Nelson's syndrome

Fountas, Athanasios; Karavitaki, Niki

DOI:

[10.1016/j.ecl.2020.05.004](https://doi.org/10.1016/j.ecl.2020.05.004)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Fountas, A & Karavitaki, N 2020, 'Nelson's syndrome: an update', *Endocrinology and Metabolism Clinics of North America*, vol. 49, no. 3, pp. 413-432. <https://doi.org/10.1016/j.ecl.2020.05.004>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Title

Nelson's syndrome: an update

Authors

Athanasios Fountas, MD, MSc, Clinical Research Fellow, e-mail: a.fountas@bham.ac.uk

Niki Karavitaki, MD, MSc, PhD, FRCP, Senior Clinical Lecturer in Endocrinology & Honorary Consultant Endocrinologist, e-mail: n.karavitaki@bham.ac.uk (corresponding author)

Affiliations for both authors

¹Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK; ²Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, B15 2TH, UK; ³Department of Endocrinology, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, B15 2TH, UK.

Mailing address for both authors

Institute of Metabolism and Systems Research
College of Medical and Dental Sciences, University of Birmingham
IBR Tower, Level 2, Birmingham, B15 2TT, UK

Disclosure statement

The authors have nothing to disclose

Keywords

Nelson's syndrome, Cushing's, bilateral adrenalectomy, corticotroph tumor progression, tumor growth.

Key points (List 3 to 5 key points of approximately 25 words each that summarize the main points of the article)

1. Patients with Cushing's disease treated with bilateral adrenalectomy require long-term monitoring for the development of Nelson's syndrome.
2. Corticotroph tumor growth is essential for Nelson's syndrome diagnosis; nonetheless, gradually increasing ACTH without demonstrable tumor enlargement need to be included in the diagnostic algorithm.
3. Data on factors predicting Nelson's syndrome development are conflicting; high ACTH during the first year after bilateral adrenalectomy is the most consistently reported one.
4. Surgery followed or not by radiotherapy in cases of NS is associated higher tumor control rates compared with observation alone.
5. A subset of patients with NS will demonstrate aggressive tumor behavior; predictive factors are unknown, management is individualized and prognosis may be poor.

Synopsis

Nelson's syndrome (NS) is a potentially severe condition which may develop in patients with Cushing's disease treated with bilateral adrenalectomy (BAL). Although there is no formal consensus on what defines NS, corticotroph tumor growth and/or gradually increasing ACTH levels are important elements in the diagnostic approach. Pathogenesis of NS is still not clarified and well-established predictive factors for its development are lacking; high ACTH levels during the first year after BAL is the most consistently reported predictive parameter. Management options for NS include surgery combined or not by radiotherapy, radiotherapy alone, and observation, whilst medical treatments have not shown consistent results. Treatment strategies should be individualized. A subset of patients with NS will demonstrate aggressive tumor behavior; predictive factors for this are unknown, management can be challenging and prognosis may be poor with malignant transformation and lethal outcomes.

.

Introduction

Despite the advances in pituitary surgery, radiotherapy and medical treatment of Cushing's disease (CD), bilateral adrenalectomy (BLA) still holds a place in the management of this condition, particularly in cases refractory to other therapeutic modalities, or as an emergency measure in patients with severe manifestations of hypercortisolemia. BLA offers immediate control of the cortisol excess but Nelson's syndrome (NS) is a potential complication with various adverse sequelae¹⁻⁹.

More than 60 years since the first description of the syndrome by Don Nelson and colleagues¹⁰, this condition is still surrounded by uncertainties on its diagnosis, management and long-term outcomes. This is mainly attributed to the rarity of NS but also to the lack of sufficient quality data, as most of the studies have significant heterogeneity in their diagnostic criteria, monitoring/management approaches and treatment end points^{2,4,7,8,11-13}.

In this review, we provide an update on NS, focusing on studies published after 1990, when the use of magnetic resonance imaging (MRI) was embedded in clinical practice, and we identify areas requiring further research in this field.

Definition of NS

Currently, there is no formal consensus on what defines NS and the diagnostic criteria vary amongst available studies (Table 1). In most of the published literature, diagnosis of NS is based on three main axes: 1) radiographic evidence of corticotroph tumor growth (if tumor was evident on the pre-BLA imaging) or identification of tumor (if pre-BLA imaging was negative for tumor), 2) increased plasma adrenocorticotrophic hormone (ACTH) levels and 3) development of skin pigmentation.

