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Title

Outcomes of patients with Nelson's syndrome after primary treatment: a multicenter study from 13 UK Pituitary centers

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Abstract

Context: Long-term outcomes of patients with Nelson's syndrome (NS) have been poorly explored, especially in the modern era.

Objective: To elucidate tumor control rates, effectiveness of various treatments and markers of prognostic relevance in patients with NS.

Patients, design, and setting: Retrospective cohort study of 68 patients from 13 UK pituitary centers with median imaging follow-up of 13 years (range 1-45) since NS diagnosis.

Results: Management of Cushing's disease (CD) prior to NS diagnosis included surgery+adrenalectomy (n=30, eight patients had two and one had three pituitary operations), surgery+radiotherapy+adrenalectomy (n=17, two received >1 courses of irradiation, two had ≥2 pituitary surgeries), radiotherapy+adrenalectomy (n=2) and adrenalectomy (n=19). Primary management of NS mainly included surgery, radiotherapy, surgery+radiotherapy and observation; 10-year tumor progression-free survival was 62% (surgery 80%, radiotherapy 52%, surgery+radiotherapy 81%, observation 51%). Sex, age at CD or NS diagnosis, size of adenoma (micro-/macroadenoma) at CD diagnosis, presence of pituitary tumor on imaging prior adrenalectomy, mode of NS primary management were not predictors of tumor progression. Mode of management of CD before NS diagnosis was a significant factor predicting progression, with the group treated by surgery+radiotherapy+adrenalectomy for their CD showing the highest risk (HR 4.6; 95% CI, 1.6-13.5). During follow-up, 3% of patients had malignant transformation with spinal metastases and 4% died of aggressively enlarging tumor.

Conclusions: At 10 years follow-up, 38% of the patients diagnosed with NS showed progression of their corticotroph tumor. Complexity of treatments for the CD prior to NS diagnosis, possibly reflecting corticotroph adenoma aggressiveness, predicts long-term tumor prognosis.

Précis

In this multicentre study of patients with Nelson's syndrome, 10-year tumor progression-free survival was 62%. Complexity of treatments for the Cushing's before Nelson's diagnosis predicts prognosis.

Introduction

Cushing's disease (CD) has a prevalence of 4-6 cases per 100,000 population and an annual incidence of 1-2 per million (1-3). Its first line treatment is trans-sphenoidal adenomectomy with remission rates reported between 31% and 100% (4). Recurrence rates after initial successful surgery range between 10.6% and 20% during variable follow-up periods (5-8). Refractory hypercortisolemia from persistent or recurrent CD remains a therapeutic challenge and bilateral adrenalectomy (BLA) is one of the available management options. Despite its effectiveness in achieving immediate biochemical control, the risk for development of Nelson's syndrome (NS) or, as it has also been proposed as an alternative name in the last years, corticotroph tumor progression (9) is a potential drawback of this approach.

Consensus on what defines NS is lacking. The most widely accepted definition includes corticotroph adenoma progression associated with increasing plasma ACTH levels (with or without the presence of pigmentation). It should be noted, however, that in some published series, demonstration of enlarging pituitary adenoma has not been considered as a necessary diagnostic criterion (10-17). The prevalence of NS shows high variation amongst studies influenced by the diagnostic criteria used, the length of follow-up after BLA and possible referral bias of the reporting centers; Ritzel *et al.* in a systematic review of 24 studies including 768 patients found a median prevalence of 21% (range 0-47%) during median follow-up of 61 months (range 29-294) after BLA (18). Management options for NS include observation, surgery, radiation therapy and pharmacotherapy (alone or in combination) (19,20) but in a number of cases, aggressive tumor is associated with a poor prognosis and increased mortality (15,16,21-28).

Long-term outcomes of patients with NS, especially in the modern era, have been poorly explored. This is due to the limited number of published series, often from single centres, each with very small number of patients (given the rarity of NS), and commonly with short follow-up (14,23,26,28-38). The interpretation of their results is further complicated by the inclusion in the final analyses of tumors already showing recurrence after the primary management of NS (14,15,21,24,32,39-41), by the lack of information about other previous therapies (21,24,26,30,39,40,42) and by the heterogeneity in the criteria defining successful treatment of NS (14,15,21,23,27,30,34,35).

To elucidate the clinical behavior of corticotroph tumors after the diagnosis of NS, we performed a multicenter, retrospective, cohort study in a large series of patients who have undergone long-term follow-up from 13 UK pituitary centers, and assessed, systematically, the effectiveness of various management approaches, rates of tumor control and markers of prognostic relevance.

