are typically smaller at detection than hormonally inactive ones (2).

1.2 Symptoms and diagnosis

Clinically non-functioning pituitary microadenomas do not cause symptoms as they are located in the sella turcica and do not cause compression to the optic nerve. Clinically non-functioning macroadenomas are detected by their mass effects such as headache, visual field defects and effects of hypopituitarism as they compress the pituitary gland and the optic nerve. Most common symptom of a non-functioning adenoma is visual defect, normally bitemporal visual field defect. (2)

Prolactinomas cause galactorrhea and amenorrhea in women and decreased libido and impotence occur in men (7). Growth hormone secreting adenomas (acromegaly) cause somatic overgrowth in addition to several comorbidities such as hypertension and heart disease, diabetes mellitus, sleep apnea, and bone and joint involvement (8,9). Corticotrophin

(ACTH) secreting adenomas cause Cushing´s disease resulting in muscular weakness, osteoporosis, hypertension, hyperglycemia and weight gain (10,11). TSH secreting adenomas can in rare cases cause hyperthyroidism (12).

Magnetic resonance imaging (MRI) is the best way to evaluate pituitary adenomas. It can differentiate pituitary adenomas from other pituitary lesions, such as Rathke's cleft cysts and craniopharyngiomas in most cases. (2,13) Preoperative endocrine examinations are essential as they provide information about the function of the anterior pituitary gland. This has an effect on which treatment is chosen and if the patient needs supplement therapy perioperatively. (2,14)

1.3 Treatment

Treatment options for pituitary adenomas are surgery, medication and radiotherapy. Treatment is chosen depending on the size and nature of the tumor. Indications for surgery are eliminating the mass effect and to retain vision, normalize hormonal secretion and preserving pituitary function. Surgery is often the primary treatment for symptomatic pituitary adenomas by achieving decompression of the optic nerve and the pituitary gland. That being said, prolactinomas are often primarily treated by medication. (13,14) Surgery includes two techniques; transsphenoidal surgery and craniotomy. It is generally accepted that transsphenoidal technique is the preferred method but transcranial operations are indicated when the tumor is exceptionally large, invasive and otherwise difficult to resect by transsphenoidal means. (2,13,15)

Transsphenoidal technique is the most common way to operate pituitary adenomas. Transsphenoidal surgery can be performed by endoscopic or microscopic technique. Buchfelder et al., 2019; Couldwell, 2004; Karppinen, 2015) In endoscopic technique, the endoscope including the light source and lens is inside the sphenoid sinus and the tumor cavity whereas in microscopic technique the light source is situated outside of the head. In both techniques neuronavigation guidance can be used for proper orientation, and diamond drills are used to get through the skull and sellar floor. (16) The endoscopic technique has the

advantage of providing a volume of exposure greater than in microscopic technique thus minimally invasive procedure can be performed (13,16). No significant differences in complications or surgical outcomes are reported between these techniques (15).

Transcranial technique is used in a minority of cases. It was the first technique to resect pituitary adenomas when sir Victor Hershley suggested this technique in the late 19th century (17). In modern time this technique still has its indications in for example large invasive adenomas that cannot be fully resected by transsphenoidal means. Challenges concerning transcranial approach are risks of damaging cerebral arteries, cranial nerves such as the optical nerve, infundibulum, hypothalamus or the pituitary gland. Different approaches can be used depending on the location of the adenoma. Fronto-lateral, fronto-temporal and basal midline approaches are the three standardized methods used. (16)

Symptomatic prolactinomas are treated primarily with medication. Dopamine agonist (DA) therapy is the choice of medication, and usually has dramatic effects on the size of prolactinomas. If the medication is contra-indicated, causes difficult side-effects, the adenoma does not respond to therapy or the patient refuses to use medication, surgery is considered. (7,18) In addition to prolactinomas also many other pituitary adenomas can be treated by medication, often preoperatively. Somatostatin analogs (SSA) can be used to control excess hormone levels in GH-,and TSH- secreting adenomas as primary therapy especially with aggressive pituitary tumors, and to reduce tumor volume and growth, and to make the tumors easier to excise. (19)

