Corticotroph tumor progression after bilateral adrenalectomy (Nelson's syndrome)

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Title:

Corticotroph Tumor Progression after Bilateral Adrenalectomy (Nelson's syndrome): Systematic Review and Expert Consensus Recommendations.

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Abbreviations:
ACTH: Adrenocorticotropic hormone
BADX: bilateral adrenalectomy
Cushing's disease: CD
Cushing's syndrome: CS
Glucocorticoid: GC
MRI: magnetic resonance imaging
Nelson's syndrome: NS
Computed tomography: CT
Magnetic resonance imaging: MRI
Transsphenoidal surgery: TSS
Conventional radiotherapy: CRT
Stereotactic radiosurgery: SRS

Summary

BACKGROUND: Corticotroph tumor progression (CTP) leading to Nelson's syndrome (NS) is a severe and difficult-to-treat complication subsequent to bilateral adrenalectomy (BADX) for Cushing's disease. Its characteristics are not well described, and consensus recommendations for diagnosis and treatment are missing.

METHODS: A systematic literature search was performed focusing on clinical studies and case series (≥5 patients). Definition, cumulative incidence, treatment and long-term outcomes of CTP/NS after BADX were analyzed using descriptive statistics. The results were presented and discussed at an interdisciplinary consensus workshop attended by international pituitary experts in Munich on October 28th, 2018.

RESULTS: Data covered definition and cumulative incidence (34 studies, 1275 patients), surgical outcome (12 studies, 187 patients), outcome of radiation therapy (21 studies, 273 patients), and medical therapy (15 studies, 72 patients).

CONCLUSIONS: We endorse the definition of CTP-BADX/NS as radiological progression or new detection of a pituitary tumor on thin-section MRI. We recommend surveillance by MRI after 3 months and every 12 months for the first 3 years after BADX. Subsequently, we suggest clinical evaluation every 12 months and MRI at increasing intervals every 2-4 years (depending on ACTH and clinical parameters). We recommend pituitary surgery as first-line therapy in patients with CTP-BADX/NS. Surgery should be performed before extrasellar expansion of the tumor to obtain complete and long-term remission. Conventional radiotherapy or stereotactic radiosurgery should be utilized as second-line treatment for remnant tumor tissue showing extrasellar extension

Introduction

Cushing's disease (CD) is caused by a pituitary corticotroph adenoma producing sustained levels of adrenocorticotropic hormone (ACTH), leading to excessive glucocorticoid secretion. The treatment of choice is transsphenoidal surgery (TSS) with selective removal of the adenoma tissue. Rates for persistence of CD or recurrence after initial remission were reported with a great variability depending on the ratio of micro-/macroadenoma, the experience of the surgeons and the definition for persistence and recurrence (1, 2). Based on meta-analyses the rates for persistence and recurrence after initial TSS ranged from 22% to 24% (persistence) (3-5) and 10-12% (recurrence), (4) respectively. Studies with a longer follow-up showed higher recurrence rates. Although the highest risk for recurrent disease is observed in the first five years (6), it can occur as late as several decades after surgery and lifelong surveillance for recurrence is essential. Second-line treatments in persistent and recurrent CD include repeat transsphenoidal surgery, fractionated pituitary radiation and radiosurgery, medical therapy targeting ACTH and cortisol excess, and bilateral adrenalectomy (BADX). BADX is highly effective but leads to permanent adrenal insufficiency requiring life-long steroid replacement therapy with the risk of life-threatening adrenal crisis. Therefore, BADX is generally considered the *ultima ratio* in CD treatment used when all other treatment options have failed. The use of BADX is highly variable between centers.

One of the possible complications occurring after BADX is the subsequent growth of the corticotroph tumor. Although the exact mechanism behind corticotroph tumor progression remains to be elucidated, it is believed that disinhibition of

the corticotroph tumor might be caused by reduced glucocorticoid feedback on tumor cells.

The surveillance, diagnosis and treatment of corticotroph tumors that progress (CTP), possibly leading to Nelson's syndrome (NS) is not standardized. To our knowledge there has never been a consensus on diagnosis and treatment. Therefore, we performed a systematic review of the literature on the definition of CTP after BADX leading to NS, its cumulative incidence, treatment and outcome of CTP. The results were presented and discussed at an interdisciplinary workshop attended by international pituitary experts in Munich on October 28th, 2018.