Patients and Methods

Study design and patients

This was a retrospective cohort study from 13 UK pituitary centers. The records of the patients diagnosed with NS and followed-up in each participating center were reviewed and clinical, laboratory and imaging data, as well as treatment outcomes were recorded. The patients were identified from the databases of each center. The study was retrospective in nature and involved no intervention beyond routine patient care, and data were collected on a dedicated proforma. It was registered with and approved as a clinical audit by the respective Hospitals [Audit reference number in coordinating center (Queen Elizabeth Hospital Birmingham): 14011].

For the diagnosis of NS, imaging (evidence of corticotroph adenoma growth or, if previous pituitary imaging negative for tumor, new identification of tumor), biochemical [lack of suppressibility of plasma ACTH (<200 pg/ml) two hours after morning glucocorticoid dose (11,43) and/or gradually increasing morning ACTH levels usually checked at least 20 hours after the last glucocorticoid dose] and clinical criteria (development of skin pigmentation) were used. Given the variability of ACTH assays between centers, the long period covered by the study and the impact of timing of ACTH measurements in relationship with the dose and type of glucocorticoid, specific plasma ACTH cut-off values were not established and each center used its own protocol for this criterion.

Imaging analysis, follow-up and the management of the patients were based on the decisions of the local endocrine, neurosurgical and oncology teams. Progression of underlying corticotroph tumor was diagnosed on the basis of radiological appearances. Follow-up period was defined from the time of NS diagnosis until last pituitary imaging or, for survival estimation, until last clinical review or death.

Statistical analyses

Percentages were calculated for categorical data and medians with ranges for continuous variables. Tumor progression-free curves and overall survival curves were generated by the Kaplan-Meier method and the differences between outcomes in the various subgroups by the log-rank test. Cox regression analysis was used to assess the effect of various factors on tumor progression and Hazard

Ratios (HR) with 95% confidence intervals (CI) were estimated. There was no significant departure from proportional hazards assumptions for any of the variables. The level of significance was set at $p<0.05$. Statistical analyses were performed by IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

Results

Characteristics of patients with NS

Sixty-eight patients were included. Their characteristics are shown in Table 1. Treatment of CD included a) pituitary surgery and BLA (n=30; eight patients had two and one patient had three pituitary surgeries prior to BLA), b) pituitary surgery and radiotherapy and BLA [n=17; one patient received three courses of radiotherapy (conventional fractionated x1 and stereotactic radiosurgery x2), one patient two courses of radiotherapy (conventional fractionated x1 and gamma knife x1), one patient had two pituitary surgeries before the radiotherapy, one patient had two pituitary surgeries followed by radiotherapy and then two further pituitary surgeries; in two patients radiotherapy was offered shortly after the adrenalectomy], c) radiotherapy and BLA (n=2; in one patient radiotherapy was offered shortly after the adrenalectomy) and d) BLA only (n=19, in 12 of them after 1981, and of these, seven after 1992) [pituitary surgery was not attempted due to lack of adenoma on imaging]. Medical treatment (ketoconazole) had been offered for a short period in one patient. The median time between first pituitary surgery for CD and BLA was one year (range 3 months-21 years).

Steroid replacement after the BLA was mainly with hydrocortisone in total daily dose ranging between 15 and 40 mg [two patients were prescribed prednisolone (total daily dose 5-7.5 mg) and four were prescribed cortisone acetate (total daily dose 37.5 mg)].

NS was diagnosed between 1969 and 2018 [after 1990 in 87% (59/68) of the patients]. In 53 patients, the diagnosis was established by imaging combined with biochemical/clinical criteria. In 14 patients, the diagnosis was established by biochemical/clinical criteria [in this group, 12 cases were diagnosed after 1980 and on imaging, presence of pituitary tumor (which had not grown compared with previous scans) was documented in nine]. Specific diagnostic details were not available for one patient. The median time between BLA and NS diagnosis was 3 years (range 3 months-32 years, range between 1st and 3rd quartile 2-11 years).

The management of patients after the diagnosis of NS is shown in Table 2 and overall, it included a) pituitary surgery (n=10), b) radiotherapy (n=22; conventional fractionated in 19, Cyber knife in one and gamma knife in two), c) pituitary surgery and radiotherapy (n=18; conventional fractionated in

16, gamma knife in two – one of these patients also had a carmustin implant inserted), d) observation (n=16) and e) pasireotide (n=2, under a trial). In five of the cases offered radiotherapy for the NS, a previous course of conventional fractionated irradiation had also been administered for the management of CD prior to NS diagnosis.

