Surgical treatment of prolactinomas - our experience

Gnjidić, Živko; Kudelić, Nenad; Sajko, Tomislav; Malenica, Maša; Stipić, Darko; Rotim, Krešimir

Source / Izvornik: **Collegium Antropologicum, 2014, 38, 571 - 576**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:798505

Coll. Antropol. **38** (2014) 2: 571–576
Original scientific paper

Surgical Treatment of Prolactinomas – Our Experience

Živko Gnjidić[1], Nenad Kudelić[2], Tomislav Sajko[1], Maša Malenica[3], Darko Stipić[1] and Krešimir Rotim[1]

[1] University of Zagreb, University Hospital Center »Sestre milosrdnice«, Department of Neurosurgery, Zagreb, Croatia
[2] General Hospital Varaždin, Department of Neurosurgery, Varaždin, Croatia
[3] University of Zagreb, University Hospital Center »Sestre milosrdnice«, Department of Neuropediatrics, Zagreb, Croatia

A B S T R A C T

The dilemma of whether to apply surgical or drug treatment to prolactinomas has been ongoing for the past 30 years. The aim of this study is to compare the early postoperative values of prolactin (PRL) in two groups of patients with prolactinomas: those who underwent primary surgical-treatment, and those who underwent surgery after a dopamine agonist (DA) therapy. We present the results of surgical treatment on a series of 161 patients with prolactinomas. Surgery was the primary treatment in 65 patients, while 96 patients had surgery following a long-term treatment with a DA. All surgically treated prolactinomas were operated in the standard transsphenoidal, microsurgical approach. The criteria for hyperprolactinemia remission was a PRL level under 25 ng/ml. Early normalization of PRL was achieved in 92% of those patients who underwent primary surgical-treatment, yet it was achieved in only 42% of patients who were operated on after receiving a long-term drug treatment with a DA. The highest prevalence of postoperative normalization of PRL was achieved in a group of patients with microadenomas who were primarily operated on (98%). The worst results in postoperative normalization of PRL were found in the group of patients with macroadenomas who received a long-term drug treatment with a DA first. These results show our surgical experience in treating prolactinomas. Using surgical treatment, the best clinical outcome was acieved with microprolactinomas and intrasellar, well-confined macroprolactinomas. Nevertheless, we stress the need of an individualized approach and recommend treatment in multidisciplinary centres for pituitary diseases.

***Key words**: prolactinoma, transsphenoidal, microsurgical, dopamine agonists, hyperprolactinemia, prolactinoma surgery*

Introduction

Prolactinomas or lactotropic adenomas are the most common hormone-secreting adenomas of the pituitary gland with a prevalence of about 45% of all pituitary adenomas. Ninety-nine percent of these are histologically-benign neoplasms.

In the last half of the 20th century, the surgical treatment of prolactinomas went from being an almost completely-abandoned method, to having a sudden increase after the reaffirmation of Hardy's transsphenoidal microsurgical approach, to then again rapidly decreasing after the introduction of dopamine agonists (DA)[1–5]. Now, after complex consideration of the results of both modes of treatment, the number of operated patients has once again increased.

In the early 1970s the DAs were identified as a possible effective therapy for the treatment of hyperprolactinemia[6]. In 1973, R.M. MacLeod and J.E. Lehmeyer reported an observation of the reduction of the prolactinoma tumor mass under the influence of ergot alkaloids[7]. Shortly thereafter, the first publications on the long-term effects of bromocriptine in cases of galactorrhea and hypogonadism appeared[8].

In 1978, the U.S. Food and Drug Administration (FDA) approved the use of bromocriptine in the treatment of hyperprolactinemia caused by prolactinomas[9]. Subsequently, a vast number of studies described the normalization of prolactin (PRL) levels in more than 90% of cases and significant reductions of tumor size in

Received for publication September 11, 2012

about 85% of patients treated with bromocriptine[10]. The excitement regarding the effects of dopamine agonists was so great that in 1982 the article, Bromocriptine reduces pituitary tumor size and hypersecretion. Requiem for pituitary surgery?[11], was published by R.F. Spark and his associates**.** Following this publication, a widely accepted consensus followed using DAs as the first-line treatment in patients with prolactinomas. Shortly thereafter, long-acting DAs, kabergolin and quinagolide appeared in clinical use and were proven to be much more effective than bromocriptine[10,12,13].