In addition to medical and surgical treatments there is a third method to manage pituitary adenomas. External radiotherapy and stereotactic radiosurgery are usually the third-line therapy after surgery and medication. These methods are used to control tumor growth when other methods are insufficient. Time to achieve remission takes often years and these methods have also a risk of hypopituitarism limiting their use. Stereotactic radiosurgery is affecting much smaller area comparing to conventional radiotherapy thus is safer and has a lower risk on damaging the pituitary gland. This results in a much wider use of stereotactic radiosurgery. (1,19)

1.4 Complications

Serious complications occur rarely but risks with surgery are still present. Transient diabetes insipidus and cerebrospinal fluid leakage (CSF) are presented as most common complications in transsphenoidal surgery. (20–22) In table 1 is listed most common complications associated with transsphenoidal surgery (23,24).

Mortality rate in transsphenoidal surgery is universally under 1% (14,20,25,26). Patients undergoing transcranial operation have larger and more invasive tumors resulting in a higher complication rate (27). Elderly patients are generally safe to operate transsphenoidally after risks are evaluated carefully (21,28–30).

Table 1. The incidence of complications in transsphenoidal surgery

	Epistaxis	*Permanent DI*	*CSF leak*	*Visual loss*
Penn 2018 (%)	3.4	3.1	1.7	1.7
Iglesias 2018 (%)		0 – 10.4	1.9-10.3	

1.5 Surgical outcomes

Although pituitary adenomas are benign in nature, patients need lifelong radiological and endocrinological follow-up after surgery for detecting possible tumor regrowth (2,31). Postoperative hormonal status may be improved when compared to preoperative status. Preoperative symptoms such as headache and visual loss in addition to the symptoms caused by hormonal hypersecretion are often improved after surgery. (25) Craniotomy is performed on difficult invasive tumors thus the tumors rarely can be fully excised in single operation. Vision and pituitary function are often better preserved with transsphenoidal approach than in craniotomy. Mortality rate in craniotomy is low as well as in transsphenoidal technique. (27)

Surgical outcomes regarding tumor remnants and recurrence are evaluated with MRI. A careful follow-up by imaging is also important after radiotherapy as it may not fully prevent tumor regrowth. It is recommended that MRI is taken four months and one year after surgery as postoperative changes take about four months to resolve. After this, follow-up images are recommended to take every two to three years, and after radiotherapy even more closely. (2)

2 AIMS OF THE STUDY

The aim of this study was to evaluate the surgical outcome and follow-up in pituitary adenomas operated transcranially at Tampere University Hospital in 1996-2015. The aim was also to evaluate the reasons behind the choice of this surgery technique as transsphenoidal technique has been the treatment of choice for decades due to its less invasive technique and low complication rates.

3 PATIENTS AND METHODS

3.1 Patients

In this retrospective study we evaluated data of patients operated in Tampere University Hospital between January 1st, 1996 and December 31st, 2015. Information of the patients was collected from the medical records of the Tampere University Hospital. Study population was collected based on a Fimlab pathology tissue bank of Pirkanmaa hospital district. Tissue samples of pituitary adenomas that were collected from Tampere University hospital between 1.1.1996-31.12.2015 were collected in this study. 346 adenomas were operated but two

patients were excluded due to lack of information about resected tumors. Of these 344 patients operated for the first time, 27 were operated transcranially. This article considers only the patients who underwent craniotomy.

The study was approved by the research ethics committee of Tampere University Hospital.

3.2 Clinical characteristics and clinical outcomes

All patient records were reviewed retrospectively, and information about tumors´ pathological diagnosis and immunohistochemical staining, preoperative comorbidities, pre- and postoperative hormone status, MRI scans of which tumor dimensions and locations were examined, age at the time of surgery and sex, medications for hormonal over secretion and visual status were collected. Surgeon, intraoperative complications, duration of surgery, duration of hospital care were also reviewed. One-year follow-up information was evaluated including MRI scans, visual status, medication and pituitary hormone function. Information of the last control visit was also reviewed including hormonal status.

