What is the current clinical practise in pituitary adenoma surgery in Europe? European Pituitary Adenoma Surgery Survey (EU-PASS) results - technical part

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Abstract

Pituitary adenoma surgery has evolved rapidly in recent decades, changing clinical practice markedly and raising new challenges. There is no current consensus or guidelines for perioperative care that includes possible complication management. This study aims to determine current practice across European neurosurgical centers. We created a list of eligible departments performing pituitary adenoma surgery based on cooperation with EANS, National neurosurgical societies, and personal communication with local neurosurgeons. We contacted the chairpersons from each department and asked them (or another responsible neurosurgeon) to fill out the survey. The survey consisted of 58 questions. For further analysis, departments were divided into subgroups: “academic”/“non-academic center”, “high-volume”/“low-volume”, “mainly endoscopic”/“mainly microscopic”/“mixed practise” and by geographical regions. Data from 254 departments from 34 countries were obtained. The average time to complete the survey was 18 min. Notably, the endoscopic approach is the predominant surgical approach in Europe, used in 56.8% of the centers. In routine cases without intraoperative cerebrospinal fluid leak, high-volume centres are less pedantic with sellar closure when compared with low-volume centres. On the other hand, when a postoperative cerebrospinal fluid leak occurs, high-volume centres are more active and indicate early reoperation. Less than 15% of the participating centres perform early postoperative MRI scans. Marked variation was noted among different groups of respondents and some contentious issues are discussed. Such information can encourage useful debate about the reasons for the variations seen and perhaps help develop standardised protocols to improve patient outcomes. A future research focus is to compare European results with other regions.

Introduction

Pituitary adenoma surgery has evolved rapidly in recent decades thanks to the advent of modern technologies such as the endoscope and intraoperative MRI. These changes reflect a shift in clinical practice and bring new challenges to the field.

There is no current consensus or guidelines regarding perioperative care that includes possible complication management. Thus far, only a few smaller focused surveys have been conducted on this topic [17, 18, 32].

This study aims to shed light on technical aspects of pituitary surgery and perioperative patient care. We created an international investigational team of neurosurgeons and performed an online survey among a large number of European departments.

Materials And Methods

All 39 European member societies of EANS were approached to distribute the survey to their departments of neurosurgery.

Our goal was to cover as many as possible of neurosurgical departments in Europe that perform pituitary adenoma surgery. We created a list of eligible departments based on cooperation with EANS, national neurosurgical societies and personal communication with local neurosurgeons. Each member of the study group approached their national peers with a request to participate in the survey. Direct mailing to the Department of Neurosurgery chairpersons within Europe was performed to attain as high coverage as possible. Each member of the study group covered his country. DN and MM were responsible for countries not covered by the remaining members of the study group. The goal was to enroll pituitary centers of excellence and all departments performing pituitary adenoma surgery.

The request was to complete the survey (<https://www.surveymonkey.com/r/eu-pass>) by the respective departments' chairpersons or pass it to a neurosurgeon in charge of the pituitary program. The target was to get one completed survey per department.

The survey consisted of 58 questions, which could be divided into three sections:

- A. Demographics (countries, caseload per center, surgeons involved in pituitary surgeries, residents engaged in pituitary surgeries, pituitary boards)
- B. Different types of adenoma and their treatment (acromegaly, Cushing disease, prolactinomas, non-functioning adenomas)
- C. Techniques (navigation, intraoperative imaging, technique of the surgery, postoperative MRIs, follow-up)

The study period started on 1 April 2019 and closed on 30 June 2019. This paper analyses questions in section C, i.e. technical issues. The remaining sections will be covered in future papers.

A univariate analysis was planned based on the following variables:

- Academic/non-academic centers (based on participant answers)
- High-volume/low-volume centers. We defined a high-volume centre as a centre in which more than 30 surgeries for pituitary adenomas are performed per year [8].
- Technique applied in the centre: “mainly endoscopic” (>90% of surgeries are performed endoscopically), “mainly microscopic” (>90% microscopically and >90% microscopically endoscope-assisted) and “mixed practise”.
- Regions: according to United Nations Statistics Division (Fig. 1) [35]

Statistics

Basic descriptive statistic in terms of counts and percentages were calculated for each survey question. Differences in responses to survey questions based on selected grouping variables (academic centre, surgical technique, case volume per year and region) were examined by a Pearson's chi-square test (with a Fisher's exact test as an alternative when appropriate) with adjusted residuals. Level of statistical

significance was set at $\alpha = 0.05$. Microsoft Excel and a statistical software SPSS version 25 were used for statistical analyses and data processing.