Following the breakthrough of DA as a treatment option, it was recommended that surgical treatment be only applied in patients with a poor response to drug therapy, intolerance to medicament treatment, prolactinomas with large cystic-parts, cases of spontaneous liquorrhea, cases of those with rapid development of neurological deficits (as in adenoma apoplexy), or in the case of an individual patient's refusal of long-term drug therapy[14,15].

In light of these new standards for treatment, the number of surgically treated prolactinomas rapidly decreased. However, soon thereafter, a new perspective was found. It was observed that under the action of bromocriptine there were varying degrees of calcification, amyloid deposits, perivascular and interstitial fibrosis in the extracellular space, and that the prolactinomas' cells contracted[16–18]. These changes in the adenoma tissue complicated selective, surgical removal of the tumor, resulting in significantly-lower postoperative normalization rates of PRL[19]. Once again, these observations led to a review of prolactinoma treatment methods.

Subjects and Methods

At our clinic during a 25 year period from 1982 to 2007, more than 1,300 patients with pituitary adenomas were operated upon, of which 161 were prolactinomas (12.4%). Surgery was the primary mode of treatment in 65 (40%) patients, while 96 (60%) patients underwent surgery after a long-term drug therapy with a DA.

All surgically-treated prolactinomas underwent a standard transsphenoidal, transseptal microsurgical approach operation performed by a single neurosurgeon[3].

As for the definition of remission for hyperprolactinemia, we used the normalization of basal values of PRL concentrations below 25 ng/mL.

Results

The age of the patients ranged from 17–70 years, with an average age of 37.11 years, median age of 36 years, and a SD of 11.81. Gender: women 134 (83.22%), men 27 (16.78%).

There were 98 microprolactinomas (60.8%) and 63 macroprolactinomas (39.2%). We found a statistically--significant difference of the incidence of micro and macroadenomas between men and women (Table 1). Amongst male patients, the majority were macroprolactinomas (88%) while women had microprolactinomas in 70% of cases (Table 1).

TABLE 1
DISTRIBUTION BY GENDER AND SIZE OF ADENOMAS

	Men No (%)	Women No (%)	Total No (%)
Microadenomas	3 (11.11%)	95 (70.89%)	98 (60.8%)
Macroadenomas	24 (88.88%)	39 (29.10%)	63 (39.2%)
Total	27 (16.78%)	134 (83.22%)	161 (100%)

(Fisher exact test) $p<0.001$

Before surgery, the serum PRL levels ranged from 40–920 ng/mL, median 160 ng/mL, mean/average value of 207.63 ± 158.31. After surgery, the values of PRL dropped significantly from 4–250 ng/mL, median 23 ng/mL, mean/ average value 28.26 ± 24.55.

Following surgery, the normalization of PRL values (<25 ng/mL) was achieved in 100 patients (62.2%) patients, while the 61 (38.8%) remaining patients had PRL values greater than 25 ng/mL (Table 2).

TABLE 2
SUCCESS OF SURGICAL THERAPY DEPENDING ON PRIMARY TREATMENT METHOD

	Postoperative PRL <25 ng/mL	Postoperative PRL >25 ng/mL	Total
Primary surgical treatment	60 (92%)	5 (8%)	65 (40.3%)
Primary treatment with a DA	40 (42%)	56 (58%)	96 (59.6%)
Total	100 (62.2%)	61 (38.8%)	161 (100%)

Evidence of a statistically significant difference of postoperative normalization of PRL frequency: PRL: $\chi^2 = 42.24$, df = 1, $p< 0.001$.

In the group of primary operated-upon patients, we found a statistically-significant difference in early postoperative normalization of PRL between the groups of patients with micro and macroadenomas (Table 3).

In the group of patients who were previously treated with a DA, the postoperative difference in the normalization of PRL between the micro and macroadenoma was also found to be statistically significant (Table 4).

