

TO THE ACADEMIC COUNCIL OF THE FACULTY OF MEDICINE
UNIVERSITY OF BELGRADE

At the session of the Academic Council of the Faculty of Medicine in Belgrade, held on May 27, 2026, under number 11800/9-JM, a committee was appointed for the evaluation of the completed doctoral dissertation entitled:

“Outcomes of transnasal transsphenoidal resection treatment for pituitary tumors and prognostic factors for growth of residual or recurrent pituitary tumor”

of the candidate, Dr. Jelena Maletković, MSc, employed at the University of California Los Angeles (UCLA)

Name of Mentor and Co-mentor	Title	Scientific Field	Institution of Employment
Dr Sandra Pekić Djurdjević	Professor	Internal Medicine - Endocrinology	FMUB *
Dr Anthony Heaney	Professor	Internal Medicine - Endocrinology	UCLA

* Faculty of Medicine, University of Belgrade

The committee for the evaluation of the completed doctoral dissertation was appointed consisting of the following members:

Name of Committee Member	Title	Scientific Field	Institution of Employment
Dr Djuro Macut	Professor	Internal Medicine - Endocrinology	FMUB
Dr Dragana Miljić	Professor	Internal Medicine - Endocrinology	FMUB
Dr Milica Medić Stojanoska	Professor	Internal Medicine - Endocrinology	Medical School Novi Sad

Based on the analysis of the submitted doctoral dissertation, the Committee for the Evaluation of the Completed Doctoral Dissertation unanimously submits the following to the Scientific Council of the Faculty of Medicine:

REPORT

A) **Overview of the Content of the Doctoral Dissertation**

The doctoral dissertation of Dr. Jelena Maletković is written on a total of 109 pages and is divided into the following chapters: Introduction, Objectives, Material and Methods, Results, Discussion, Conclusions, and Literature. The dissertation contains a total of 31 tables and 13 graphs. The doctoral dissertation includes an abstract in Serbian and English, the candidate's biography, data regarding the committee, and a list of abbreviations used in the text.

The **Introduction** defines the basic anatomical, physiological, and general characteristics of the pituitary gland, as well as the types of pituitary tumors. Their detailed classification based on clinical and histopathological characteristics is presented. Surgical treatment is fully and adequately described: indications, surgical technique, as well as the expected postoperative outcome. An overview of current knowledge regarding factors influencing the outcome of surgical treatment for pituitary tumors is also presented.

The **Objectives** of the study are precisely defined. The main objective of this research is a comprehensive evaluation of the success of transnasal transsphenoidal surgical treatment of pituitary tumors by analyzing the frequency of postoperative remission in two university centers, with a specific focus on distinct tumor subtypes treated either at UCLA (non-functional tumors and prolactinomas) or in both institutions (acromegaly and Cushing's disease). In addition to determining remission rates, the study aims to thoroughly investigate the impact of a wide range of demographic, radiological, and pathohistological factors—such as sex, age, tumor size, cavernous sinus invasion (KNOSP score), hormonal activity, immunohistochemical profile, Ki-67 index, and the specific institution where the procedure was performed—on predicting the presence of residual tumor or recurrence. The ultimate purpose of these analyses is to utilize the identified risk factors to propose precise corrections and optimize the schedule of postoperative patient monitoring, thereby reducing the need for redundant imaging and hormonal analyses in low-risk patients, while intensifying surveillance for those at high risk of recurrence.

The **Materials and Methods** chapter states that this is a retrospective study conducted across two university centers: the Department of Neurosurgery at the University of

California, Los Angeles (UCLA) and the Center for Neuroendocrinology at the University Clinical Center of Serbia (UCCS) in Belgrade. The research included adult patients of both sexes who underwent transnasal transsphenoidal (TNTS) surgical removal of a pathohistologically confirmed pituitary adenoma between January 2008 and December 2014, with a minimum postoperative follow-up period of 3 years.

This study was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade, and the Ethics Committee of the University Clinical Center of Serbia. The Results chapter provides a detailed and clear presentation of all obtained results.

The **Discussion** is written clearly and transparently, presenting data from other research alongside a comparative analysis of the results obtained in this doctoral dissertation.

The **Conclusions** succinctly outline the most important findings derived from the results of the study.

The Literature section contains a list of 213 references.