Results

The minimum time to complete the survey was 12 min (mean time was 18 min). Duplicates are highly improbable because of the time spent on one survey and subsequent checks to rule out duplicate IP addresses used for one survey. There were no partially filled-in surveys. All surveys returned were completed (i.e. completion rate was 100%).

Data from 34 countries were obtained. Five countries (Armenia, Kazakhstan, Kosovo, North Macedonia, Moldova) did not return the survey.

Altogether, 254 departments of neurosurgery within Europe completed the survey. Most of the returned surveys came from Germany (60), followed by Italy (28), France (22), the UK (16), the Czech Republic (13) and Spain (10). The lowest return rates were from Russia (1), Ukraine (5), Turkey (5) and Poland (7) when compared with the number of inhabitants and number of neurosurgical centers.

First, we present the respondents' responses to each question. Second, we describe statistically significant results based on group differences by the academic centre, surgical technique (microscopic/endoscopic), case volume per year (low-volume centre/high-volume centre) and region.

General results

The first group of questions focused on CSF leakage and its management. In Q41 (How do you close the sella in cases without intraoperative CSF (ioCSF) leakage? multiple answers possible), 133 centres answered that they use tissue glue, 94 a collagen sponge, 68 dural substitutes, 56 do not close the sella, 48 bone, 35 fat, 20 use a nasoseptal flap, 20 other material and 12 fasciae (Fig. 2). In Q42 (How do you close the sella in cases with ioCSF leakage? multiple answers possible), 199 centres use tissue glue, 170 fat, 109 fasciae, 100 nasoseptal flaps, 95 dural substitutes, 85 collagen sponge, 55 bone, 40 other material and none answered, "we don't close the sella" (Fig. 2). In Q43 (Do you use fluorescein in standard pituitary surgery to detect intraoperative leaks?), only two centres answered "yes". In Q44 (How often do you insert a lumbar drain directly after pituitary surgery in case of intraoperative CSF leakage?) 24 centres answered "always", 31 "mostly", 53 "sometimes", 79 "rarely" and 65 "never" (Fig. 3). In Q45 (If yes, how many days do you leave the lumbar drain open?) 51 respondents answered "1-3 days", 122 "4-5 days" and 11 "more than 6 days" (Fig. 4). In Q46 (Do you administer antibiotics in inserted lumbar drains?), 30 answered "always", 64 "case by case" and 116 "never". For Q47 (For suspected postoperative CSF leaks, what do you base your decision on? (multiple answers possible), 190 "answered clinical examination", 85 beta-2 transferrin", 78 "beta trace protein" and 29 "CT cisternography" (Fig. 5). In Q48 (What do you do for postoperative low flow CSF leaks?), 24 centres answered, "Indicate reoperation always on the day of diagnosis", 42 "Indicate reoperation always, but surgery may be postponed for 1-2 days", 139 "Insert a lumbar drain + bed rest", 27 "Insert a lumbar drain + no bed rest" and 19 "bed rest

only”(Fig. 6). In Q49 (How often do you perform expanded approaches for pituitary adenomas?), 236 centres answered 0-30% of the cases, 11 centres 40-60% and 1 centre 70-100%. In Q50 (How often do you use nasoseptal or other pedicled flaps in these cases with an expanded approach?), 99 centres answered “mostly”, 83 “sometimes” and 68 “never”.

The second group of questions investigated intraoperative imaging and the use of neuronavigation. In Q51 (How often do you use intraoperative MRI (iMRI) in pituitary adenoma surgery?), 217 centres do not have iMRI available, 13 use iMRI “almost always”, 15 in “selected cases” and 7 do not use iMRI despite its availability. In Q52 (How often do you use intraoperative CT (iCT) in pituitary adenoma surgery?), 197 centres do not have iCT available, 4 use iCT “almost always”, 16 in “selected cases” and 34 do not use iCT despite its availability. In Q53 (Do you use neuronavigation for endonasal pituitary surgery?), 129 centres answered, “for all cases”, 99 for “selected cases”, 21 do not use neuronavigation and 3 do not have neuronavigation available (Fig. 7). In subsequent Q54 (If yes, what image set(s) do you use?), 102 centres answered, “CT and MR fusion”, 65 “MRI T1 contrast”, 23 “MRI T1 contrast and T2 fusion”, 19 “CT non-contrast”, 17 “CT angiography” and 3 “MRI T2” (Fig. 8).