TABLE 3
NORMALIZATION OF PRL IN PATIENTS TREATED WITH PRIMARY SURGERY

	No, (%)	PRL <25 ng/mL	PRL >25 ng/mL
Microprolactinomas	54 (83%)	53 (98%)	1 (2%)
Macroprolactinomas	11 (17%)	7 (63.6%)	4 (36.4%)

Fisher exact test $p=0.002$

TABLE 4
NORMALIZATION OF PRL IN PATIENTS OPERATED AFTER A LONG-TERM DRUG THERAPY

	No (%)	PRL <25 ng/mL	PRL >25 ng/mL
Microprolactinomas	44 (46%)	31 (70.4%)	13 (29.6%)
Macroprolactinomas	52 (54%)	9 (17.3%)	43 (82.7%)

χ^2=27.69; df=1; p<0.001

PRL levels in patients with microadenomas prior to surgery ranged from 40–270 ng/mL, median 139 ng/ml, mean 170.07±120.16. Following surgery, PRL values fell to 4–64 ng/mL, median 19.5 ng/mL, mean 20.37±11:43. In the macroadenoma group, the PRL serum level before surgery was in the range of 58–920 ng/mL, median 200 ng/ml, mean 266.05±190.77. After surgery, serum PRL levels ranged from 8–250 ng/mL, median 35.40 ng/mL, mean 54±30.15. The difference in values of PRL before and after surgery was statistically significant in both groups p<0.001 (Table 5).

TABLE 5
PRL LEVELS BEFORE AND AFTER SURGERY IN GROUPS WITH MICRO AND MACROADENOMAS

	PRL before surgery in ng/mL	PRL after surgery in ng/mL
Microadenomas	170.07±120.16	20.37±11.43
Macroadenomas	266.05±190.77	40.54±30.15
Total	207.63±158.31	28.26±24.55

Fischer exact test, p<0.001

The degree of invasiveness was determined on the basis of neuroradiological criteria (34, 35, 36) and the World Health Organization's guidelines of a five-level classification of pituitary adenomas (37). In the group of invasive tumors, 90% were macroadenomas where in the group of noninvasive tumors, only 30% were macroadenomas (Table 3). In our series, a statistically-significant difference was found in the degree of invasiveness between micro and macroadenomas (Fisher exact test (p<0.001)). In our group of patients, there was a total of 22 invasive prolactinomas, of which two were microadenomas and 20 were macroadenomas. There were 139 noninvasive adenomas, of which 96 were microadenomas and 43 were macroadenomas (Table 6).

TABLE 6
INVASIVENESS OF PROLACTINOMA

	Invasive adenomas	Noninvasive adenomas	Total No (%)
Microadenomas	2 (9.09%)	96 (69.06%)	98 (60.8%)
Macroadenomas	20 (90.91%)	43 (30.94%)	63 (39.2%)
Total	22 (13.66%)	139 (86.33%)	161 (100%)

Fisher exact test p<0.001

Complications

Twenty-two patients (13.6%) had transitory diabetes insipidus (DI) lasting up to one week. Four patients (2.5%) had DI lasting one month and one patient (0.6%) had DI that remained permanently. Hypocorticism was recorded postoperatively in two patients (1.25%), and panhypopituitarism in one patient (0.6%). One patient (0.6%) had paresis of the abducens nerve 3 months p ostoperatively. There was no mortality in this series.

The long-term follow-up data of operated patients has not been completed. After the dissolution of the former state of Yugoslavia, many patients became inaccessible, some did not respond to the invitation for a medical examination, or the medical reports of some of the patients were useless for proper analysis. However, reliable long--term monitoring of PRL values was obtained from 81 patients with a follow-up range of 2–23 years. It should be noted that out of 52 patients who postoperatively had acceptable values of PRL, 7 (13.46%) of them had a recurrence of hyperprolactinemia during the long-term follow-up. In two of these patients hyperprolactinemia developed after a year, in one patient after three years, in another two patients after four years, in one after 7 years, and in one after 12 years. Three patients from this group had recidivism of the adenoma verified by postoperative MRI scans, but there was no need for revisional surgery. Two patients were treated with a DA and one underwent treatment with Gamma Knife®.

Discussion

Our experience in primary surgical treatment of prolactinomas showed improvement with a two times better result than surgery after a DA. This is particularly evident in cases of microadenomas and intrasellar well-contained /defined adenomas.