Methods of Literature Search and Consensus

Objective: The objective of the current analysis was to develop an expert consensus for the management of patients with CTP after BADX leading to NS.

Methods: We performed a systematic literature search on MEDLINE using the search terms "Nelson's syndrome" or "Nelson syndrome" or "bilateral adrenalectomy" and "Cushing's disease". We searched for systematic reviews, clinical studies and case series (≥5 patients). The search was limited to human studies and English language. We identified 635 publications, of which 80 met the inclusion criteria and were deemed to be relevant. The studies covered cumulative incidence (34 studies, 1275 patients undergoing BADX and 328 diagnosed with NS), surgical outcome (12 studies, 187 patients), outcome of radiation therapy (21 studies, 273 patients), and outcome of medical therapy (15 studies, 72 patients).

Evidence: We analyzed definition, key features, cumulative incidence, treatment and long-term outcomes of CTP/NS after BADX using descriptive statistics. The majority of the available data were of low quality (observational studies, unsystematic clinical experience, no randomized trials) and key outcome parameters could often not be defined due to the heterogeneity of the studies. For this reason, evidence was not formally graded. Analogue to the *Grading of Recommendations, Assessment, Development, and Evaluation Group* criteria (GRADE), we used "recommend" for strong recommendations and "suggest" for weak recommendations (7).

Consensus Process: We achieved consensus by collecting the best available evidence and conducting one group meeting on October 28, 2018 and exchanged multiple e-mail communications.

History, Terminology and Key Features

In 1958 Don H. Nelson published the first description of a progressive ACTH-producing pituitary tumor following BADX; a case of deep pigmentation after BADX had already been recognized by Dr. Allan W. Spence at London's St Bartholomew's Hospital in 1957 (8). The syndrome, initially coined "post adrenalectomy syndrome", was characterized by hyperpigmentation, elevated ACTH and an expanding sellar mass (9). One year later in 1959, Robert M. Salassa reported the first series of 5 patients with a progressive corticotroph tumor after bilateral adrenalectomy (10). Over time, the terminology "Nelson's syndrome" was more widely used than "Nelson-Salassa syndrome" as indicated by the number of references in the scientific domain (Pubmed search: 598 hits vs 5 hits, April 2020).

In early studies, NS was often defined by the appearance of the clinical manifestations such as hyperpigmentation or a visual field defect. With advances in neuroimaging and the availability of computed tomography (CT) and later magnetic resonance imaging (MRI), clinical and laboratory indicators became less important for the diagnosis of NS. In 2007, the term "corticotroph tumor progression (CTP)" was proposed by Guillaume Assie and collegues to amend or replace "Nelson's syndrome"(11). This alternative terminology shifts the focus to the key feature of NS: An expanding pituitary corticotroph tumor as the primary clinical problem occurring subsequent to removal of both adrenal glands (BADX). However, NS is well established as medical eponym, and a change in medical terminology is difficult to achieve (12). Therefore, we suggest keeping NS as a supplement to CTP.

Consensus Recommendation 1: We suggest amending the terminology from "Nelson's syndrome" (NS) to "Corticotroph Tumor Progression after bilateral adrenalectomy/Nelson's syndrome" (CTP-BADX/NS, no grading).

Definition and Diagnosis of CTP-BADX /NS

Corticotroph tumor progression in pituitary imaging

In early publications, skull radiographs were used for diagnosing sellar masses (13-25). The assumption of pituitary tumor progression was based on findings of sellar enlargement, and distortion or thinning of the dorsum sellae. Also, clinical signs of tumor infiltration such as loss of vision were used for diagnosis. Since the 1980s pituitary tumors have been diagnosed with tomographic techniques (CT and later MRI, (11, 26-42)). Although CT allowed more accurate description

and earlier identification of pituitary tumor progression, diagnostic criteria were still heterogeneous. Some studies defined CTP-BADX/NS by the presence of a pituitary tumor on a post-adrenalectomy scan, while other studies requested progression or new occurrence. There were also inconsistencies in the interpretation of tumor size as a diagnostic marker. In the majority of studies, the presence of a microadenoma was sufficient to diagnose CTP-BADX/NS, while some publications required macroadenomas (≥10 mm) or the need for clinical intervention (29, 31, 35, 39). From 2007 onwards, the definition of CTP-BADX/NS became more consistent, requiring significant tumor progression on neuroimaging (11, 38, 41, 42). Serial MRI with assessment of diameter, volume and potential parasellar extension has become the gold standard for the detection and evaluation of pituitary masses.