Outcomes of patients after NS diagnosis

Median follow-up from diagnosis of NS until last imaging was 13 years (range 1-45) (imaging monitoring data were available for 65 patients).

Steroid replacement at last assessment was mainly with hydrocortisone in total daily dose ranging between 10 and 30 mg [four patients were on prednisolone (total daily dose 5-7.5 mg)].

i) Tumor progression in the whole group of patients with NS

During the follow-up period, 18 patients had further tumor progression associated with increase in their ACTH levels. The 10-year tumor progression-free survival was 62% for the whole group. There was a significant difference in these rates according to type of primary treatment for the NS: 80% for surgery, 52% for radiotherapy alone, 81% for surgery and radiotherapy and 51% for observation (p=0.029); in pairwise comparisons, there were significant differences between surgery *vs* observation, surgery and radiotherapy *vs* observation, and surgery and radiotherapy *vs* radiotherapy (p<0.05), whereas for surgery *vs* radiotherapy alone, significance was borderline (p=0.054). Details on tumor progression-free survival are shown in Figure 1 and Table 3. Analysis of the group of patients diagnosed with NS after 1990 showed 10-year progression-free survival 57% (71% for surgery, 46% for radiotherapy alone, 76% for surgery and radiotherapy and 46% for observation; p=0.057).

ii) Tumor progression in the group with NS diagnosis based on imaging combined with biochemical/clinical criteria

In this group, the 10-year tumor progression-free survival was 65%, but there was no significant difference in rates according to type of primary treatment for the NS: 78% for those treated with

surgery, 38% for radiotherapy, 85% for surgery and radiotherapy and 72% for observation (p=0.079). Details on tumor progression-free survival are shown in Figure 2 and Table 3.

The patient offered pasireotide as primary treatment, received this for 12 months and during this period, tumor stability was reported. Two years later, a 6 months course of temozolomide was given due to increasing ACTH levels (not associated with tumor enlargement). This led to reduction in ACTH concentrations and tumor size, with no evidence of tumor progression after two years further follow-up.

iii) Tumor progression in the group with NS diagnosis based on biochemical/clinical criteria

In this group, the 10-year progression-free survival was 50% (Table 3). The small number of cases in each management subgroup did not allow further analyses.

The patient on pasireotide had a short course of this treatment, which was stopped due to development of diabetes mellitus; five years later, the tumor remained stable.

iv) Predictors of tumor progression after the primary management of NS

Cox regression analysis showed that sex, age at CD or NS diagnosis, size of adenoma (micro-/macroadenoma) at CD diagnosis, presence of pituitary tumor on imaging prior to adrenalectomy, interval between adrenalectomy and diagnosis of NS (<3 or ≥3 years, based on our median interval for NS diagnosis), mode of primary management for NS and the diagnostic criteria for NS (imaging combined with biochemical/clinical or only biochemical/clinical criteria) were not predictors of tumor progression. Mode of management of CD before the diagnosis of NS was a significant factor predicting tumor progression with the group treated by surgery and radiotherapy and BLA showing the highest risk (HR 4.6; 95% CI, 1.6-13.5) (Table 4). This finding remained even after adjusting for mode of primary management for the NS. These results did not change after analyzing the data of the group diagnosed by imaging combined with biochemical/clinical criteria (Table 4) or of the group diagnosed with NS after 1990.

v) Outcomes of patients with tumor progression after primary management of NS

The 18 patients with further tumor growth were offered various therapies which are shown along with outcomes until last follow-up in Table 5. Amongst them, at last assessment, only one had ACTH levels within the reference range. Three patients showed further tumor growth and two had malignant transformation of their tumor (with spinal metastases) (7 and 14 years after the diagnosis of NS).

vi) Mortality

Median follow-up from diagnosis of CD until last review or, if the patient died, until date of death was 26 years (range 5-60) and from diagnosis of NS until last review or, if the patient died, until date of death was 16 years (range 0.5-48).

During the follow-up period, 13 patients died; in three of them, death was due to causes directly related to the NS (all had an enlarging mass extending in the brain and in one of them there were also spinal metastases) at the age of 73, 45 and 60 years.

The 5- and 10-year overall survival rates since NS diagnosis were 81% and 69%, respectively.