Similar experience was published by M. Losa, who stated that in most cases, the transsphenoidal surgery of prolactinomas can be definitive therapy, particularly in patients with intrasellar tumors[20]. On the basis of similar results, A. Liuzzi responded to R.F. Spark's publication from 1982, Bromocriptine reduces pituitary tumor size and hypersecretion. Requiem for pituitary surgery?[11], by making an opposing statement and asking: »Microprolactinomas: why requiem for surgery?«[21]. In a publication by H.E. Turner in 1999, he emphasized that patients with hyperprolactinemia, particularly those with microprolactinomas, could often achieve satisfactory permanent improvement using the transsphenoidal microsurgical approach by an experienced neurosurgeon. He pointed out that the cost of the operation, which often provides a permanent cure is the same to a ten-year cost of uncomplicated therapy with a DA[22], and is also cheaper than a lifelong drug therapy[23].

In a study named »Therapeutic controversy: management of prolactinomas«, after discussing the biological and social circumstances of each individual patient, M.E. Molitch and associates came to a very similar conclusion

about the benefits of surgical therapy[24]. In a publication by S.G. Soule, a low therapy success rate was presented for prolactinomas pretreated with a DA compared with those prolactinomas treated with surgery as the first-line method. It was also suggested that resistance to drug therapy is associated with resistance to surgical treatment[25].

Poor success rates in the normalization of PRL values after surgery in patients pretreated with DAs could be attributed to fibrous induration of the adenomas. In an article from 1982, A.M. Landolt reported better normalization of PRL values in patients with microprolactinomas who were not preoperatively treated with bromocriptine[26]. He claimed that bromocriptine pre-treatment, subsequent fibrosis, and loss of clear boundaries between the adenoma and normal pituitary tissue reduces the possibility of selective removal of the tumor, resulting in significantly lower postoperative normalization of PRL[26]. In 1986, using light microscopy, M.M. Esiri and associates also confirmed and described fibrous induration of adenomas induced by DAs. They described an increase in tissue fibrosis in accordance with the duration of therapy. Prolonged use of DAs changes the gland and the border between normal tissue and the adenoma resulting in an obscure difference in color and consistency making microdissection after primary DA therapy very difficult[27].

However, some authors have different and even contradictory experiences concerning DA therapy[28,29]. M.E. Sughrue claims that preoperative treatment with DAs, in addition to decreasing tumor size, increases the possibility of surgical removal of the tumor and achieves better postoperative control of prolactin[30]. The only study in which there were no documented side effects of prolonged pretreatment with DAs, was by G. Faglia and associates dating from 1983. They discontinued medicament DA therapy about 8.4 months before surgery, which may have allowed the reversibility of bromocriptine-induced changes in tumor consistency[31].

Differences in treatment success between macroprolactinomas and microprolactinomas

Our data shows that the highest incidence of normalization of PRL values was achieved in a group of patients with microadenomas primary operated upon (98%) (Table 5). Patients with macroadenomas who were on previous long-term DA medicament therapy (17.3%) had the worst results (Table 6).

This corresponds to the results of J.G.M. Klijn and associates who found that tumor volume is closely correlated with serum PRL levels and thus becomes quite a reliable indicator of the expected surgical results, which was later confirmed in several other studies[32]. Other authors have had similar conclusions on the impact of tumor size and preoperative PRL levels on the success of the operation[33]. K. Sinkunas found a very high percentage (90%) of postoperative normalization of PRL levels in women with microprolactinomas who were not treated with DAs prior to surgery. He proposed that the main prerequisites for a good final result with surgical treatment of prolactinomas were younger age, noninvasive tumors, serum prolactin values lower than 2309 mU/L, and no usage of DAs prior to surgery[34].

Invasiveness

We have found that there is a much higher incidence of invasive adenomas in macroadenomas (Table 6), which corresponds to the opinion that size and invasiveness are the main factors that influence the degree of success of the operation. R.V. Randall published that the normalization of PRL levels occurred in 5 of 10 patients (50%) with macroadenomas, but in only 5 of 25 (25%) patients with invasive adenomas[35]. In l987, J.S. Bevan and associates described successful treatment of only 28.6% of macroprolactinomas and there was not a single successful normalization of PRL values in the subgroup of 8 tumors which were invasive before surgery[36]. Similarly, in 1992, J. Webster and associates reported successful treatment in 80% of 30 patients with adenomas of 10–19 mm in diameter while the treatment success in those with tumors of 20 mm or more was only 57%[37].