B) Verification of the Originality of the Doctoral Dissertation

The Similarity Index value obtained by checking the originality of the doctoral dissertation—i.e., the determined percentage of overlap—using the iThenticate software is 4%. The predominant reasons for the resulting degree of overlap are citations, proper names, and bibliographical data regarding the used literature, which is in compliance with Article 9 of the Regulations on the Procedure for Verifying the Originality of Doctoral Dissertations Defended at the University of Belgrade ("University of Belgrade Gazette", No. 204/18).

C) Brief description of the achieved results

A study of 124 patients with a pituitary tumor, followed for a minimum of three years post-surgery, showed that 15.3% of patients had a residual tumor three months after the intervention, with older age and larger initial tumor size identified as key predictors of growth. The overall incidence of tumor growth during follow-up was 13.7%, with age identified as the only statistically significant predictor of long-term recurrence.

The UCLA Center study demonstrated a high success rate for the surgical treatment of pituitary tumors, with 68% normal findings in clinically non-functioning pituitary adenomas after three months and 55.2% permanent remission in growth hormone-secreting tumors (acromegaly). The results indicate a need for long-term follow-up, as a smaller percentage of patients showed growth of a residual or recurrent tumor over a three-year period. The UCLA study included 11 patients with ACTH-secreting tumors (Cushing's disease), where 90% achieved early remission following TNTS surgery, while 82% of

patients remained in stable remission after three years. Both micro- and macroadenomas, including one silent corticotroph tumor, were recorded among patients with Cushing's disease, with successful long-term control achieved through medication or adrenalectomy in case of recurrence. Analysis of the Ki-67 proliferative index in 115 patients (average $2.9 \pm 3.2\%$) showed that its values did not significantly differ between tumors with subsequent growth and those that remained stable.

Although a Ki-67 value greater than 3% is considered a predictor of more aggressive behavior, the majority of patients with this elevated index did not have an early residual tumor or a subsequent recurrence; an exception was the subgroup that already had a definitive residual tumor three months after surgery, where as many as 5 out of 6 patients showed further growth during the three-year follow-up period. Preoperative assessment of invasiveness using the KNOSP score was clearly associated with treatment outcomes after three months. Among patients without a postoperative residual tumor, the vast majority (92%) had non-invasive tumors (G0–G2), while in patients with a definitive residual tumor, the percentage of invasive forms (G3b and G4) was significantly higher, standing at 26%. In cases where true tumor recurrence was detected during the three-year follow-up, the KNOSP score confirmed a mixed nature, with half of the tumors being non-invasive, while the other half showed potential or definitive invasion of the cavernous sinus.

A study conducted at the Center for Neuroendocrinology of the UKCS, which included 78 patients followed for 3 to 11 years after transnasal transsphenoidal (TNTS) surgery, showed that smaller tumor size (microadenoma) was the primary predictor of successful treatment for acromegaly and Cushing's disease. Initial remission was achieved in 36 patients, while 42 remained uncured, with a significantly higher success rate in microadenomas compared to macroadenomas. Long-term follow-up indicated a high recurrence rate in Cushing's disease patients who had macroadenomas, while in patients with persistent growth hormone hypersecretion, successful control was achieved through radiation or medical therapy.

A pooled data analysis from both centers included patients with hormonally active pituitary tumors (32 with ACTH-secreting tumors and 86 with growth hormone-secreting tumors). In patients with Cushing's disease, a similar distribution of tumor sizes was observed in both centers, with a dominance of microadenomas (over 70%). Early postoperative remission after three months was recorded in 13 out of 21 patients at the UKCS and 10 out of 11 patients at UCLA, with statistical analysis showing no significant difference in the success of biochemical remission depending on the treatment center ($p=0.115$). During the three-year follow-up, the majority of cured patients maintained stable remission, with recurrence occurring in two patients from the UKCS and one from UCLA.

D) Comparative analysis of the doctoral dissertation with results from the literature

1. Non-functioning adenomas (NFAs) and follow-up strategy. Our conclusions show that NF tumors at UCLA have a three-month cure rate of 68%, but also the highest incidence of postoperative residual growth. We proposed lengthening the intervals between follow-up nuclear magnetic resonance (NMR) scans in patients with no residual tumor (to 2 years, and subsequently every 3–5 years). Penn et al. (2018) confirm that transsphenoidal surgery is the first-choice therapy for NFAs with mass effect. The authors emphasize that early postoperative NMR (within 3–6 months) is precisely crucial for detecting residual tissue, which completely aligns with our three-month protocol. Huang and Molitch (2018), in their guidelines for NFA follow-up, state that imaging intervals can be safely extended in patients with complete resection. Our proposal to delay the subsequent radiography for at least two years in the case of a negative initial finding fully follows this consensus and contributes to reducing costs and contrast exposure. Chanson and Brochier (2005), as well as Mercado et al. (2017), point out that NFAs have a high potential for late, clinically silent growth of the residue, which justifies our conclusion that these tumors had the shortest duration of remission and require careful, yet optimized long-term surveillance.