Discussion

This is the largest study to date reviewing outcomes of patients with NS with prolonged follow-up. We found that the 10-year tumor progression-free survival was 62% and that surgery with or without adjuvant radiotherapy offered as primary treatment for the Nelson's had tumor control rates 81% and 80%, respectively. Amongst a number of factors assessed, complexity of CD treatment prior to the diagnosis of NS was the only significant predictor of tumor progression. The management of the patients with tumor progression was variable and, in this group, five developed metastatic disease or further tumor growth [28% (5/18) - 8% of the total series with imaging follow-up)].

Studies assessing outcomes of patients with NS managed primarily by surgery combined or not with radiotherapy are extremely limited and of small sample size (usually <5 cases) (9,22,28,33,34,37,44). Xing *et al*., in a series of 23 patients treated with surgery between 1980 and 1999 and followed for a mean period of 3.6 years, found further tumor growth in 17.4% (31). Similar results were reported by Zielinski *et al.*, in 10 patients offered surgery between 2000 and 2005; tumor progression was found in 20% of the cases during mean follow-up of 45.3 months (23). The short monitoring interval is a limitation of both reports. In another series by Kelly *et al.* of 13 patients, managed between 1978 and 1993 and followed-up for a median period of 17 years, tumor growth was reported in 14.3% (1/7) of those managed by surgery and radiotherapy (15). Less optimal outcomes have been reported by Kemink *et al.* in 15 cases diagnosed with NS between 1969 and 1998; further tumor progression was found in 3 out of 6 patients (50%) who had surgery as primary treatment for the NS during median follow-up of only 2.2 years (27).

In our study, tumor progression-free survival was only 52% when radiotherapy was administered as primary treatment for the NS. Notably, 4 out of 22 patients in this group had already received a course of conventional fractionated irradiation for the management of their CD, possibly reflecting a more aggressive corticotroph tumor behavior. This group may also represent selected cases not amenable to surgical management due to tumor location and this needs to be taken into account when interpreting the results. Previous literature assessing the impact of this approach as primary treatment for the NS is scarce, as most relevant studies include cases with already recurrent NS in their analyses

(21,26,39,42). Further tumor growth was reported in 16.7% (2/12) and in 0% (0/5) of patients with NS treated primarily with stereotactic radiosurgery by Graffeo *et al*. (follow-up duration not available) and Vik-Mo *et al.* (median follow-up 9.4 years), respectively (22,42). Selection bias and small sample size challenge the practical significance of these studies. Interestingly, Assie *et al.* (9), in a series of 21 patients with corticotroph adenoma progression after BLA, showed that at least in the first years after BLA, in most cases, tumor growth had no clinically detectable sequelae and was treatable (by surgery and/or radiotherapy). This series included a selected group of patients, as those offered pituitary irradiation prior to BLA had been excluded. Furthermore, the tumor progression was detected at an early stage (81% presenting as microadenomas) due to close monitoring protocols after the adrenalectomy.

Surveillance is an approach usually considered for patients with NS and small tumors not causing mass effects to vital surrounding structures. In our series, observation was associated with a 51% tumor progression-free survival at 10 years and in most of these cases, active treatment (surgery, radiotherapy, medical therapy or combination of these) was subsequently offered. High rates of tumor progression have been reported by Kemink *et al.*; this was 87.5% (7/8) for patients managed conservatively and followed-up for a median period of 2.5 years (27). In six of these cases, surgery or radiotherapy was offered, whereas in the seventh one, massive pituitary hemorrhage occurred five years after diagnosis of NS.

Since the first description of NS, there has been heterogeneity in its diagnostic criteria and a formal consensus is still not available (43). Currently, the most widely accepted strategy involves demonstration of corticotroph adenoma progression. Nonetheless, rising ACTH levels, even in the absence of obvious tumor enlargement, may lead to the development of adrenal rest tumors and cause significant negative psychological effects due to pigmentation, and as such need to be considered as a criterion in the diagnosis of NS (45-49). In 79% of our cases, diagnosis was established by imaging combined with biochemical/clinical criteria. Analysis of the outcomes specifically for this group showed 10-year tumor progression-free survival of 65% with no significant difference between the various primary treatments for the NS (p=0.079), possibly due to the small sample size. In 21% of the cases, biochemical/clinical criteria had been applied by the treating clinicians and notably, in 9 out of

12 patients, a corticotroph tumor was already present on imaging. Various management approaches had been used and the 10-year corticotroph tumor progression-free probability was 50%. The limited number of cases did not allow further analyses according to type of NS management in this subgroup.