Arguments in favor of surgical treatment

When choosing any treatment method, possible adverse effects should be kept in mind. Numerous publications warn of fibrotic changes in pituitary tissue, and in vital organs such as the heart and lungs[38–45]. Additionally, the European Medicines Agency (EMA) issued a press-release in 2008 warning of increased risk of fibrosis due to the use of bromocriptine, cabergoline, dihydro-ergocriptine, lisurid and pergolin.

Nausea, vomiting, dizziness, hypotension, and headaches were found to be frequent side-effects. Chronic use of Das was found to cause painful peripheral vasospasms and psychiatric symptoms (depression and anxiety), especially in those with a previous psychiatric history having further advancement of their disease[45]. There is also a possibility of liquorrhea which sometimes occurs after contraction of macroadenomas[46,47]. Numerous patients on DA therapy, despite normalization of PRL levels and regression of clinical manifestations, often experienced anxiety due to the fact that DAs did not destroy the tumor mass itself, and is instead still present in their bodies. They also feared the possibility of disease relapse after cessation of DA therapy[45].

Perioperative complications of selective transsphenoidal adenomectomy are rare and highly dependent on both the expertise of the neurosurgeon and the equipment of the health facility[3,5,48–50]. About 50% of patients with macroadenomas were found to have various forms of preoperative hypopituitarism related to the long-term compressive effect of the tumor. Hypopituitarism resulting from operative trauma is also often seen in these patients, while improvement of the pituitary function rarely occurs after the surgery[51]. Those patients with macroprolactinomas and hypopituitarism should receive standard adjuvant hormone therapy.

The recurrence of hyperprolactinemia after a long period (1–7 years) of normalization of PRL values that we found in our series is difficult to explain. A similar observation has been described only by J.A. Thomson so far, but with no rational explanation[52]. It could be the case of a new prolactinoma growth in the remaining healthy tissue of the pituitary gland or incomplete removal of the primary tumor.

Due to the possibility of pseudoprolactinoma, it is important to emphasize that a reliable diagnosis of prolactinoma can be confirmed exclusively by immunohistochemical verification, which is not possible without surgery[3,53].

The goals of prolactinoma therapy are very demanding. They consist of removing symptoms and signs of hyperprolactinemia including infertility, sexual dysfunction, osteoporosis, normalizing the hormonal status, preserving residual pituitary function, correcting visual field deficits and dysfunction of other cranial nerves, removing clinical and radiological signs of tumor existence, preventing progression or recurrence of the disease, improving quality and length of the patients' life, and preventing complications. These objectives are difficult to achieve even with the combination of multiple treatment modalities[3].

The goals of treatment for micro and macroprolactinomas are similar, but for most microprolactinomas control of the tumor mass is not as clinically significant, because it will not cause neurological deficits, nor grow quickly enough to create a potential risk over time. In most cases of macroprolactinomas which have the potential to create neurological effects, the control of tumor growth and its reduction in size is a priority in relation to the treatment of hypogonadism[54].

In 2006, M. Gillam and associates analyzed the results of 50 published studies of prolactinoma treatment. With regard to the importance of tumor size and PRL levels prior to and immediately post-surgery, they emphasized the expertise of neurosurgeons as the dominant factor in achieving good postoperative results[54]. According to the results of this analysis, the rate of recidivism of hyperprolactinemia after initial postoperative normalization of PRL values varies among different clinical centers and ranges between 0 and 50 percent. It should be noted that the majority of recidivisms were not confirmed by neuroradiological imaging. Patients with gigantic adenomas (>40 mm) and considerable invasion of the cavernous sinuses were found to have almost no chance of successful surgical treatment.