Precise volumetric measurement of pituitary tumors is often hampered by their irregular morphology, particularly after surgical resection, and standardized methods for imaging interpretation remain to be validated.

Summary: Radiological evidence of progression or a new occurrence of a pituitary tumor after BADX on MRI have become the basis for the diagnosis of CTP-BADX/NS in current clinical practice.

Hyperpigmentation

Hyperpigmentation of the skin and mucous membranes after bilateral adrenalectomy is a common clinical feature caused by binding of ACTH and other POMC splicing products to the melanocortin-1 receptor (MC1R) Objective evaluation and quantification of this criterion is difficult because an individual's skin color is influenced by many factors, such as ethnicity or sun exposure. The

presence of MC1R genetic variants might also affect the degree of skin darkening, as previously reported for primary adrenal insufficiency (43). However, hyperpigmentation has served as a diagnostic criterion in several studies and has been documented in many publications. In earlier studies, before tomographic imaging was widely available, hyperpigmentation after BADX was more prevalent than expanding pituitary tumors (13-24, 26, 28, 30, 32, 35, 36). Interestingly, a recent study showed that a considerable number of patients with tumor progression on MRI had no obvious hyperpigmentation, indicating that tumor progression on MRI imaging might precede hyperpigmentation in some cases (42).

Although hyperpigmentation seems a less reliable diagnostic criterion than MRI documented tumor progression, it has clinical significance as a potential indicator of ACTH increase after BADX. In addition, hyperpigmentation can impact negatively on quality of life, especially at a younger age. The phenotypic changes associated with skin darkening are relevant for self-image and social interactions.

Summary: The new development or intensification of hyperpigmentation is an indicator of potential CTP and should lead to further diagnostic steps. A possible psychosocial impact on the affected patients, especially in children and adolescents, should also be carefully monitored in clinical practice.

ACTH elevation

ACTH as a tumor marker for CTP-BADX/NS has been measured and evaluated in most studies. Systematic comparisons between reports are difficult and limited by the use of different analytical methods (RIA vs. automated immunoassays),

309 different units (pmol/l vs. pg/ml) and different blood sampling protocols (e. g. in
310 the morning before or in the morning following hydrocortisone substitution).
311 The latter aspect needs special consideration since it has been shown that ACTH
312 concentrations are profoundly influenced by the interval to the last
313 glucocorticoid replacement dose (GC) (44). Another factor is that aggressive
314 pituitary tumors after BADX might secrete high molecular weight ACTH, which
315 cannot be detected by routine ACTH assays, resembling some 'silent'
316 corticotroph adenomas (45). In general, ACTH measurement is challenging with
317 complex preanalytical requirements. As a consequence, there is some
318 controversy about the reliability of automated immunoassays (46, 47). Thus,
319 caution is required not only in the interpretation of available research data but
320 also in the use of plasma ACTH cut-offs as the basis for clinical decision making.
321 Since spontaneous fluctuation of plasma ACTH can occur, monitoring of the
322 ACTH level over time might be valuable to detect a progressive rise.
323 Most studies analyzed in the context of the present work showed increasing
324 ACTH levels in patients following BADX. Similar to hyperpigmentation, ACTH
325 elevation was more prevalent than radiologically-documented pituitary tumor
326 progression, especially in earlier studies with less sophisticated imaging
327 techniques (26, 28, 39). In direct comparison, average ACTH values were higher
328 in patients with CTP-BADX/NS compared to patients without CTP-BADX/NS
329 (956 vs 276 pg/ml (211 vs 61 pmol/l) (11, 34, 40, 48). The threshold of ACTH
330 that could discriminate between patients with and without CTP-BADX/NS in
331 different studies ranged from 200 to 700 pg/ml, with a mean of 396 pg/ml (44 to
332 154 pmol/l, mean 87 pmol/l) (11, 21, 23, 28, 32, 34, 36, 38). *Summary*: A

consistent ACTH threshold indicating CTP-BADX/NS, as well as the timing of sampling remains to be established.