Radiographic evidence of corticotroph tumor growth is the most frequently used criterion for NS diagnosis, either alone^{4,13-16}, or in combination with increased ACTH levels and/or

pigmentation^{2,17-29}. In the MRI era, early detection of marginal tumor growth (even before clinical manifestations become evident) is possible, giving ground to the concept of replacing the term NS with “corticotroph tumor progression”¹⁴. Notably, the definition of tumor growth varies significantly in the published studies. In the majority, no specific size or volume criteria have been described and simply radiographic evidence of corticotroph tumor growth or identification of new tumor (when previous pituitary imaging was negative) was sufficient for NS diagnosis^{2,15-17,19-21,23-26,28,29}. In other studies, increase in tumor size of at least two mm in one dimension compared with previous imaging was a requirement^{4,14}, while in another report, growth was accepted only if tumor volume exceeded 10% of its original one¹³. Further applied criteria include growth of adenoma that led to surgery or radiotherapy^{12,30}, or presence of a macroadenoma²⁷.

Markedly elevated ACTH levels have been used as a sole diagnostic criterion of NS^{31,32}, or together with imaging findings¹⁷, skin pigmentation^{33,34} or both^{19,20,22-25,27,28}. However, the ACTH values differ between studies and no specific cut-off has as yet been defined (Table 1). Furthermore, the timing of the ACTH sampling is rarely reported or, when provided, it varies considerably between the series (simply fasting ACTH^{23,27}, or at any time point^{31,33} or in mid-afternoon²⁸). Interestingly, despite the suppressive effect of glucocorticoid treatment on ACTH levels, the impact of timing of glucocorticoid administration on the ACTH values has been taken into account in only three studies; in Thompson *et al.*¹⁹, patients were refrained from steroid replacement for 24 hours and in Mccance *et al.*²⁸, ACTH measurement was performed 6-8 hours after the last dose of hydrocortisone. Finally, ACTH >200 pg/ml 120 min after the usual hydrocortisone morning dose was considered diagnostic for NS by Jenkins *et al.*³².

Skin pigmentation has been used as a diagnostic criterion of NS in combination with corticotroph tumor growth and/or increased ACTH levels^{18-20,22-25,27-29,33,34}, only one series had adopted it as the only criterion²¹. Nowadays, with the advances in the hormone assays and in

neuroradiology techniques, diagnosis of NS can occur at an early stage making pigmentation less common as a presenting manifestation of NS.

Taking into account the above data but also the lack of studies establishing reliably diagnostic criteria for NS, the view of the authors is that diagnosis should rely on corticotroph tumor growth detected on pituitary MRI (evidence of tumor enlargement or, if previous pituitary imaging negative, new identification of tumor – compared with pre-BLA imaging), and/or gradually increasing ACTH levels in a patient compliant on adequate glucocorticoid replacement. Specific cut-off values for ACTH have not been validated and a suggested approach includes an increase in plasma ACTH (taken at 08:00 am, 20 hours after the last dose of glucocorticoid and before that morning's dose) of 100 pg/ml compared to a previous measurement (taken under the same conditions), or failure to suppress plasma ACTH to less than 200 pg/ml two hours after the morning glucocorticoid dose³⁵.

Epidemiology

The prevalence of NS ranges between 0 and 60%^{2,4,12-30,32,34,36-46} (Table 1) and is mainly influenced by the diagnostic criteria, the length of follow-up, and possible referral bias of the reporting centers. Notably, in the study with rate of 0%, there was no information for the diagnostic approach and the length of the follow-up was short [mean: 2.7 years (range 1.2-4.8)]⁴². Based on specific diagnostic criteria used, prevalence is between 5 and 53.4% for positive imaging^{4,13-16}; the 5% rate was reported by Mehta *et al.*¹³, where definition of NS required >10% increase of tumor volume compared to its original one, and, therefore, smaller growths were not included; in the remaining series, rates were $\geq 25\%$ ^{4,14-16}. Prevalence ranges between 32.4% and 55.6%^{32,34} for increased ACTH levels combined or not with skin pigmentation, and between 8.6% and 46.7% for radiological tumor growth, increased ACTH levels and skin pigmentation^{19,20,22-25,27,28}.

The interval between BLA and NS detection also varies between series (Table 1) reflecting again the differences in the diagnostic strategy. When only positive imaging was required, NS was diagnosed at mean/median period of 2-3 years after BLA^{4,14,16}, while when diagnosis was based on biochemical/clinical criteria, the median latency of NS onset was 1-5.7 years^{32,34}. The mean interval between BLA and NS diagnosis also differs significantly in studies in which all criteria (radiographic, biochemical and clinical) had to be met, ranging from 15 months to 16 years^{20,22,23,27}.