Conclusion

Based on our results, our experience, and the work of other authors, we believe that pituitary tumors should be treated in multidisciplinary centers with an experienced neurosurgeon. We emphasize that while the experience and expertise of the neurosurgeon is an important factor in treatment success, approach to the patient must be individualized. Our surgical experience (presented in this paper) shows that primary surgical treatment of prolactinomas is a viable therapeutic modality, especially in cases of microprolactinomas and intrasellar, well confined macroprolactinomas.

The limitation of this study is that it does not present the whole cohort of patients treated. The results of exclusively medicament treatment of prolactinomas are missing thus making it impossible to compare and draw conclusions regarding the treatment method of choice.

Acknowledgements

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. This research did not receive any specific grant from any funding agency in the public, commercial or non-for-profit sector.

REFERENCES

1. GANDHI C, Post K, Neurosurgery Focus, 11 (2001) 1. DOI: 10.3171/foc.2001.11.4.8. — 2. GNJIDIĆ Ž, KOVAČ D, PETRIC V, SAJKO T, TALAN-HRANILOVIĆ J, Liječ vjesn, 124 (2002) 389. — 3. GNJIDIĆ Ž, Liječ vjesn, 126 (2004) 26. — 4. GROSVENOR A, LAWS E, Pituitary, 11 (2008) 337. DOI: 10.1007/s11102-008-0095-5. — 5. GNJIDIĆ Ž, SAJKO T, KUDELIĆ N, MALENICA M, Acta Clin Croat, 45 (2006) 53. — 6. PASTEELS JL, DANGUY A, FRÉROTTE M, ECTORS F, Ann Endocrinol (Paris), 32 (1971) 188. — 7. MACLEOD RM, LEHMEYER JE, Cancer Res, 33(4) (1973) 849. — 8. THORNER MO, MCNEILLY AS., HAGAN C, BESSER MG, British Medical Journal, 2 (1974) 419. — 9. VANCE ML, EVANS WS, THORNER MO, Ann Intern Med,100 (1984) 78. — 10. CICCARELLI E, CAMANNI F, Drugs, 51 (1996) 954. DOI: 10.2165/00003495-199651060-00004. — 11. SPARK RF, BAKER R, BIENFANG DC, BERGLAND R, JAMA, 247 (1982) 311. DOI: 10.1001/jama.247.3.311. — 12. WEBSTER J, PISCITELLI G, POLLI A, FERRARY CL, ISMAIL I, SCANLON MF, N Engl J Med, 331 (1994) 904. DOI: 10.1056/NEJM199410063311403. — 13. COLAO A, MEROLA B, SARNACCHIARO F, DI SARNO A, LANDI ML, MARZULLO P, CERBONE G, FERONE D, LOMBARDI G, Hormone Research, 5 (1995) 222. DOI: 10.1159/000184630. — 14. GROSSMAN A, BASSER GM, BMJ, 290 (1985) 182. DOI: 10.1136/bmj.290.6463.182. — 15. NOMIKOS P, BUCHFELDER M, FALBUSCH R, Journal of Neuro-Oncology, 54 (2001) 139. DOI: 10.1023/A:1012905415868. — 16. TINDALL GT, KOVACS K, HORVATH E, THORNER MO, J Clin Endocrinol Metab, 55 (1982) 1178. — 17. LANDOLT AM, OSTERWALDER V, J Clin Endocrinol Metab, 58 (1984) 1179. — 18. BEVAN JS, ADAMS CB, BURKE CW, MORTON KE, MOLYNEUX AJ, MOORE RA, ESIRI MM, Clin Endocrinol (Oxf,) 26 (1987) 541. — 19. LANDOLT AM, Prolactinomas: preoperative bromocriptine treatment. Surgical results. In: BARROW DL (ed), Perspectives in Neurological Surgery (Quality Medical Publishing, St. Louis, 1990). — 20. LOSA M, MORTINI P, BARZAGHI R, GIOIA L, GIOVANELLI M, J Clin Endocrinol Metab, 87 (2002) 3180. DOI: 10.1210/jc.87.7.3180. — 21. LIUZZI A, OPPIZZI G, J Endocrinol Invest, 19(3) (1996) 196. DOI: 10.1016/S0026-0495(96)90090-6 — 22. TURNER HE, ADAMS CB, WASS JA, Eur J Endocrinol, 140 (1999) 43. DOI: 10.1530/eje.0.1400043 — 23. COULDWELL WT, WEISS MH, Pituitary, 7 (2004) 31. — 24. MOLITCH ME, THORNER MO, WILSON C, J Clin Endocrinol Metab, 82 (1997) 996. DOI: 10.1210/jc.82.4.996. — 25. SOULE SG, FARHI J, CONWAY GS, JACOBS H, POWELL M, Clinical Endocrinology, 44 (1996) 711. DOI: 10.1046/j.1365-2265-1996.738559.x. — 26. LANDOLT AM, KELLER PJ, FROESCH ER, MUELLER, Lancet, 2 (1982) 657. — 27. ESIRI MM, BEVAN JS, BURKE CW, ADAMS CBT, J Clin Endocrinol Metab, 63 (1986) 383. — 28. WEISS MH, TEAL J, GOTT P, WYCOFF R, YARDLEY R, APUZZO MLJ, GIANNOTA SL, KLETZKY O, MARCH C, Neurosurgery, 12 (1983) 180. — 29. PERRIN G,