Pituitary hormone levels were examined in all patients preoperatively. Plasma growth hormone (GH), insulin-like growth factor-1 (IGF-1), prolactin (PRL), adrenocorticotrophic hormone (ACTH), cortisol, thyroid-stimulating hormone (TSH), free thyroxin (FT4), testosterone in men, estradiol (E2) in women, luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels were evaluated. Tumor dimensions were characterized from a CT scan or MRI pictures by a radiologist. Due to lack of recording of tumors in three dimensions, the tumors were evaluated by their maximum diameter. According to their maximum diameter, they were classified as microadenomas (< 1cm), macroadenomas (1-4 cm) or giant adenomas (>= 4cm).

Tumor types were defined by immunohistochemical staining and clinical features. Immunohistochemical staining was performed to the resected tumors by a pathologist. Tumors were categorized according to the 2017 WHO criteria. Preoperative hormonal over secretion of the pituitary adenoma was defined by hormonal over secretion and clinical

features, such as galactorrhea, somatic overgrowth, strias, etc. If tumor was immunohistochemically positive but did not cause elevation of that specific hormone in the blood, it was defined as a clinically inactive adenoma. Null cell adenomas were immunohistochemically negative.

Preoperative and postoperative hormone insufficiency was studied. Preoperative hormonal status was compared to status at 3 months and 1 year postoperatively. We analyzed if preoperative hormonal oversecretion was cured (remission) and if hypopituitarism was cured or caused by operation.

3.3 Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics version 24.0. Analyses were performed with Chi-square-test and Mann-Whitney U-test. String variables were stated as median, min and max. Due to a small population size statistical power was left weak, and the results are descriptive in nature.

4 RESULTS

4.1 Clinical features

The study population consisted of 27 patients who underwent craniotomy. The median age was 55 years (14-81 years). Most of the operated patients were men, accounting 17 patients (63.0%). Men were younger than women at the time of diagnosis having the mean age of 45 years. Women operated had the mean age of 53 years (p=0.29).

Preoperative symptoms were subjective vision symptoms (n= 17, 63.0 %), nausea (n= 1, 3.7 %), headache (n= 3, 11.1 %), hemiplegia (n= 1, 3.7 %) , exhaustion (n= 1, 3.7 %), vertigo (n= 3, 11.1 %), unconsciousness (n= 1, 3.7 %), loss of hearing (3.7 %), galactorrhea (n=1, 3.7 %) and memory loss (n= 1, 3.7 %). Some of the symptoms may not have origined from the adenoma but were indications for imaging the head leading to the diagnosis of pituitary adenoma.

Visual loss or defect in visual fields occurred in 15 patients (55,6%) preoperatively in ophtalmological examination. Two patients´ vision was not recorded as one patient´s vision was not examined and the other patient´s examination failed for unknown reason. Ten patients (37%) did not suffer from any visual signs preoperatively.

The patient characteristics are listed in table 2. Preoperative information of pituitary function was found on all 27 patients. Not all of the hormones were examined in all of the patients if the clinical status did not suggest a hormone deficit. A total of 12/27 (44.4%) patients had pituitary deficiency preoperatively. Hypothyroidism was rather common (n= 10, 37.0%) while 4/23 (17.3%) of the patients had hypocortisolism and 8/17 (47.1%) patients had hypogonadism, and only 2/16 (12.5%) patients had low growth hormone levels. Hyperprolactinemia was the most common hormone to be oversecreted as 13/23 (56.5%) patients had it preoperatively. 2/16 (12.5%) of the patients had acromegaly and none had Cushing´s disease.