The pathophysiological mechanisms leading to NS are not completely understood. Tumor progression driven by the reduced negative glucocorticoid feedback on CRH production after the BLA or reflection of the natural history of a tumor programmed to behave aggressively from the outset are suggested hypotheses (20). Given that not all patients will develop NS after BLA, tumors showing progression are most likely a subset with an aggressive phenotype (43). Notably, it has been suggested that *USP8* mutations do not drive corticotroph adenoma progression that leads to NS (50). Data on factors predicting further tumor growth after the primary management of NS have not been previously published. In our study, amongst a number of parameters assessed, only mode of management of the CD prior to NS diagnosis was a significant predictive factor. Interestingly, the hazard ratio for those treated by pituitary surgery and radiotherapy and BLA was 4.6 (p=0.006); this group had received multiple treatments for their CD and the possibility that the complexity in their management reflects corticotroph adenoma aggressiveness from the outset cannot be excluded.

Recurrent NS represents a challenging clinical scenario; management remains individualised and due to the scarce relevant literature it is not evidence-based. Studies focusing on long-term outcomes after surgery alone are not available. Gamma knife radiosurgery halted tumor progression in four NS patients with recurrent corticotroph tumor during median follow-up of 3.85 years (42). In our series, a number of approaches (including surgery, radiotherapy, pasireotide, chemotherapy, temozolomide and monitoring, alone or in combination) were employed with varied success. Three patients showed further tumor growth, while two (3% of those with imaging follow-up data) had malignant transformation (7 and 14 years after the diagnosis of NS). Notably, the overall reported rate of pituitary carcinomas is only 0.1-0.2% of all pituitary tumors (51). Cases of aggressive or malignant tumor behavior have been previously reported and can be associated with high mortality (15,16,21-28). Overall, 4.4% (3/68) of our patients died due to NS-related causes. Our understanding of the relevant pathogenetic mechanisms is still limited and, unfortunately, identification of tumors at risk for progression to carcinoma remains difficult (51).

Data on the effectiveness of pharmacotherapy with sodium valproate, octreotide, dopamine agonists, cyproheptadine and peroxisome proliferator-activated receptor γ agonists in NS are limited and inconclusive or not optimal (19,20,52). More recently, pasireotide has been shown to reduce ACTH levels in NS but its effects on tumor volume have not been clearly established (53,54). Furthermore, biochemical and radiological improvement has been reported in some (55,56), but not all (57) published cases of aggressive tumors treated with temozolomide. In our series, pasireotide and temozolomide had been used on an individual basis and robust conclusions on their effectiveness in NS resistant to other treatments are not possible. Nonetheless, based on the European Society of Endocrinology Clinical Practice Guidelines, temozolomide is recommended in the treatment of aggressive pituitary tumors and carcinomas and needs to be considered in cases of aggressive Nelson's tumors (58).

The strengths of our study are the large number of patients (with the vast majority diagnosed in the MRI era allowing earlier NS detection) and the systematic assessment of tumor behavior during a long follow-up period. Limitations include its retrospective design (although prospective studies on this topic may not be practically feasible) and the potential selection bias in the management approaches offered, as these were tailored to the individual patient rather than based on an established algorithm.

In conclusion, our multicenter study provides systematic data on long-term tumor behavior in the context of NS. Tumor progression was diagnosed in 38% of the cases at 10 years follow-up. Surgery +/- radiotherapy after the NS diagnosis show 10-year progression-free survival rates between 80 and 81%. Complexity of previous treatments for the CD prior to NS diagnosis, possibly reflecting corticotroph adenoma aggressiveness, predicts tumor prognosis after the diagnosis of NS. Malignant transformation was diagnosed in 3% of our patients, as opposed to the 0.1-0.2% reported rate of carcinoma in all pituitary adenomas highlighting the potential distinct position of NS in the landscape of pituitary tumors. Based on our results, detection of corticotroph tumor progression is an important element in the diagnosis of the syndrome. Nonetheless, biochemical criteria (lack of suppressibility of plasma ACTH two hours after morning glucocorticoid dose and/or gradually increasing morning ACTH levels usually checked at least 20 hours after the last glucocorticoid dose) without

identification of tumor enlargement on imaging need to be also considered in the diagnostic approach of this condition, as in this particular group, tumor progression was detected in 36% and 50% of the cases at 5 and at 10 years follow-up, respectively. Furthermore, based on our series, active management with surgery combined or not with radiotherapy is a suggested management approach as it is associated with more optimal outcomes in terms of tumor control. This is particularly relevant for cases requiring complex treatments for the CD prior to the diagnosis of NS. Small tumors not causing mass effects to surrounding structures could be managed by surveillance and in a number of cases, active treatment will be later necessary. Due to its rarity, predictors for malignant transformation guiding therapeutic algorithms has not been possible. Further studies elucidating the pathophysiology and molecular predictive factors for corticotroph tumor progression after BLA will open avenues for improvements in the management and prognosis of these patients.