TRELUYER C, TROUILLAS J, SASSOLAS G, GOUTELLE A, Pathol Res Pract, 187 (1991) 587. DOI: 10.1016/S0344-0338(11)80151-2. — 30. SUGHRUE ME, CHANG EF, TYREL JB, KUNWAR S, WILSON CB, BLEVINS LS JR, Pituitary, 12 (2009) 158. DOI: 10.1007/s11102-008-0135-1. — 31. FAGLIA G, MORIONDO P, TRAVAGLINI P, GIOVANELLI MA, Lancet, 1 (1983) 133. — 32. KLIJN JGM., LAMBERTS SWJ., DE JONG FH, DOCTER R, VAN DONGEN KJ, BIRKENHAGER JC, Clinical Endocrinology, 12 (1980) 341. — 33. NOMIKOS P, BUCHFELDER M, FALBUSCH R, Journal of Neuro-Oncology, 54 (2001) 139. DOI: 10.1023/A:1012905415868. — 34. SINKŪNAS K, RASTENYTE D, DELTUVA VP, KNISPELIS R, TAMASAUSKAS A, Medicina (Kaunas), 43(9) (2007) 691. — 35. RANDALL RV, LAWS ER, JR, ABBOUD CF, EBERSOLD MJ, KAO PC, SCHEITHAUER BW, Mayo Clinic Proceedings, 58 (1983) 108. — 36. BEVAN JS, ADAMS CB, BURKE CW, MORTON KE, MOLYNEUX AJ, MOORE RA, ESIRI M M, Clin Endocrinol (Oxf), 26 (1987) 541. — 37. WEBSTER J, PAGE MD, BEVAN JS, RICHARDS SH, DOUGLAS-JONES AG, SCANLON MF, Clin Endocrinol (Oxf), 36 (1992) 35. DOI: 10.1111/j.1365-2265.1992.tb02900.x. — 38. TAAL BG, SPIERINGS EL, HILVERING C, Thorax, 38 (1983) 396. — 39. BOWLER JV, ORMEROD IE, LEGG NJ, Lancet, 2 (1986) 466. — 40. WARD CD, THOMPSON J, HUMBY MD, J Neurol Neurosurg Psychiatry, 50 (1987) 1706. — 41. REDFIELD MM, NICHOLSON WJ, EDWARDS WD, TAJIK AJ, Ann Intern Med, 117 (1992) 50. — 42. PFITZENMEYER P, FOUCHER P, DENNEWALD G, CHEVALON B, DEBIEUVRE D, BENSA P, PIARD F, CAMUS P, Eur Respir J, 9 (1996) 1013. DOI: 10.1183/09031936.96.09051013. — 43. SHAUNAK S, WILKINS A, PILLING JB, DICK DJ, J Neurol Neurosurg Psychiatry, 66 (1999) 79. — 44. COLAO A, GALDERISI M, DI SARNO A, PARDO M, GACCIONE M, D'ANDREA M, GUERRA E, PIVONELLO R, LERRO G, LOMBARDI G, J Clin Endocrinol Metab. 93(10) (2008) 3777. DOI: 10.1210/jc.2007-1403. — 45. GNJIDIĆ Ž, Suvremeni međunarodni konsenzusi o izboru metode liječenja i standardizacija rezultata terapije s posebnim osvrtom na troškove liječenja. In:Gnjidić Ž (ed) Suvremeno kirurško liječenje tumora hipofize (Medicinska naklada, Zagreb, 2004). — 46. HILDEBRANDT G, ZIERSKI J, CHRISTOPHIS P, LAUN A, SCHATZ H, LANCRANJAN I, KLUG N, Acta Neurochir (Wien), 96 (1989) 107. — 47. HOLNESS RO, SHLOSSBERG AH, HEFFERNAN LP, Neurology, 34 (1984) 111. — 48. CIRIC I, RAGIN A, BAUMGARTNER C, PIERCE D, Neurosurgery, 40 (1997) 225. DOI: 10.1097/00006123-199702000-00001. — 49. BARKER 2ND FG, KLIBANSKI A, SWEARINGEN B, J Clin Endocrinol Metab, 88 (2003) 4709. DOI: 10.1210/jc.2003-030461. — 50. SUDHAKAR N, RAY A, VAFIDIS JA, Br J Neurosurg, 18 (2004) 507. — 51. NELSON JR AT, TUCKER JR HS, BECKER DP, J Neurosurg, 61 (1984) 577. — 52. THOMSON JA, GRAY CE, TEASDALE GM, Neurosurgery, 50 (2002) 36. DOI: 10.1097/00006123-200201000-00007. — 53. GNJIDIĆ Ž, Pregled suvremenih terapijskih mogućnosti i smjernica kirurškog liječenja tumora selarne regije. In: GNJIDIĆ Ž (ed), Suvremeno kirurško liječenje tumora hipofize (Medicinska naklada, Zagreb, 2004). 54. GILLAM M, MOLITCH M, LOMBARDI G, COLAO A, Endocrine reviews, 27 (2006) 485. DOI: 10.1210/er.2005-9998.