Conclusions

In earlier descriptions, CTP-BADX/NS was defined by the typical triad (hyperpigmentation, elevated ACTH, and progressive pituitary adenoma). While the expanding pituitary tumor is the primary clinical problem, hyperpigmentation and elevated plasma ACTH are concomitant features. Available data suggest that hyperpigmentation and elevated ACTH are neither specific nor sensitive enough to be classified as primary diagnostic criteria for CTP-BADX/NS. Nonetheless, hyperpigmentation and ACTH excess are important clinical and biochemical evidence after BADX for CD, and possible indicators for CTP-BADX/NS. Longitudinal changes indicating an increase in ACTH seem to be more indicative for CTP-BADX/NS than an individual ACTH value after BADX. To standardize, sampling for ACTH measurement is recommended at 08:00 a.m. prior to the morning dose of GC (49).

Consensus Recommendation 2: As a primary criterion for the definition and diagnosis of CTP-BADX/NS, we recommend radiological evidence of corticotroph tumor progression or the new detection of a radiologically visible pituitary tumor after BADX. We further suggest hyperpigmentation and a progressive rise in plasma ACTH after BADX (assessed by immunoassay, at 08:00 h prior to the morning dose of GC) as non-mandatory secondary criteria of CTP-BADX/NS.

Cumulative incidence of CTP-BADX/NS

Cumulative incidence of Nelson's syndrome in adults

Studies were excluded if the definition of CTP-BADX/NS was not given in the publication. The remaining 34 studies were analyzed on the basis of imaging modality (radiography versus tomography).

In the pre-tomography area, CTP-BADX/NS was mainly diagnosed by skull radiography. From 1971 until 1985, 10 publications investigated the cumulative incidence of CTP-BADX/NS in adults diagnosed with Cushing's disease who underwent BADX (13-15, 17, 19-24). CTP-BADX/NS occurred in 20% (0% - 46%) of the patients.

In studies published from 1990 onwards, CT and MRI have been mainly used for pituitary imaging. The mean cumulative incidence of CTP-BADX/NS in these studies was 29%, ranging from 8% to 53%. The large variability was due to the fact that the diagnostic criteria for CTP-BAD/NS were still heterogeneous (11, 26-42, 48). As an example, the lowest cumulative incidence of CTP-BADX/NS (8%) was observed in a study where CTP-BADX/NS was defined by the need for intervention for a pituitary tumor (39). A more consistent definition was introduced from 2007 onwards, with CTP-BADX/NS mainly defined by the new occurrence or significant corticotroph tumor progression on CT or MRI scans. The mean prevalence of CTP-BADX/NS in these studies was 43% (28-53%) (11, 38, 41, 42).

Predictive factors

Some publications were able to establish factors associated with an increased risk of developing CTP-BADX/NS (Table 2). High ACTH plasma concentrations in

the first year after BADX seemed to be predictive of CTP-BADX/NS (11, 21, 28, 34, 48). Patients with an obvious adenoma (33, 34) or larger tumor size before BADX (6mm vs. 1mm (42)) had an increased cumulative incidence of CTP-BADX/NS after BADX. Additionally, young age at BADX was positively associated with the appearance of CTP-BADX/NS. Patients younger than 35 years at BADX seem to have a particularly increased risk (22, 29, 37, 42). Cushing's disease has a female preponderance and more female than male patients undergo BADX. In 11 studies, specification of gender allowed calculation of the gender-related risk of CTP-BADX/NS (15-17, 21, 22, 29, 34, 36, 38, 42, 48). The majority of BADX patients were female (394 of 500). The mean proportion of female patients who developed CTP-BADX/NS was equivalent to the proportion of female patients in the group that was not diagnosed with CTP-BADX/NS (77.7 % vs. 78.4 %). While CD has higher preponderance in females, the cumulative incidence of CTP-BADX/NS is not sexually discordant. The effect of pregnancy on CTP-BADX/NS has been investigated in 11 women who became pregnant at a median time interval of 3.5 years after BADX by serial pituitary MRI bevor, during and after pregnancy. Interestingly, pregnancy did not accelerate corticotroph tumor progression (50).

The effect of radio therapy before BADX and prophylactic radio therapy on the risk of CTP-BADX has not been clarified yet and will be discussed later.

Patients with aggressive adenomas, not controlled by surgery and radiation, have a higher probability to undergo BADX for persistent or recurrent disease. These resistant adenomas might either be particularly sensitive to the loss of feedback inhibition after BADX or exhibit a distinct intrinsic aggressiveness. So

far, histopathological examination of pituitary tumors from transsphenoidal surgery *prior* to BADX could not identify a subtype that predicts the development of CTP-BADX/NS. Staining patterns as well as mitotic rates and Ki-67 immunopositive nuclei from previous TSS were not different between patients developing CTP-BADX/NS and patients without CTP-BADX/NS (11, 42).