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Legends for figures and tables

Table 1. Characteristics of patients with Nelson's syndrome.

Table 2. Primary management of Nelson's syndrome.

Table 3. Tumor progression-free survival after Nelson's syndrome diagnosis.

Table 4. Hazard ratios of Nelson's tumor progression after its primary treatment estimated according to mode of management of Cushing's disease using the Cox regression model.

Table 5. Management and outcomes of patients with further corticotroph tumor progression after the primary management of Nelson's syndrome.

Figure 1. (a) Tumor progression-free survival for the total group of patients with Nelson's syndrome, (b) Tumor progression-free survival according to management approach for the Nelson's syndrome.

Figure 2. Cases with Nelson's syndrome diagnosis based on imaging combined with biochemical/clinical criteria: (a) Tumor progression-free survival for the total group of patients with Nelson's syndrome, (b) Tumor progression-free survival according to management approach for the Nelson's syndrome.

644

645 **Table 1.**

Total number	68
Sex	
Males/females	10/58
Age at diagnosis of Cushing's disease	
Median (range) (years)	30 (11-69)
Size of adenoma at diagnosis of Cushing's disease	
Microadenoma	37
Macroadenoma	8
No information	23*
Management of Cushing's disease	
Pituitary surgery and adrenalectomy	30
Pituitary surgery and radiotherapy and adrenalectomy	17
Radiotherapy and adrenalectomy	2
Adrenalectomy	19
Presence of pituitary tumor on imaging prior to adrenalectomy	
Yes	23 (MRI 19, CT 4)
No	20 (MRI 15, CT 5)
No information	25**
Median age at diagnosis of Nelson's syndrome	
Median (range) (years)	42 (13-73)

646 MRI: Magnetic resonance imaging; CT: computed tomography

647 * In 17/23 patients, Cushing's disease was diagnosed before 1990.

648 **In 20/25 patients, adrenalectomy took place before 1990.

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Table 2.

All patients	
Pituitary surgery	10
Radiotherapy*	22
Pituitary surgery and radiotherapy**	18
Observation	16
Pasireotide	2
Patients diagnosed based on positive imaging combined with biochemical/clinical criteria	
Pituitary surgery	9
Radiotherapy*	16
Pituitary surgery and radiotherapy**	16
Observation	11
Pasireotide	1
Patients diagnosed based on biochemical/clinical criteria	
Pituitary surgery	1
Radiotherapy	5
Pituitary surgery and radiotherapy	2
Observation	5
Pasireotide	1
Patient with no available diagnostic criteria	
Radiotherapy	1

*Four patients had a previous course of conventional fractionated radiotherapy for the management of Cushing's disease.

**One patient had a previous course of conventional fractionated radiotherapy for the management of Cushing's disease.

Table 3.

Groups of patients	*Tumor progression-free survival*			
	5 years	10 years	15 years	*p* value
All patients				
Total group (n=63)	77%	62%	49%	
Pituitary surgery (n=10) Radiotherapy (n=21) Pituitary surgery and radiotherapy (n=17) Observation (n=15)	80% 80% 87% 70%	80% 52% 81% 51%	80% 35% 73% 31%	0.029
Nelson's syndrome diagnosis based on positive imaging combined with biochemical/clinical criteria				
Total group (n=49)	80%	65%	53%	
Pituitary surgery (n=9) Radiotherapy (n=15) Pituitary surgery and radiotherapy (n=15) Observation (n=10)	78% 71% 92% 90%	78% 38% 85% 72%	78% 28% 75% 36%	0.079
Nelson's syndrome diagnosis based on biochemical/clinical criteria				
Total group (n=14)	64%	50%	43%	

Two patients offered pasireotide for the management of Nelson's syndrome have been excluded from the Kaplan Meier analyses.

Table 4.