Pathogenesis

Pathogenesis of NS remains unknown. Loss of the negative glucocorticoid feedback on the hypothalamus with subsequent increase in corticotropin-releasing hormone production leading to corticotroph neoplasia and NS has been proposed as one theory⁴⁷. However, although studies in rodents support this^{48,49}, relevant evidence from human studies is still lacking. Furthermore, the fact the NS does not develop in all CD patients treated with BLA suggests that other factors may also be implicated. A second hypothesis suggests that NS represents the natural history of an aggressive corticotroph tumor. However, despite the new insights on the molecular pathogenesis of corticotroph tumors⁵⁰, the mechanisms driving tumor progression and leading to NS remain poorly understood. Corticotroph tumor growth has been associated with reduced expression of E-cadherin (with Nelson's tumors demonstrating lowest expression compared to corticotroph micro- or macroadenomas); this molecule plays a role in cell-cell adhesion in epithelial tissues and its decreased expression has been correlated with increased invasiveness and metastatic potential for different types of tumors⁵¹. On the other hand, the prevalence of *USP8* mutations is similar between CD and Nelson's tumors suggesting that *USP8* mutations do not drive corticotroph adenoma progression that leads to NS⁵².

Predictive factors for development of NS after BLA

Identification of factors predicting the development of NS has proven to be difficult, as a number of studies have provided conflicting results.

High ACTH levels in the first year after BLA is the most consistently found predictive factor in most^{2,14,16} but not all¹⁷ reports published after 1990. No definitive threshold value of ACTH has been, as yet, defined and, although Assie *et al.*¹⁴ suggested that a >100 pg/ml increase of ACTH levels in the first year after BLA is a predictor of corticotroph tumor growth, this finding has not been further evaluated.

Presence of a pituitary adenoma prior to BLA has been also proposed as a risk factor^{24,32} but this has not been confirmed in other series^{14,20}. Controversy also exists on the role of pituitary radiotherapy in preventing NS development [administered either as therapeutic intervention for the hypercortisolism (prior to BLA) or as prophylactic measure (at the time of BLA)]. Although some studies have showed a protective effect^{20,22,32}, this has not been confirmed in others^{23,24}. Young age at the time of BLA has been proposed as a risk factor by Keming *et al.*²⁷, but subsequent studies did not confirm this^{14,22,24}, while short duration of CD has also been found to be predictive¹⁴, but not in all studies^{22,27}. High urinary cortisol levels before BLA has been identified as predictive factor in the study of Sonino *et al.*²⁴, but not in the Pereira *et al.*²³, while the presence of residual adrenal tissue after BLA has not been confirmed to be protective against the development of NS^{14,22}. Finally, Nagesser *et al.*²² suggested that insufficient glucocorticoid replacement therapy after BLA may be associated with NS development, but this factor has not been assessed in further studies.

Monitoring for development of NS after BLA

Given the lack of widely accepted factors for the development of NS, all patients with CD treated with BLA require monitoring; this should be life-long, as diagnosis of NS has been

reported as late as 32 years after BLA¹. Formal guidelines on an effective follow-up protocol are not available but this should include measurement of plasma ACTH levels and imaging surveillance.

Given the impact of timing of ACTH measurements in relationship with the dose and type of glucocorticoid, blood sampling for ACTH needs to be performed at least 20 hours after the last administration of glucocorticoid and prior to the morning dose^{35,53}. A second ACTH sample two hours after the morning glucocorticoid dose will help discriminate if ACTH responds or not to the negative feedback of steroids^{32,35,47}. Increase of the morning plasma ACTH levels (20 hours off glucocorticoid) >100 pg/ml compared to previous measurements and/or plasma ACTH >200 pg/ml two hours after the morning glucocorticoid dose should be further investigated with a pituitary MRI³⁵.

Biochemical surveillance is recommended at 6-monthly intervals for the first 3 years and annually thereafter. The frequency of the imaging monitoring varies amongst authors^{35,53,54} and a proposed approach includes high resolution pituitary MRI 6-12 months after the BLA and then yearly. If plasma ACTH remains low after the initial three years of annual monitoring, the imaging interval can be extended to every other year.

Management of NS

The long-term outcomes of patients with NS after primary management have been poorly assessed, especially in the modern era. Drawbacks of the limited published series include small number of patients, differences in the length of follow-up and heterogeneity in the criteria defining successful treatment of NS (Table 2). Furthermore, in some studies, the inclusion in the analyses of tumors already showing regrowth after their primary management^{3,5,7,55-59} and the lack of information on previous therapies^{3,5,6,57-61} makes the interpretation of their results difficult.