The third group of questions focused on postoperative care and patient follow-up. In Q55 (Do you perform early MRI (i.e. within 1-3 postoperative days,) 36 centres answered “routinely”, 120 “for selected cases” and 96 “never” (Fig. 9). In Q56 (Do you systematically assess anosmia?), 96 centres answered “routinely”, 66 “for selected cases” and 89 “never”. In Q57 (Do you routinely assess nasal morbidity?), 76 centres answered “yes, clinical examination by a neurosurgeon”, 112 “yes, clinical examination by an ENT doctor”, 14 “yes, clinical examination and by quality of life questionnaires” and 50 do not assess nasal morbidity. In Q58 (When do you perform the first follow-up scan?), 36 centres answered, “in 1-2 months”, 204 “in 3-4 months” and 12 “in more than 4 months” (Fig.10). In Q59 (Do you personally follow up the patient?), 229 centres answered “yes” and 23 “no”.

Academic/non-academic centres

Analysing results of academic and non-academic centres (Q2), we found only two questions with statistically significant differences. Academic centres more often use fat graft for sellar closure in cases without intraoperative CSF leakage (Q41, $p=0.013$). Similarly, academic centres more often use fascia graft for sellar closure in patients with intraoperative CSF leakage (Q41, $p=0.034$).

High-volume/low-volume centres

High-volume centres more often use endoscopic surgical techniques (Q9, $p=0.005$). In no CSF leakage high-volume centres use significantly less often tissue glue ($p=0.008$) and fat graft ($p=0.003$) and significantly more often do not close sella at all ($p<0.001$). Also, in intraoperative CSF leak high-volume centres insert lumbar drainage (LD) directly after pituitary surgery more often (Q44, $p=0.002$). For postoperative low-flow CSF leak, high-volume centre indicates early reoperation more frequently than low-volume centres (Q48, $p=0.013$). High-volume centres do not use iCT more often despite its availability

($p=0.028$). In the postoperative course low-volume centres more often perform routine postoperative MR scans (Q55, $p=0.015$) and less frequently assess anosmia (Q56, $p=0.018$).

Endoscopic/microscopic technique

With no CSF leak, endoscopic centres more often do not close sella after adenoma resection (Q41, $p=0.015$). In cases with intraoperative CSF leak endoscopic centres more frequently use nasoseptal flap (Q42, $p<0.001$) and less regularly insert lumbar drain directly after surgery compared with microscopic centres (Q44, $p=0.042$). Endoscopic centres more frequently assess anosmia (Q56, $p=0.005$) and nasal morbidity (Q57, $p=0.003$).

Regions

Centres from the western region close sella more often with tissue glue after surgery with ioCSF leak (Q42, $p=0.017$). Centres from western, southern and northern regions less often use beta trace protein for poCSF leak, while eastern centres more often use CT cisternography (Q47, $p<0.001$). Nasoseptal flaps are used more often in the northern and less often in the western region (Q50, $p<0.001$). For neuronavigation, eastern centres more often use MRI scans than MRI/CT fusion (Q54, $p=0.048$). Eastern and southern centres less often perform early postoperative MR scans (Q55, $p<0.001$). Centres in the southern region assess anosmia less frequently than others (Q56, $p<0.001$). Northern centres more often conduct early postoperative scans than southern centres (Q58, $p=0.007$). In southern centres patients are less frequently followed up by operating neurosurgeons (Q59, $p<0.001$).

Discussion

Sella reconstruction

Based on our respondents' answers, techniques of sellar closure vary widely among European centres (see above). No randomised trials are available comparing different techniques. The Napoli group recommend some closure only in cases of ioCSF leak, prolapse of the diaphragm or significant bleeding [7]. The Pittsburgh group reviewed the literature and concluded that for low-flow intraoperative CSF leak in the sellar region (the most common situation in pituitary adenoma surgery) closure with fat graft or vascularised nasoseptal flap should be performed [29].

The most popular technique among our respondents is tissue glue (without ioCSF leak 133 centres, with ioCSF leak 199 centres). The literature reflects widespread clinical use of fibrin glue during pituitary surgeries [7, 16, 31]. Cavallo et al. even used repeated endoscopic endonasal fibrin glue injections in the sphenoid sinus cavity for postoperative CSF leak while the patient is awake (i.e. without need for reoperation under general anaesthesia) [9]. A systematic review that included all neurosurgical procedures by Esposito et al. showed there is a lack of randomised studies evaluating the effectiveness and safety of fibrin sealants in the prevention of postoperative cerebrospinal fluid leakage [12]. Among the limited studies available, evidence from a single randomised controlled trial indicates that fibrin

sealants provide a higher rate of intraoperative watertight closure of the dura suture line than control, albeit with a higher rate of postoperative CSF leakage [15]. A possible explanation of this result may be that the fibrin clot induced by the sealant degrades in time by natural (physiologic) fibrinolysis [13] and therefore does not create a permanent CSF barrier. A retrospective study by Mohindra et al. analysed results in 27 patients after endoscopic endonasal surgery with poCSF leak. The authors concluded that repairs with and without fibrin glue are equally effective and CSF repair without fibrin saves costs [23].