The radiological and immunohistochemial characteristics of the adenomas are listed in table 3. Information about tumor size was found on 23 patients. The mean maximum size of the resected tumors was 39,5 mm (20-80 mm). 14 (60.9 %) of the tumors were macroadenomas and nine (39.1 %) were giant adenomas. Fourteen (52%) of the resected adenomas were immunohistochemically inactive (null cell adenomas). The type of one adenoma was left unsure with an unclear immunohistochemical result.

Table 2. Clinical characteristics

Patient characteristics	**N = 27**
Gender	
Male n (%)	17 (63.0)
Female n (%)	10 (37)
Age (years)	48.1 ± 18.7
Preoperative visual defect n (%)	15 (55.6)
Preoperative hypopituitarism n (%)	12 (44.4)

Table 3. Adenoma characteristics

Adenoma characteristics	***N = 26 (%)***	
Clinically inactive adenoma	20 (76.9)	
Hormonally active adenoma	6 (23.1)	
Immunohistochemical staining		Hormonally active adenoma N=6 (%)
Null cell adenoma	14 (53.8)	
GH	4 (15.4)	2 (33.3%)
PRL	6 (23.1)	4 (66.6%)
ACTH	1 (3.85)	0
TSH	1 (3.85)	0
FSH	2 (7.69)	0
Maximum adenoma diameter	N = 23	
1-4 cm	14 (60.9)	
> 4 cm	9 (39.1)	

4.2 Surgery

Craniotomies were performed by six different surgeons in addition to assisting surgeons. The duration of the surgeries was found in only six operations, varying from 1.28 hours to 5.09 h.

The indications for choosing craniotomy as the surgery technique were large diameter and location of the tumor in sixteen (59.3 %) patients. One (3.7 %) tumor was resected by craniotomy because of a transnasal polype operation a week earlier. Two (7.4 %) of the tumors were operated transcranially as the surgeons started operating suspecting the tumor

was not a pituitary adenoma. In seven (25.9 %) cases the indication was not mentioned in patient records.

The mean total time being in the hospital was 9 days (4-35 days), including the time patient first arrived to the hospital prior to surgery to the time he left the operative hospital. 12 of the 27 (44.4 %) patients were discharged home after hospital period, one patient was discharged to a primary care, six patients to a neurological unit, five patients to an internal medicine ward, one to a rehabilitation unit and one to a psychogeriatric ward. One patient´s discharge location was left unclear.

4.3 Surgical outcome and follow-up

There were no inpatient deaths in our study. Three deaths occurred in follow-up. Two of the patients died for unknown reasons and one patient died for other reason. Patients were re-evaluated postoperatively. Vision was evaluated one year after surgery and hormonal status was evaluated on the last control visit. Median follow-up time was 3.82 years (0.083-11.5). Vision examination information was found in 14 out of 26 patients. One patient had passed away before the one-year examination thus was not included in these analyses. 12 patients did not have one-year follow-up information about vision.
Visual deficits pre- and postoperatively are shown in table 4. Visual impairment occurred in 15 (56.6 %) patients preoperatively. 13/14 patients had vision loss postoperatively. One patient who didn´t have vision loss preoperatively had normal vision one year after surgery. Nine patients who had vision loss preoperatively had visual deficit in follow-up. Six patients having visual deficit preoperatively did not have records on vision in follow-up. None of the patients having vision loss preoperatively and examined year after surgery had normal vision in follow-up.

Pituitary function pre- and postoperatively is shown in table 5. There was no clinical significance between pituitary function pre- and postoperatively comparing to macroadenomas and giant adenomas (p=0.22).