Surgery

Surgical removal of the Nelson's tumor has been associated with growth rates ranging between 0% and 50% during variable follow-up periods^{1,2,7-9,11,62} (Table 2). The series reporting 0% growth rate had only four patients monitored for a short interval (median 39 months)¹⁰. In the largest to date study of patients with NS from 13 UK pituitary centers, the 10-year tumor progression-free survival was 80% for those treated by surgery¹.

There is no consensus on the definition on NS remission after treatment and this has been delineated in only four studies^{7-9,11}. The proposed criteria included: 1) ACTH <200 pg/ml two hours after the morning glucocorticoid dose⁷, 2) ACTH <200 pmol/l after stopping glucocorticoid replacement therapy for at least 24 hours and tumor size <10 mm⁸, 3) ACTH <70 pg/ml two hours after the morning glucocorticoid dose and no evidence of tumor growth⁹ and 4) ACTH <200 pg/ml after stopping glucocorticoid replacement therapy for 24 hours and no MRI evidence of tumor¹¹. The reported remission rates were between 33 and 100%, but the small number of cases in each study (4-10 patients) challenges the validity of these rates. Nonetheless, small tumor size and no extrasellar extension have been associated with long lasting remission^{8,11}.

Radiotherapy

Radiotherapy is an alternative treatment for NS either alone or after pituitary surgery.

Adjuvant radiotherapy is mainly used in cases of incomplete tumor removal aiming to control its growth rate. Kelly *et al.*⁷, reported tumor growth in one out of seven patients (14%) managed by surgery and radiotherapy during a 17-year median follow-up (range 9-20 years); however, this patient had an already recurrent tumor. Remission of NS (ACTH <200 pg/ml two hours after morning glucocorticoid dose) with no residual tumor was achieved in four (57%) patients; in the remaining two, ACTH decreased and one had no residual tumor, while the second had

stable residuum. In the UK Nelson's study, tumor growth probability was 19% at 10 years in those managed by surgery and radiotherapy¹.

Pituitary irradiation as a primary treatment of NS has been used in patients not candidates for surgery, either due to tumor location or because of significant comorbidities. Tran *et al.*⁶³ reported normal ACTH levels in 50% (2/4) of patients treated with radiotherapy, with the remaining of them being on clinical remission (no clear definition for this was provided) during median follow-up of 3 years. In the series by Espinosa-de-Los-Monteros *et al.*, primary treatment with radiotherapy in four patients followed-up for median period of 4.4 years resulted in tumor shrinkage in two and stable size in the other two patients¹⁷. The 10-year tumor progression-free survival for those treated solely with radiotherapy in the UK Nelson's study was 52%¹; in this series, four of 22 patients from this group had already received a previous course of irradiation for their CD and the possibility that they had more aggressive tumors cannot be excluded.

Studies assessing the effects of stereotactic radiosurgery (SRS) in controlling Nelson's tumor growth have shown promising results (ranging between 60% and 100%)^{3,5,6,56,58,59,61}. However, these data need to be interpreted with caution as information on other therapeutic interventions prior to SRS are not provided^{3,5,6,58,59}. In the three studies evaluating the efficacy of SRS as primary treatment of NS, no further tumor progression was reported in 83.4% (10/12) and in 100% (5/5 and 3/3) of the cases, respectively^{4,56,61}. However, selection bias and small sample size challenge the practical significance of these data.

The effects of proton radiotherapy on NS have been reviewed in only one study⁶⁰; normal ACTH levels were achieved in 75% (6/8) of the patients and tumor control in 100% (6/6) of them. Nonetheless, this study has limitations similar to those assessing SRS efficacy.

Observation

Imaging surveillance is mostly considered in patients with small tumors, not causing mass effects to vital surrounding structures. In the UK Nelson's study, there was 51% tumor progression-free survival at 10 years in patients under surveillance, and in the majority of the cases, active treatment (surgery, radiotherapy, medical therapy or combination of these) was subsequently offered¹. High tumor growth rates have been also reported by Kemink *et al.*⁸, with 87.5% (7/8) of the conservatively managed patients demonstrating further corticotroph tumor growth during median follow-up of 2.5 years. In six of these cases, surgery or radiotherapy was offered, whereas in the seventh one, massive pituitary hemorrhage occurred five years after the diagnosis of NS. In contrast, in the study of Pereira *et al.*²³, four patients were managed conservatively and in two of them (followed-up for three and four years respectively), no tumor growth was demonstrated; the other two were followed-up for less than one year.