However, CTP-BADX/NS histology showed low p27 labeling indices and higher proliferation rates than corticotroph pituitary tumors from patients not undergoing BADX (51-53). Therefore, the role of histopathology and new molecular markers for the development of CTP-BADX/NS remains to be established by further research (54). Recently, somatic driver mutations in the ubiquitin specific protease 8 (*USP8*) gene have been implicated in the pathogenesis of Cushing's disease (55). These mutations appear to have a similar prevalence in CTP-BADX/NS, excluding the possibility that they drive the corticotroph tumor progression that leads to CTP-BADX/NS (56). Overall, progressing corticotroph tumors seem to be a heterogeneous group in terms of molecular characteristics and clinical behavior. and molecular pathways involved in growth regulation need to be further elucidated.

Cumulative incidence of Nelson's syndrome in childhood

Three publications investigated the cumulative incidence of CTP-BADX/NS in childhood, all dating back to the pre-tomography era. The mean cumulative incidence of CTP-BADX/NS was considerably higher compared to results in adult patients (45%, 25-67%) (16, 18, 25). The lack of more recent data is most likely due to the rare occurrence of CD in childhood, and the restrictive use of BADX after evolution of transsphenoidal microsurgery (57).

Time interval between BADX and diagnosis of CTP-BADX/NS

The mean time interval between BADX and diagnosis of CTP-BADX/NS was 5.3 years (9-11, 13-22, 56). However, the occurrence of CTP-BADX/NS has been reported from as little as 2 months up to 27 years after BADX (18, 38). In more recent studies, using CT or MRI imaging and more consistent criteria for CTP-BADX/NS, the time between BADX and CTP-BADX/NS was 2.5 years (0.2-8) (11, 38, 41, 42). A previous study reported a median growth rate of 3 mm/year (0.5-21 mm) [38]: From these data, surveillance by tomographic imaging every 12 months for the first 3 years seems reasonable.

Conclusions

The large variability in the cumulative incidence of CTP-BADX/NS and in the time of development after BADX may be mainly due to the lack of consistent diagnostic criteria. This emphasizes the need for a clear and standardized definition. CT and especially MRI imaging have a higher sensitivity than clinical and radiographic signs for the diagnosis of CTP-BADX/NS. The high CTP-BADX/NS cumulative incidence of around 40% in more recent publications probably reflects the true incidence of corticotroph tumor progression detected at an early stage. Since MRI allows diagnosis of tumor progression in the subclinical state, a diagnosis of CTP-BADX/NS does not necessarily need treatment but requires close follow-up

Consensus Recommendation 3.1: We recommend close surveillance in patients with any of the following conditions: 1. high plasma ACTH after BADX or

458 an increasing ACTH level; 2. visible corticotroph tumor prior to BADX; 3. patients
459 younger than 35 years of age. The role of histopathological and molecular
460 markers for the prediction of CTP-BADX/NS remains to be evaluated.
461
462 **Consensus Recommendation 3.2**: We recommend surveillance by MRI imaging
463 (1-2 mm slice thickness) after 3 months and every 12 months for the first 3 years
464 after BADX. CT should be only suggested as a method of second choice in patients
465 with contraindications for MRI. We suggest clinical surveillance every 12 months
466 and MRI imaging at increasing intervals every 2-4 years (depending on ACTH
467 and clinical parameter) afterwards. In high-risk patients, closer surveillance
468 might be required.
469
470 **Outcome of pituitary surgery in CTP-BADX/NS**
471 *Surgical series of patients with CTP-BADX/NS*
472 Successful surgical treatment of CTP-BADX/NS remains a great challenge.
473 Because of the rarity of the syndrome, only 12 relevant clinical studies on
474 outcome of neurosurgery have been reported since 1976 (187 patients).
475
476 *Total hypophysectomy versus selective adenomectomy*
477 Most experts agree that neurosurgical resection of the pituitary tumor should be
478 the first-line therapy in patients with CTP-BADX/NS. In the early years, total
479 hypophysectomy was considered the preferred technique because of the
480 potentially aggressive behavior of these tumors, a tendency to recurrence, and
481 disappointing results of selective adenomectomy (58, 59). For example, in 1980
482 a study reported tumor control in 4 of 19 tumors by selective adenomectomy,

whereas 4 patients died as direct consequence of the tumor (59). Nevertheless, with advances in microsurgery, the outcomes of pituitary surgery have improved, leading to the recommendation to use selective adenomectomy as the preferred technique (60).