D. Stipić

University of Zagreb, University Hospital Center »Sestre milosrdnice«, Department of Neurosurgery, Vinogradska 29, 10000 Zagreb, Croatia
e-mail: stipic@gmail.com

PROLAKTINOMI – KIRURŠKO ILI MEDIKAMENTOZNO LIJEČENJE?

S A Ž E T A K

Dilema, operirati ili medikamentozno liječiti prolaktinome prisutna je već 30 godina. Cilj ovog istraživanja je usporediti normalizaciju ranih postoperativnih vrijednosti prolaktina (PRL) u dvije skupine bolesnika sa prolaktinomima: primarno kirurški liječenih i onih koji su kirurški liječeni nakon prethodne terapije agonistima dopamina (DA). U ovom članku prezentirani su rezultati operacijskog liječenja 161 bolesnika s prolaktinomom. Operacija je bila primarni način liječenja u 65 bolesnika, dok je 96 bolesnika operirano nakon dugotrajne medikamentozne terapije s DA. Svi kirurški tretirani prolaktinomi operirani su standardnim, transsfenoidalnim, mikrokirurškim pristupom od strane jednog operatera. Kao definiciju remisije hiperprolaktinemije koristili smo normalizaciju koncentracije bazalnih vrijednosti prolaktina (PRL) ispod 25 ng/mL. U primarno operiranih bolesnika postignuta je rana postoperativna normalizacija PRL u 92% slučajeva, a u operiranih nakon dugotrajne medikamentozne terapije sa DA u samo 42% slučajeva. Najbolje rezultate u normalizaciji koncentracije prolaktina postigli smo u skupini bolesnika sa mikroadenomima koji su primarno operirani (98%), a najlošije rezultate u skupini bolesnika s makroadenomima koji su prethodno bili na dugotrajnoj medikamentoznoj terapiji s DA (17,3%). Ovi rezultati prikazuju naše iskustvo u kiruškom liječenju prolaktinoma. Najbolji klinički rezultat imali smo sa mikroprolaktinomima i intraselarnim, dobro ograničenim makroprolaktinomima. Ističemo potrebu multidisciplinarnog i individualnog pristupa u izboru metode liječenja.