Medical therapy

Different types of pharmacotherapy have been used for the control of ACTH levels and/or the corticotroph tumor in patients with NS, including dopamine agonists, sodium valproate, octreotide and lanreotide, serotonin antagonists and peroxisome proliferator-activated receptor γ agonists. Despite their beneficial effects in some cases, their efficacy has not been consistently reproduced^{35,47,64}. However, it has been suggested that pharmacotherapy could be an option when all other management approaches have failed⁵⁴. Pasireotide has been recently investigated as a medical treatment in NS in a small case series where it resulted in reduction of ACTH levels, but with no significant change in the size of the tumor during an 28 week administration period⁶⁵.

Recurrent and aggressive NS

A small subset of patients will demonstrate further corticotroph tumor growth after their primary treatment of NS. Given the rarity of the condition, the identification of relevant predictive factors is challenging. Notably, in the UK Nelson's study, the highest risk was found in patients treated with pituitary surgery, radiotherapy and BLA for their CD prior to NS diagnosis¹. This group had received the most complex treatments for their CD possibly reflecting an aggressive corticotroph tumor from the outset¹.

Management of these patients is individualized and also tailored to previously offered treatments. Furthermore, the reported responses to treatment are variable and range from tumor stability (during variable monitoring intervals) up to multiple growths and malignant transformation^{1,4,6-8}. In the latter scenario, there is poor prognosis and increased mortality^{1-8,11,66}. Temozolomide has been used for the treatment of such aggressive tumors with beneficial results in some^{67,68} but not all published cases^{1,69}.

Conclusions and future directions

More than 60 years since its first description, NS remains a fascinating but also enigmatic entity. A formal consensus on the diagnosis and management of this condition is still lacking. Patients with CD offered BLA require long-term monitoring for the development of NS. Corticotroph tumor growth is essential for diagnosis; nonetheless, gradually increasing ACTH levels without radiographic evidence of corticotroph tumor growth need to be included in the diagnostic algorithm. Surgery followed or not by radiotherapy is associated with higher tumor control rates compared with observation alone. The latter option can be offered to patients with small lesions, not causing mass effects to vital surrounding structures but close follow-up is essential to detect further tumor progress and ensure appropriate treatment. The small subset of tumors demonstrating aggressive behaviour is intriguing and may reflect an aggressive

corticotroph tumor from the outset. Further studies focusing on all aspects of this condition are needed and, will hopefully, facilitate the development of tumor-targeted therapeutic agents.

References

1. Fountas A, Lim ES, Drake WM, et al. Outcomes of patients with Nelson's syndrome after primary treatment: a multicenter study from 13 UK Pituitary centers. *J Clin Endocrinol Metab.* 2019.
2. Cohen AC, Goldney DC, Danilowicz K, et al. Long-term outcome after bilateral adrenalectomy in Cushing's disease with focus on Nelson's syndrome. *Archives of endocrinology and metabolism.* 2019;63(5):470-477.
3. Caruso JP, Patibandla MR, Xu Z, Vance ML, Sheehan JP. A Long-Term Study of the Treatment of Nelson's Syndrome With Gamma Knife Radiosurgery. *Neurosurgery.* 2018;83(3):430-436.
4. Graffeo CS, Perry A, Carlstrom LP, et al. Characterizing and predicting the Nelson-Salassa syndrome. *J Neurosurg.* 2017;127(6):1277-1287.
5. Wilson PJ, Williams JR, Smee RI. Nelson's syndrome: single centre experience using the linear accelerator (LINAC) for stereotactic radiosurgery and fractionated stereotactic radiotherapy. *J Clin Neurosci.* 2014;21(9):1520-1524.
6. Pollock BE, Young WF, Jr. Stereotactic radiosurgery for patients with ACTH-producing pituitary adenomas after prior adrenalectomy. *Int J Radiat Oncol Biol Phys.* 2002;54(3):839-841.
7. Kelly PA, Samandouras G, Grossman AB, Afshar F, Besser GM, Jenkins PJ. Neurosurgical treatment of Nelson's syndrome. *J Clin Endocrinol Metab.* 2002;87(12):5465-5469.