Transsphenoidal versus transcranial approach

The transsphenoidal approach is a relatively effective and safe procedure, and it is the preferred technique when feasible (37, 60-65). However, the outcomes of neurosurgery in CTP-BADX/NS are worse in comparison to those achieved in other types of pituitary tumors. Kasperlik-Zaluska and coworkers divided CTP-BADX/NS into three stages: stage I, pituitary microadenoma without any signs of invasion; stage II, pituitary macroadenoma without any invasion; stage III pituitary macroadenoma with extrasellar/parasellar invasion (37). In their series of 30 patients undergoing surgery, the transsphenoidal approach appeared to be the method of choice for stages I and II. They recommended a transcranial intervention, sometimes combined with radiotherapy, in patients with tumors having a large extrasellar invasion. In these cases, combined therapy may be the only way to attain partial remission, which was defined by the authors as a distinct improvement in the clinical course of NS, with reduced size of the pituitary tumor and decreased - but still exceeding the upper limit of normal - plasma ACTH levels. Similarly, Zielinski *et al*, recommend the transsphenoidal approach in the pre-invasive phase and the transcranial approach in invasive tumors (65). Our consensus panel emphasized transsphenoidal surgery as the preferred technique in the majority of the cases,

depending mostly on tumor localisation and growth direction, similar to the approach in other subtypes of pituitary tumors.

The interval between BADX and neurosurgery ranged from 7 months to 18 years, indicating the unpredictable behavior of these tumors (59, 60). Significant progression of the corticotroph tumor can occur quickly, leading to an extra-sellar extension (62). In large tumors pituitary apoplexy can occur, leading to neurological complications and even death (37, 60). A significant proportion of CTP showed aggressive growth behaviour (13-21%) (37, 59). Cases of anaplastic pituitary tumors have been reported (37, 66).

Remission rates of surgery

The most relevant studies reporting on the outcome of pituitary surgery in patients with CTP-BADX/NS are summarized in Table 3. Remission rates after surgery ranged between 17% and 80%: Outcome was mainly influenced by tumor volume and the degree of extrasellar extension. However, different criteria of remission have been used over the years. All authors agree that a more favorable prognosis with fewer complications after neurosurgery occurs in microadenomas and intrasellar macroadenomas, whereas large tumors with cavernous sinus invasion have a low chance of complete tumor excision (62). Intrasellar tumors have been reported to be in remission after neurosurgery in 70-80% of the cases, leading also to a more pronounced reduction of plasma ACTH levels (60, 66, 67). The best surgical outcome in those patients treated at an early stage was documented in a large cohort of 30 patients with CTP-BADX/NS(37). Wilson and coworkers reported that none of the 10 patients with

macroadenomas had normalized plasma ACTH levels after neurosurgery (59). In Zielinski's report, all cases that did not achieve remission after surgery were grade IV tumors (according to the Knosp scale) with infiltration of the cavernous sinus (65, 68). The extent of parasellar growth, as measured by the Knosp scale, was established as the main factor influencing the effectiveness of surgical treatment. Accordingly, remission was documented only in patients with small tumors and limited intrasellar extension. All these data support early surgery, preferably before supra- or parasellar extension occurs.

Considering that tumors in patients with CTP-BADX/NS in historic series were mainly macroadenomas, visual field alterations secondary to optic chiasm compression occurred in 10%-51% of cases (58-63, 65-67). Neurosurgery can achieve improvement in visual defects through decompression of the optic chiasm (58, 61, 63, 65). Cranial nerve palsies such as cranial nerve III paresis, are also reported pre-operatively in this population with a frequency of 23%(61). Its complete or partial resolution after neurosurgery is documented (58, 61).

Long-term follow-up after surgery

A limited number of studies have reported long-term follow-up after neurosurgery in CTP-BADX/NS (Table 3). Xing and coworkers reported a mean follow-up of 3.6 years after neurosurgery in 23 patients with CTP-BADX/NS, with recurrence in 13% (63). Wislawski *et al*. documented the follow-up of 10 patients, ranging from 6 months to 10 years, and observed recurrences in 2 patients (20%), within 1 and 1.5 years respectively (66). In the series of Kelly *et al*., long-term follow-up at a median of 17 years demonstrated normal

pigmentation, plasma ACTH levels less than 200 pg/ml (44 pmol/l) and no visible pituitary tumor in 6 of 13 patients with CTP-BADX/NS (61). In a small cohort of 6 patients with intrasellar CTP-BADX/NS, only one had a recurrent ACTH elevation after 10 years follow-up, without evidence of tumor regrowth (60).