Confirming CSF leak

Most respondents diagnose postoperative CSF leak by clinical examination. Obviously, in cases of massive transparent nasal discharge, this is a sufficient procedure. Sometimes, when only a few drops of liquid can be seen, the situation is less straightforward. CSF combined with blood can leave a “halo” on bed sheets or gauze. This “ring sign” has been discussed as the first clinical sign of a CSF leak. Although such an immediate indicator would be convenient, the reliability of this sign is poor. Dula and Fales studied this phenomenon and concluded that any other clear fluids mixed with blood form a “ring sign” [11].

Significantly fewer respondents selected beta trace protein (BTP) and beta-2 transferrin (B2T). The most specific CSF protein is BTP [3], with slightly higher sensitivity and specificity than B2T [26]. From a laboratory standpoint, BTP is easier to manage and the assay is faster. The advantage of B2T is that it can be measured in the lowest sample volumes when analysing pure CSF samples [3]. Mecro et al. stated the costs for B2T to be 50 USD per sample and for BTP 20 USD per sample [21].

Radionuclide cisternography (RNC) is a more invasive, more expensive and less accurate test than B2T or beta trace protein. Based on these facts, RNC should not be routinely used to confirm the presence of a CSF leak [26]. RNC is usually reserved for cases when a sample of nasal discharge is not available for laboratory testing.

Lumbar drainage for CSF leak

The role of LD in preventing and treating postoperative CSF leak is unclear. A significant number (n=24 “always”, n=31 “mostly”, n=53 “sometimes”) of our respondents insert LD in the event of intraoperative CSF to prevent postoperative leakage. The majority of respondents (n=166) insert LD in case of postoperative CSF instead of reoperating directly. Caggiano et al. retrospectively analysed 811 patients and concluded that use of LD was correlated with longer immobilisation and hospitalisation without providing statistically significant advantages in preventing or treating ioCSF or poCSF leak in low- and high-risk patients [6]. Duration of CSF drainage via LD varies widely among our respondents (n=51 “1-3 days”, n=122 “4-5 days”, n=11 “more than 5 days”) and the literature does not provide reliable data to make any recommendations.

Neuronavigation

The vast majority of respondents use neuronavigation (n=228). Some 50.8% (n=129) of the respondents use neuronavigation for every case and 39.0% (n=99) for selected cases. We cannot say how those cases are selected in the latter group or how frequent neuronavigation is applied. In most centres combined CT and MR scans are used at the same time (n=102). While CT navigation is helpful during the nasal and sphenoid phase, MR navigation provides better orientation in a sellar stage [22].

Intraoperative imaging

Intraoperative imaging is not widely available among European centres (iMRI available n=35, iCT available n=54). iMRI, if available, is used in pituitary surgeries by most of the respondents (n=28). iMRI can identify possible residual tumours and therefore increase the radicality of resection [28]. Considering high-field iMRI ($\geq 0.5T$), sensitivity and specificity for residual tumor identification are more than 90%, which exceeds an endoscope's capability. Berkmann et al. showed better endocrinological results when using iMRI in a lower incidence of postoperative hypopituitarism [4] and a higher remission rate in functioning adenomas [24].

On the other hand, iCT is not routinely used by most centres where available (used in 20 of 54). The obvious reason is the limited diagnostic value of CT for pituitary masses. However, iCT might be helpful for navigational purposes in selected cases [19].

Postoperative imaging

Early postoperative MRI scans are performed routinely in 36 centres (13.4%), for selected cases in 120 centres (47.2%), while 96 centres (37.8) do not perform early MR scanning at all. The role of early imaging is often questioned, mainly because of difficulty in identifying residual tumours and interpreting early postoperative changes, such as persistent cavity enlargement, accumulation of haemorrhagic material and fat packing [27]. Stofko et al. showed that early postoperative MRI scan provides accurate and reliable information regarding residual tumor presence compared with reconstruction and packing materials with sensitivity 100% and specificity 97.9% [33].

Nasal morbidity and anosmia

Quality of life after resection of pituitary adenoma is becoming an important outcome measure with improving surgical results. However, a significant proportion of centres still do not routinely assess nasal morbidity or anosmia. A recent prospective study showed that the risk of olfaction deterioration after endoscopic binostril endonasal pituitary adenoma resection without any flap was as low as 1.5% [25]. Sinonasal complications are common after transsphenoidal surgery, but spontaneous resolutions within 3-12 months have been reported [2].