Mode of treatment of Cushing's disease	HR (95% CI)	*p* value
Total Group		
Pituitary surgery and adrenalectomy (reference)		
Radiotherapy and adrenalectomy	0.848 (0.098-7.319)	0.881
Pituitary surgery and radiotherapy and adrenalectomy	4.573 (1.554-13.450)	0.006
Adrenalectomy	0.251 (0.048-1.312)	0.102
Group of those diagnosed with positive imaging combined with biochemical/clinical criteria		
Pituitary surgery and adrenalectomy (reference)		
Radiotherapy and adrenalectomy	0.502 (0.058-4.344)	0.532
Pituitary surgery and radiotherapy and adrenalectomy	3.881 (1.331-11.321)	0.013
Adrenalectomy	0.264 (0.053-1.315)	0.104

HR: Hazard ratio, CI: Confidence intervals

694 **Table 5.**

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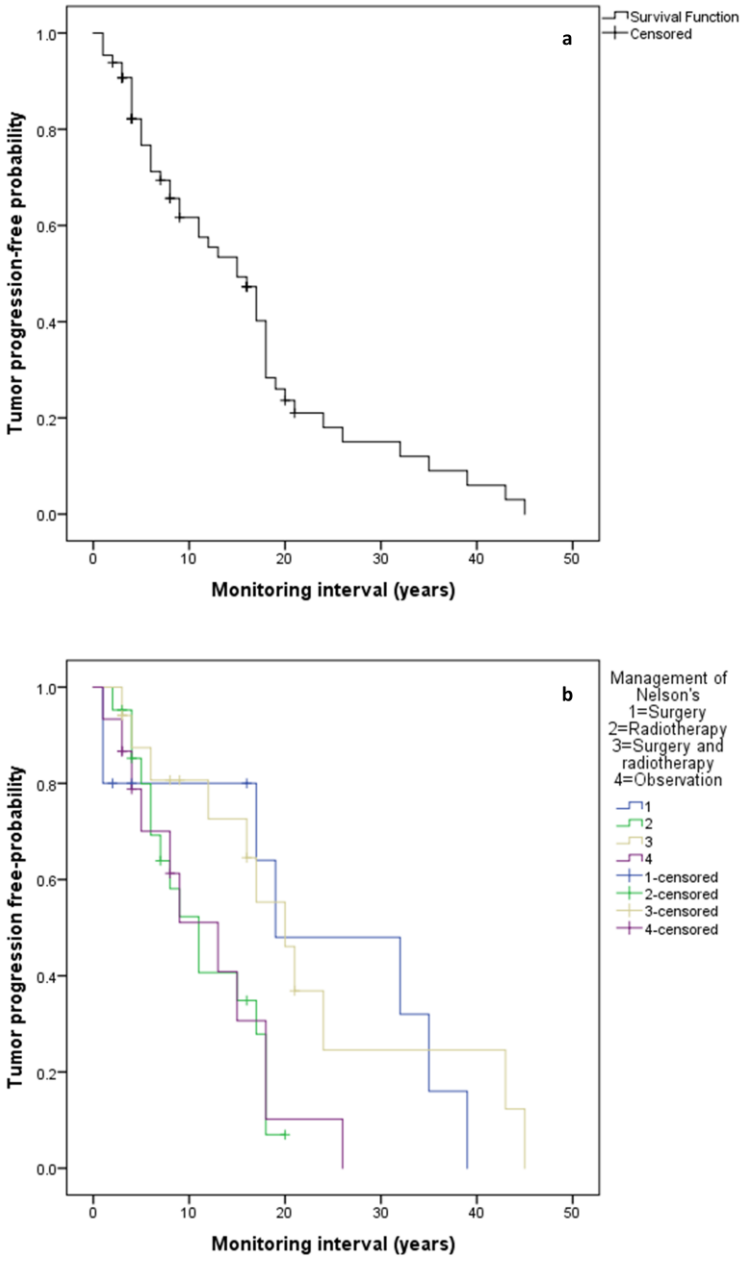
Patient number	Management of further corticotroph tumor progression	Outcome
1	TSS, chemotherapy, RT, unsuccessful trials of cabergoline, octreotide, rosiglitazone	Spinal metastases detected 8 years after RT treated surgically 13 years after detection of spinal metastases: empty sella, stable spinal metastases
2	Gamma knife, chemotherapy interrupted by stroke, pasireotide trial ceased due to diabetes, unsuccessful trials of cabergoline and octreotide	8 years after gamma knife: stable tumor on imaging
3	Stereotactic radiosurgery	8 years after stereotactic radiosurgery: tumor reduced in size
4	Stereotactic radiosurgery	10 years after stereotactic radiosurgery: tumor reduced in size
5	TSS and Cyber knife	3 years after Cyber knife: tumor increased in size, awaiting further management decisions
6	TSS	8 years after TSS: stable tumor on imaging
7	Awaiting further management decisions	
8	Monitoring	4 years after detection of tumor progression: stable tumor on imaging
9	TSS	Further increase in tumor size 2 years after TSS managed by gamma knife 4 years after gamma knife: stable tumor on imaging
10	Stereotactic radiosurgery	4 months after stereotactic radiosurgery: stable tumor on imaging
11	Diagnosed with spinal metastases treated by local RT and temozolomide	Gradual increase in tumor size and death due to pituitary carcinoma 3 years after detection of metastatic disease
12	TSS and Pasireotide	1 year after TSS: stable tumor on imaging
13	TSS	18 years after TSS: stable tumor on imaging
14	RT	10 years after RT: stable tumor on imaging
15	TSS and stereotactic radiosurgery	6 years after stereotactic radiosurgery: reduction in tumor size on imaging
16	Gamma knife	9 years after gamma knife: stable tumor on imaging
17	TSS and chemotherapy (capecitabine and lomustine)	Died shortly after TSS
18	TSS, chemotherapy (capecitabine and lomustine), temozolomide	Stable for 2 years followed by increase in size treated with cabergoline and TSS Died 6 years after TSS due to tumor progression