8. Kemink SA, Grotenhuis JA, De Vries J, Pieters GF, Hermus AR, Smals AG. Management of Nelson's syndrome: observations in fifteen patients. *Clin Endocrinol (Oxf)*. 2001;54(1):45-52.
9. Burke CW, Adams CB, Esiri MM, Morris C, Bevan JS. Transsphenoidal surgery for Cushing's disease: does what is removed determine the endocrine outcome? *Clin Endocrinol (Oxf)*. 1990;33(4):525-537.
10. Nelson DH, Meakin JW, Dealy JB, Jr., Matson DD, Emerson K, Jr., Thorn GW. ACTH-producing tumor of the pituitary gland. *N Engl J Med*. 1958;259(4):161-164.
11. Zielinski G, Witek P, Maksymowicz M. Outcomes in pituitary surgery in Nelson's syndrome--therapeutic pitfalls. *Endokrynol Pol*. 2015;66(6):504-513.
12. Osswald A, Plomer E, Dimopoulou C, et al. Favorable long-term outcomes of bilateral adrenalectomy in Cushing's disease. *Eur J Endocrinol*. 2014;171(2):209-215.
13. Mehta GU, Sheehan JP, Vance ML. Effect of stereotactic radiosurgery before bilateral adrenalectomy for Cushing's disease on the incidence of Nelson's syndrome. *J Neurosurg*. 2013;119(6):1493-1497.
14. Assie G, Bahurel H, Coste J, et al. Corticotroph tumor progression after adrenalectomy in Cushing's Disease: A reappraisal of Nelson's Syndrome. *J Clin Endocrinol Metab*. 2007;92(1):172-179.
15. Imai T, Funahashi H, Tanaka Y, et al. Adrenalectomy for treatment of Cushing syndrome: results in 122 patients and long-term follow-up studies. *World J Surg*. 1996;20(7):781-786; discussion 786-787.
16. Moreira AC, Castro M, Machado HR. Longitudinal evaluation of adrenocorticotrophin and beta-lipotrophin plasma levels following bilateral adrenalectomy in patients with Cushing's disease. *Clin Endocrinol (Oxf)*. 1993;39(1):91-96.

17. Espinosa-de-Los-Monteros AL, Sosa-Eroza E, Espinosa E, Mendoza V, Arreola R, Mercado M. LONG-TERM OUTCOME OF THE DIFFERENT TREATMENT ALTERNATIVES FOR RECURRENT AND PERSISTENT CUSHING DISEASE. *Endocr Pract.* 2017;23(7):759-767.
18. Xing B, Zhang N, Ren ZY, et al. [Effects of adrenalectomy on the treatment of Cushing disease]. *Zhonghua Wai Ke Za Zhi.* 2008;46(8):592-594.
19. Thompson SK, Hayman AV, Ludlam WH, Deveney CW, Loriaux DL, Sheppard BC. Improved quality of life after bilateral laparoscopic adrenalectomy for Cushing's disease: a 10-year experience. *Ann Surg.* 2007;245(5):790-794.
20. Gil-Cardenas A, Herrera MF, Diaz-Polanco A, Rios JM, Pantoja JP. Nelson's syndrome after bilateral adrenalectomy for Cushing's disease. *Surgery.* 2007;141(2):147-151; discussion 151-142.
21. Dalvi AN, Thapar PM, Vijay Kumar K, et al. Laparoscopic adrenalectomy: Gaining experience by graded approach. *J Minim Access Surg.* 2006;2(2):59-66.
22. Nagesser SK, van Seters AP, Kievit J, Hermans J, Krans HM, van de Velde CJ. Long-term results of total adrenalectomy for Cushing's disease. *World J Surg.* 2000;24(1):108-113.
23. Pereira MA, Halpern A, Salgado LR, et al. A study of patients with Nelson's syndrome. *Clin Endocrinol (Oxf).* 1998;49(4):533-539.
24. Sonino N, Zielesny M, Fava GA, Fallo F, Boscaro M. Risk factors and long-term outcome in pituitary-dependent Cushing's disease. *J Clin Endocrinol Metab.* 1996;81(7):2647-2652.
25. O'Riordain DS, Farley DR, Young WF, Jr., Grant CS, van Heerden JA. Long-term outcome of bilateral adrenalectomy in patients with Cushing's syndrome. *Surgery.* 1994;116(6):1088-1093; discussion 1093-1084.