Academic/non-academic centres

Particularly noteworthy is that few differences were observed between academic/non-academic centres. Academic centres use fat graft more often for surgeries without ioCSF leak and fascia for surgeries with

ioCSF leak. One would expect differences in questions investigating the availability of iMRI or nasoseptal flap use, but this is not the case.

High-volume/low-volume centres

Not surprisingly, pituitary adenoma patients are often concentrated in high-volume centres, while others are operated in departments with fewer cases per year. For various neurosurgical conditions, increasing surgeon and hospital volumes correlate with improved outcomes, such as mortality, complication rates, length of stay, hospital charges and discharge disposition [10].

High-volume centres more often use endoscopic techniques. In routine cases without ioCSF leak, high-volume centres are less pedantic with sellar closure than low-volume centres. On the other hand, when poCSF leak occurs, high-volume centres are more active and indicate early reoperation. It seems that neurosurgeons in high-volume centres are more confident with their judgement of the absence of intraoperative CSF leakage and dare not close sella in these cases at all. On the other hand, in high-volume centres a more initiative-taking approach in postoperative CSF leakage was observed.

Endoscopic vs. microscopic approach

We divided centres into three groups: “mainly endoscopic” (>90% surgeries performed endoscopically, n=141), “mainly microscopic” (>90% microscopically and >90% microscopically with endoscope assistance, n=54) and “others” (n=53) based on Q9. Nowadays, the endoscopic approach is the predominant surgical approach in Europe, used in 56.8% of the centres.

The endoscopic technique enables a better view in the sella, which might be a reason for more selective sellar closure. Endoscopic centres more often do not close sella after adenoma resection without ioCSF leakage but in cases with ioCSF leak, they more frequently use the nasoseptal flap. Endoscopic centres also more frequently assess anosmia and nasal morbidity. One may speculate that it is better visualisation of the nasal cavity and better sense of the nasal mucosa's surgical changes that motivate endoscopic surgeons to investigate more nasal functions.

Our results reflect the literature that considers the endoscopic approach a current standard of care [5, 30]. Based on recent meta-analyses, the endoscopic approach is superior over the microscopic approach in terms of a higher rate of gross total resection [1], complication rate [14], endocrinological results [5] and preservation of olfactory function [20]. Also, results for residual or recurrent pituitary adenomas are slightly better with the endoscope [13].

The learning curve for the endoscopic technique is probably steeper than for microscopy. Zaidi et al. assessed the learning curve and compared a less experienced surgeon using a fully endoscopic procedure and a very experienced surgeon using a microscopic transsphenoidal procedure. In a cohort of patients with non-functioning adenomas, a less experienced endoscopic surgeon and a more experienced microscopic surgeon yielded similar EOR, endocrine outcomes and complications despite vastly different levels of surgeon experience [34].

Study limitations and strengths

The main limitations of our study are related to study design. Every survey suffers from sampling bias that depends mainly on response rate. In addition, the quality of responses relies on the integrity of the respondents. We also failed to receive a high response rate from some European countries (see results). Most results came from Germany, Italy, UK, Czech Republic and Spain.

We achieved a large sample of data with a very high response rate and 100% completion rate. We want to emphasise that every respondent in our survey represents one neurosurgical centre.

So far, this study represents the largest survey on pituitary adenoma surgery in Europe.

Conclusion

We performed a Europe-wide online survey that offers insight into current clinical practice in patients treated for pituitary adenoma. Marked variation was noted among different groups of respondents and some controversial points are discussed. Notably, the endoscopic approach is the predominant surgical approach in Europe, used in 56.8% of the centres. In routine cases without ioCSF leak high-volume centres are less pedantic with sellar closure when compared with low-volume centres. On the other hand, when poCSF leak occurs, high-volume centres are more active and indicate early reoperation. Less than 15% of the participating centres perform early postoperative MRI scans.

Such information can encourage constructive debate about the reasons behind the variations seen and perhaps help develop standardised protocols to improve our patients' outcome. Comparing European results with other regions (e.g., North America) is one future direction of the research.

Declarations

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Figures

Figure 1

European regions according to United Nations. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

Figure 2

Question 41 and 42

Figure 3

Question 44

Figure 4

Question 45

Figure 5

Question 47

Figure 6

Question 48

Figure 7

Question 53

Figure 8

Question 54

Figure 9

Question 55

Figure 10

Question 58