Table 4. Visual deficits pre- and postoperatively. (p=0.50)

		Postoperative visual deficit, n=14	
Preoperative visual deficit, n= 25, (%)		*yes*	*no*
	yes	9 (64.3)	0 (0)
	no	4 (28.6)	1 (7.14)

Table 5 Hormonal status pre- and postoperatively

Hormonal status	***Preoperative n (%)***	***Postoperative n (%)***
Normal pituitary function	10 / 27 (37.0)	3 / 27 (11.1)
Hypopituitarism	12 / 27 (44.4)	21/ 27 (77.8)
Hypothyroidism	10 / 23 (43.5)	21 / 24 (87.5)
Hypocortisolism	4 / 23 (17.4)	15 / 24 (62.5)
Hypogonadism	8 / 17 (47.1)	8 / 14 (57.1)
Hyperprolactinemia	13 / 23 (56.5)	6 / 22 (27.3)
Acromegaly	2 / 16 (12.5)	2 / 13 (15.4)

5 DISCUSSION

Craniotomy is not the first choice when operating pituitary adenomas. However, there are aggressive and invasive adenomas that need surgery to reduce tumor mass and prevent vision loss. These patients suffer already preoperatively from visual impairment and hypopituitarism due to the tumor size. This means that in addition to the invasive surgery that causes damage in the operative area, the tumor itself has damaged the pituitary gland and optic nerve by compressing them. This is shown in our study in the number of vision deficits and impairment of pituitary gland function in follow-up. In our study there was no improvement in vision after surgery, which indicates that the surgery cannot necessarily undo the damage the tumor has caused preoperatively.

The general characteristics of the patients were in line compared with other studies. There were more men (63 %) operated than women, which has been noted in previous studies (32).

Although the prevalence of adenomas is not higher in men than in women, previous studies indicate that more aggressive tumors occur more often in men. Previous studies have shown that men are older than women at the time of diagnosis. (5) This was not shown in our study as the mean age of men operated in our study was eight years less than that of women. This is not in line with other studies although our study population is small and is not statistically significant. The mean age of all patients in our study was slightly higher compared to other studies. (5,32) This may also be explained by our small study population.

In our study the pituitary function was impaired in the majority of patients (77,8 %) evaluated at follow-up. In previous studies deficits of the pituitary gland has been shown to be greater after craniotomy than transsphenoidal surgery occurring up to 15 % of patients (27). Nomikos et al. compared patients who underwent transsphenoidal ja transcranial surgeries and noticed that pituitary function was impaired in 69 % of patients one year after transsphenoidal surgery whereas the percentage in patients who underwent transcranial surgery was 95 % (33). In our study the pituitary gland impairment was less common in follow-up although higher than in many other studies. Our high pituitary gland impairment rate can be explained by our small study population. Higher impairment rates in transcranial approach can be caused by the invasive technique that easily damages the tissue in the operative area such as the pituitary gland, but also the mass effect of the large tumors have damaged the pituitary gland itself preoperatively explaining the higher incidence of pituitary gland impairment.

Vision loss was common preoperatively as several tumors were large and were in contact with the optic chiasm. The outcomes of vision impairment show that craniotomy rarely normalizes the vision if it´s already damaged. Although one could presume that craniotomy preserves remaining vision so that patients don´t lose their vision completely, studies have been controversial about the vision loss after craniotomy (27). The challenge in our study was the lack of systematic information about vision. Vision and visual fields were examined but there was big variation in how they were recorded. This resulted in difficulty to create a variable that included the changes in vision, and we ended up creating a simple variable of either no vision deficit or vision deficit to some degree. If visual examinations were recorded prospectively and were comparable with each other the analyses of vision deficit could have been made more accurately.

We must remember that the study population included larger adenomas which had challenging locations. The initial characteristics at the time of diagnosis of these adenomas were challenging and would not most likely have been ideally resected by transsphenoidal technique.

6 CONCLUSIONS

Transcranial technique is safe with a low mortality rate. Surgery does not improve the pituitary function and vision impairment according to our study. The outcomes of transcranial surgery look concerning but it should be kept in mind that patients undergoing craniotomy have difficult, large and invasive tumors that cannot be primarily resected transsphenoidally. Our study population was small because the vast majority is operated transsphenoidally, thus more studies of patient outcomes of primary transcranial surgery are needed to better understand the risks involved with this invasive surgery technique as there are still a number of patients who need craniotomy as their first line treatment.

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