2. Growth hormone-secreting tumors (Acromegaly). Our conclusions indicate an initial remission rate of 55% at UCLA and 39% at UKCS, with no statistically significant difference between the centers. The majority of cured patients remained stable during the three-year follow-up, and tumor size (microadenoma) was identified as a critical factor for success in both centers. Melmed et al. (2018) published the Consensus Statement on Acromegaly Therapeutic Outcomes. This consensus states that surgical remission rates for macroadenomas globally range between 40% and 60%, while for microadenomas they exceed 80–85%. Our results from UCLA (55% overall remission, where macroadenomas comprise the majority of the sample) fit ideally into these international standards. The consensus proposed by Melmed also emphasizes that in case of persistent disease (which was the case for a portion of our patients at UKCS and UCLA), the use of somatostatin receptor ligands (SRLs) or pegvisomant is mandatory, corresponding to the therapeutic approach described in our results.

3. Prolactinomas and hyperprolactinemia. Our conclusion reports a biochemical and radiological remission rate of 67% at UCLA following prolactinoma surgery, with one hundred percent stability over three years. Melmed et al. (2011) published the Endocrine Society Clinical Practice Guideline. These guidelines clearly define that medical therapy (dopamine agonists such as cabergoline) is the first-line treatment for most prolactinomas. However, surgical treatment is indicated in patients who do not tolerate medication, exhibit therapy resistance, or present with macroprolactinomas causing visual impairment. The guidelines state that surgical remission achieved by an experienced neurosurgeon (which

aligns with our data for a single surgeon at UCLA) is around 70–80% for microprolactinomas and significantly lower for macroprolactinomas. Our rate of 67% is fully consistent with the Endocrine Society guidelines regarding surgical outcomes.

4. Outcome predictors (tumor size, patient age, Ki-67, and KNOSP). Our conclusions identify tumor size and older age as significant negative predictors of resection and outcome, whereas the Ki-67 index and KNOSP score at UCLA did not reach statistical significance for predicting aggressiveness within this cohort. In the cited literature (Penn et al., 2018; Mercado et al., 2017), tumor size is universally considered the strongest predictor of complete surgical resection due to anatomical constraints within the sellar region, which directly corroborates our findings. Although some broader studies imply that a Ki-67 > 3% and a higher KNOSP score (cavernous sinus invasion) are markers of poorer outcomes, our results demonstrate isolated significance of Ki-67 only within the subgroup that already presented with an early three-month residual remnant. This nuance in our conclusions suggests that Ki-67 alone, without a radiological correlate post-surgery, does not possess absolute predictive power.

5. Surgical expertise. The high rates of early remission (78.2% at UCLA) and the absence of a statistical difference in outcomes between the centers (UKCS and UCLA) support the thesis from the literature that transsphenoidal surgery in specialized, high-volume university centers yields consistent and excellent results.

6. Follow-up optimization. Our recommendation to extend the intervals between follow-up imaging scans after complete resection represents a direct contribution to the ongoing debate led by Huang and Molitch (2018) and offers a practical clinical tool to reduce the frequency of follow-up NMR imaging for patients.

E) Published papers that are part of the doctoral dissertation

Jelena Maletkovic, Marvin Bergsneider, Won Kim, Marilene B. Wang, Jeffrey D. Suh, Michael Linetsky, Noriko Salamon, Sandra Pekic Djurdjevic, Anthony P. Heaney. **“Reassessing Routine Postoperative Imaging in Acromegaly: Insights from a Cohort with Biochemical Remission”**. *Surgeries*; 2026; 7:43. doi: 10.3390/surgeries7020043. M22, IF 1.0

F) Decisions of the Faculty's Ethics Committee and other necessary ethical approvals

The research for the doctoral dissertation of Dr. Jelena Maletković was conducted with the approval of the Ethics Committee of the Faculty of Medicine, University of Belgrade, dated June 26, 2018, under reference number: 2650/VI-8, and the Ethics Committee of the healthcare institution University Clinical Center of Serbia on May 7, 2026, under reference number 455/18.