696 TSS: transsphenoidal surgery, RT: radiotherapy

697 **Figure 1.**



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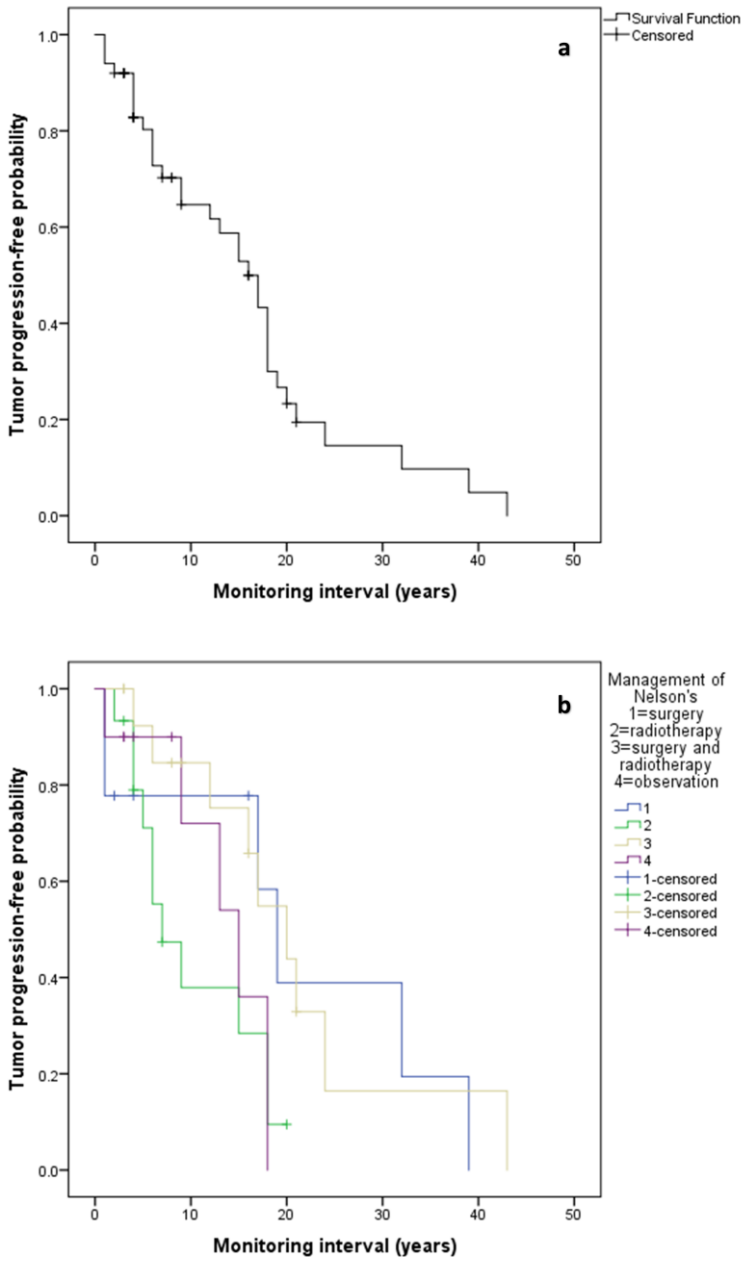
704 **Figure 2.**



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