26. Misra D, Kapur MM, Gupta DK. Incidence of Nelson's syndrome and residual adrenocortical function in patients of Cushing's disease after bilateral adrenalectomy. *J Assoc Physicians India*. 1994;42(4):304-305.
27. Kemink L, Pieters G, Hermus A, Smals A, Kloppenborg P. Patient's age is a simple predictive factor for the development of Nelson's syndrome after total adrenalectomy for Cushing's disease. *J Clin Endocrinol Metab*. 1994;79(3):887-889.
28. McCance DR, Russell CF, Kennedy TL, Hadden DR, Kennedy L, Atkinson AB. Bilateral adrenalectomy: low mortality and morbidity in Cushing's disease. *Clin Endocrinol (Oxf)*. 1993;39(3):315-321.
29. Grabner P, Hauer-Jensen M, Jervell J, Flatmark A. Long-term results of treatment of Cushing's disease by adrenalectomy. *Eur J Surg*. 1991;157(8):461-464.
30. Sarkis P, Rabilloud M, Lifante JC, et al. Bilateral adrenalectomy in Cushing's disease: Altered long-term quality of life compared to other treatment options. *Ann Endocrinol (Paris)*. 2019;80(1):32-37.
31. Smith PW, Turza KC, Carter CO, Vance ML, Laws ER, Hanks JB. Bilateral adrenalectomy for refractory Cushing disease: a safe and definitive therapy. *J Am Coll Surg*. 2009;208(6):1059-1064.
32. Jenkins PJ, Trainer PJ, Plowman PN, et al. The long-term outcome after adrenalectomy and prophylactic pituitary radiotherapy in adrenocorticotropin-dependent Cushing's syndrome. *J Clin Endocrinol Metab*. 1995;80(1):165-171.
33. Ding XF, Li HZ, Yan WG, Gao Y, Li XQ. Role of adrenalectomy in recurrent Cushing's disease. *Chin Med J (Engl)*. 2010;123(13):1658-1662.
34. Littlely MD, Shalet SM, Beardwell CG, Ahmed SR, Sutton ML. Long-term follow-up of low-dose external pituitary irradiation for Cushing's disease. *Clin Endocrinol (Oxf)*. 1990;33(4):445-455.

35. Munir A, Newell-Price J. Nelson's Syndrome. *Arq Bras Endocrinol Metabol.* 2007;51(8):1392-1396.
36. Nagendra L, Bhavani N, Pavithran PV, et al. Outcomes of Bilateral Adrenalectomy in Cushing's Syndrome. *Indian J Endocrinol Metab.* 2019;23(2):193-197.
37. Prajapati OP, Verma AK, Mishra A, Agarwal G, Agarwal A, Mishra SK. Bilateral adrenalectomy for Cushing's syndrome: Pros and cons. *Indian J Endocrinol Metab.* 2015;19(6):834-840.
38. Tiyyatah BN, Kalavampara SV, Sukumar S, et al. Bilateral simultaneous laparoscopic adrenalectomy in Cushing's syndrome: safe, effective, and curative. *J Endourol.* 2012;26(2):157-163.
39. Prevedello DM, Pouratian N, Sherman J, et al. Management of Cushing's disease: outcome in patients with microadenoma detected on pituitary magnetic resonance imaging. *J Neurosurg.* 2008;109(4):751-759.
40. Hawn MT, Cook D, Deveney C, Sheppard BC. Quality of life after laparoscopic bilateral adrenalectomy for Cushing's disease. *Surgery.* 2002;132(6):1064-1068; discussion 1068-1069.
41. Wright-Pascoe R, Charles CF, Richards R, Fletcher P, Hanchard B, Kelly D. A clinico-pathological study of Cushing's syndrome at the University Hospital of the West Indies and a review of the literature. *West Indian Med J.* 2001;50(1):55-61.
42. Vella A, Thompson GB, Grant CS, van Heerden JA, Farley DR, Young WF, Jr. Laparoscopic adrenalectomy for adrenocorticotropin-dependent Cushing's syndrome. *J Clin Endocrinol Metab.* 2001;86(4):1596-1599.
43. Invitti C, Pecori Giraldi F, de Martin M, Cavagnini F. Diagnosis and management of Cushing's syndrome: results of an Italian multicentre study. Study Group of the Italian

- Society of Endocrinology on the Pathophysiology of the Hypothalamic-Pituitary-Adrenal Axis. *J Clin Endocrinol Metab.* 1999;84(2):440-448.
44. Feleke Y, Abdulkadir J, Johnson O, Munie T. Cushing's syndrome: a ten year experience at Tikur Anbassa Hospital. *Ethiop Med J.* 1998;36(1):19-26.
 45. Chapuis Y, Pitre J, Conti F, Abboud B, Pras-Jude N, Luton JP. Role and operative risk of bilateral adrenalectomy in hypercortisolism. *World J Surg.* 1996;20(7):775-779; discussion 779-780.
 46. Favia G, Boscaro M, Lumachi F, D'Amico DF. Role of bilateral adrenalectomy in Cushing's disease. *World J Surg.* 1994;18(4):462-466.
 47. Barber TM, Adams E, Wass JA. Nelson syndrome: definition and management. *Handb Clin Neurol.* 2014;124:327-337.
 48. Gertz BJ, Contreras LN, McComb DJ, Kovacs K, Tyrrell JB, Dallman MF. Chronic administration of corticotropin-releasing factor increases pituitary corticotroph number. *Endocrinology.* 1987;120(1):381-388.
 49. Wynn PC, Harwood JP, Catt KJ, Aguilera G. Regulation of corticotropin-releasing factor (CRF) receptors in the rat pituitary gland: effects of adrenalectomy on CRF receptors and corticotroph responses. *Endocrinology.* 1985;116(4):1653-1659.
 50. Sbiera S, Deutschbein T, Weigand I, Reincke M, Fassnacht M, Allolio B. The New Molecular Landscape of Cushing's Disease. *Trends Endocrinol Metab.* 2015;26(10):573-583.
 51. Evang JA, Berg JP, Casar-Borota O, et al. Reduced levels of E-cadherin correlate with progression of corticotroph pituitary tumours. *Clin Endocrinol (Oxf).* 2011;75(6):811-818.