G) Conclusion (justification of the scientific contribution)

The doctoral dissertation entitled "Outcomes of Surgical Treatment of Pituitary Tumors via Transsphenoidal Endoscopic Approach and Prognostic Factors for Tumor Recurrence and Residual Tumor Growth" by Dr. Jelena Maletković represents an original scientific contribution to the comprehensive, comparative, and long-term evaluation of outcomes following transnasal transsphenoidal (TNTS) surgical treatment of pituitary tumors. Through a parallel analysis of data from two eminent university centers (UCLA and UKCS), this study provides valuable insights into predicting postoperative remission, early identification of recurrence risks, and modalities for the long-term follow-up of patients with various histopathological subtypes of adenomas. The implementation of a rigorous methodological criterion—mandatory multi-year postoperative follow-up (ranging from 3 to 11 years)—directly enhanced the quality and reliability of the obtained results. Although this approach numerically reduced the final sample size of patients, it enabled a clear definition of factors influencing the stability of biochemical and radiological remission over time. In this manner, this work scientifically confirms that the treatment facility (UCLA compared to UKCS) does not have a statistically significant impact on the success rate of initial cure in Cushing's disease and acromegaly, thereby affirming the consistency of surgical and endocrinological practice across highly specialized tertiary institutions.

The most important scientific and prognostic contributions of the work can be grouped into several key areas:

1) Identification of superior predictors of cure: The study clearly identifies smaller tumor dimension (microadenoma) as the strongest positive predictor of surgical remission in both centers. On the other hand, older patient age was identified as a significant factor associated with inferior surgical outcomes at UCLA, indicating the biological specificities of older patients and the need for a tailored therapeutic approach in this population group.

2) Redefining the role of Ki-67 and the KNOSP score in clinical practice: The work provides an important scientific insight by demonstrating that the general proliferative

index Ki-67 and the KNOSP score of the degree of invasiveness do not possess absolute predictive power at the level of the entire sample. However, the study elucidates a prognostic nuance—an elevated Ki-67 (>3%) becomes a highly significant marker of aggressiveness exclusively within that specific subgroup of patients who already presented with a definitive radiological residual tumor at the first three-month follow-up (with as many as 50% of these patients showing further postoperative growth).

3) Determining the clinical specificity of non-functioning adenomas (NFAs): The results prove that non-functioning tumors exhibit a significantly lower incidence of initial remission and a shorter duration of the same. They were identified as the subtype with the highest propensity for residual tumor growth or de novo recurrence, which scientifically justifies specific, careful endocrinological and radiological screening for this group of patients. The practical contribution of the work is contained in a concrete proposal for the modification of existing clinical follow-up protocols, thereby directly improving the patients' quality of life and rationalizing healthcare resources.

4) Optimization of the intervals for nuclear magnetic resonance (NMR) of the sellar region: Based on evidence that complete tumor removal (a negative NMR finding three months and one year post-surgery) carries an extremely low risk of further growth (only 6%), the work proposes a safe extension of the intervals between follow-up imaging scans. The subsequent NMR can be delayed for at least two years, and later intervals extended to 3 to 5 years. This significantly reduces the financial burden on the healthcare system and the exposure of patients to redundant examinations. In conclusion, this work scientifically establishes the importance of initial total resection as the main pillar of long-term prognosis and clearly affirms the necessity of a multidisciplinary team approach (neurosurgery, endocrinology, neuroradiology, histopathology) to achieve superior results in the treatment of patients suffering from pituitary tumors.

This doctoral dissertation was conducted in accordance with all principles of scientific research. The objectives were precisely defined, the scientific approach was original and carefully selected, and the working methodology was state-of-the-art. The results are clearly and systematically presented and discussed, and appropriate conclusions have been derived from them.

Based on all the above, and taking into account the candidate's scientific work to date, the committee proposes to the Academic Council of the Faculty of Medicine, University of Belgrade, to accept the doctoral dissertation of Dr. Jelena Maletković and approve its public defense for the purpose of acquiring the academic title of Doctor of Medical Sciences.

In Belgrade, July 7, 2026.

Committee Members:

Prof. Dr. Djuro Macut

Prof. Dr. Dragana Miljic

Prof. Dr. Milica Medic Stojanoska

Mentor:

Prof. Dr. Sandra Pekic Djurdjevic

Co-mentor:

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