52. Perez-Rivas LG, Theodoropoulou M, Puar TH, et al. Somatic USP8 mutations are frequent events in corticotroph tumor progression causing Nelson's tumor. *Eur J Endocrinol*. 2018;178(1):59-65.
53. Barber TM, Adams E, Ansorge O, Byrne JV, Karavitaki N, Wass JA. Nelson's syndrome. *Eur J Endocrinol*. 2010;163(4):495-507.
54. Banasiak MJ, Malek AR. Nelson syndrome: comprehensive review of pathophysiology, diagnosis, and management. *Neurosurg Focus*. 2007;23(3):E13.
55. De Tommasi C, Vance ML, Okonkwo DO, Diallo A, Laws ER, Jr. Surgical management of adrenocorticotrophic hormone-secreting macroadenomas: outcome and challenges in patients with Cushing's disease or Nelson's syndrome. *J Neurosurg*. 2005;103(5):825-830.
56. Ganz JC, Backlund EO, Thorsen FA. The effects of Gamma Knife surgery of pituitary adenomas on tumor growth and endocrinopathies. *Stereotact Funct Neurosurg*. 1993;61 Suppl 1:30-37.
57. Levy RP, Fabrikant JI, Frankel KA, et al. Heavy-charged-particle radiosurgery of the pituitary gland: clinical results of 840 patients. *Stereotact Funct Neurosurg*. 1991;57(1-2):22-35.
58. Marek J, Jezkova J, Hana V, et al. Gamma knife radiosurgery for Cushing's disease and Nelson's syndrome. *Pituitary*. 2015;18(3):376-384.
59. Cordeiro D, Xu Z, Li CE, et al. Gamma Knife radiosurgery for the treatment of Nelson's syndrome: a multicenter, international study. *J Neurosurg*. 2019:1-6.
60. Wattson DA, Tanguturi SK, Spiegel DY, et al. Outcomes of proton therapy for patients with functional pituitary adenomas. *Int J Radiat Oncol Biol Phys*. 2014;90(3):532-539.
61. Vik-Mo EO, Oksnes M, Pedersen PH, et al. Gamma knife stereotactic radiosurgery of Nelson syndrome. *Eur J Endocrinol*. 2009;160(2):143-148.

62. Xing B, Ren Z, Su C, Wang R, Yang Y, Hu Y. Microsurgical treatment of Nelson's syndrome. *Chin Med J (Engl)*. 2002;115(8):1150-1152.
63. Tran LM, Blount L, Horton D, Sadeghi A, Parker RG. Radiation therapy of pituitary tumors: results in 95 cases. *Am J Clin Oncol*. 1991;14(1):25-29.
64. Patel J, Eloy JA, Liu JK. Nelson's syndrome: a review of the clinical manifestations, pathophysiology, and treatment strategies. *Neurosurg Focus*. 2015;38(2):E14.
65. Daniel E, Debono M, Caunt S, et al. A prospective longitudinal study of Pasireotide in Nelson's syndrome. *Pituitary*. 2018;21(3):247-255.
66. Kasperlik-Zaluska AA, Bonicki W, Jeske W, Janik J, Zgliczynski W, Czernicki Z. Nelson's syndrome -- 46 years later: clinical experience with 37 patients. *Zentralbl Neurochir*. 2006;67(1):14-20.
67. Kurowska M, Nowakowski A, Zielinski G, et al. Temozolomide-Induced Shrinkage of Invasive Pituitary Adenoma in Patient with Nelson's Syndrome: A Case Report and Review of the Literature. *Case Rep Endocrinol*. 2015;2015:623092.
68. Moyes VJ, Alusi G, Sabin HI, et al. Treatment of Nelson's syndrome with temozolomide. *Eur J Endocrinol*. 2009;160(1):115-119.
69. Bruno OD, Juarez-Allen L, Christiansen SB, et al. Temozolomide Therapy for Aggressive Pituitary Tumors: Results in a Small Series of Patients from Argentina. *Int J Endocrinol*. 2015;2015:587893.