Recently, a large retrospective study assessed the outcome of patients with CTP-BADX/NS followed for a median of 13 years (69). Of 68 patients with CTP-BADX/NS, 28 underwent pituitary surgery (n=10 surgery only; n=18 surgery plus radiotherapy), 22 radiotherapy alone, 2 were treated with pasireotide and 16 were observed without treatment. The 10-year tumor progression-free survival was higher in patients treated with pituitary surgery, either alone or in combination with radiotherapy, attaining a figure of ~80% (69).

Side effects of surgery

Pituitary surgery in CTP-BADX/NS is associated more frequently with side effects than primary TSS, since patients are more often subjected to repeated interventions. Still, cerebrospinal fluid leak (CSF) and meningitis have been rarely reported as complications (61, 65). Hypopituitarism or the onset of new pituitary deficits is reported in 5%-30% of cases (58, 60, 62, 64, 65). Exceptionally, Kelly *et al*. described hypopituitarism after surgery in a higher percentage (69%) (61). However, a total hypophysectomy was performed in all 13 patients. Permanent diabetes insipidus has been reported in 18-38% of cases (61, 62, 65). Mortality has been described as direct consequence of tumor progression, pituitary apoplexy or metastasis rather than a surgical complication

(37, 59, 62, 65, 69). Death shortly after pituitary surgery has been reported in few patients (37, 69).

Conclusions

The limitations of this analysis are the variable criteria used to define remission of CTP-BADX/NS and the lack of detailed information regarding imaging, biochemical values and other therapies used before and/or after neurosurgery in some studies. On the other hand, neurosurgical techniques have improved considerably over the last decades through the evolution of transsphenoidal approaches and modern microinstrumentation. The published data have demonstrated that transsphenoidal surgery is the first choice of treatment for CTP-BADX/NS and can be performed safely in the majority of patients.

Consensus Recommendation 4.1

We recommend pituitary surgery as first-line therapy in patients with CTP-BADX/NS. Surgery should be performed before extrasellar expansion of the tumor occurs in order to obtain complete and long-term remission.

Consensus Recommendation 4.2

We recommend selective removal of the pituitary adenoma by a transsphenoidal approach in micro- and macroadenomas, when technically feasible.

Transcranial surgery is to be discussed exclusively for supra-diaphragmatic locations, when extended transsphenoidal approach is not achievable or not

605 perceived as the optimal benefit/risk ratio (low evidence, weak
606 recommendation).
607

Effect of prophylactic pituitary radiotherapy to prevent CTP-BADX/NS

The available literature on this subject is sparse, many studies are based on data sources from previous decades and all data are retrospective. Several studies have evaluated the effect of radiotherapy on the risk of developing CTP-BADX/NS. However, most studies have not clearly distinguished between prophylactic radiotherapy or therapeutic radiation of a corticotroph tumor prior to BADX. Additionally, the absence of a control group in several studies and the low number of patients receiving radiation limits interpretation.

Five of the studies (total n=149 patients with BADX of which 91 patients received radiation) reported a potential beneficial effect of radiation in reducing the cumulative incidence of CTP-BADX/NS (13, 21, 32, 38, 70). Conventional radiotherapy was used in 4 studies (30-50 Gy, fractionated). Two of these studies had control groups, showing a reduction in CTP-BADX/NS from 50% to 25% and 50% to 0 % in treated patients (32, 38). Radiosurgery was used in the most recent analysis with a remarkably low cumulative incidence of CTP-BADX/NS (5%) (70) after prophylactic gamma knife radiation.

In contrast to these publications, two studies (n=208 patients with BADX, of which 45 patients received radiation) could not confirm a risk reduction for CTP-BADX/NS by radiotherapy (15, 42). Another investigation found a high cumulative incidence of CTP-BADX/NS despite low dose pituitary radiation in a small group of patients (26). Together, the data are not sufficient for a general recommendation of prophylactic radiation, and the question whether radiotherapy can prevent CTP-BADX/NS remains unanswered. In particular, the

therapeutic effect of radiosurgery to prevent corticotroph tumor progression needs to be examined by further studies.

Consensus Recommendation 5.1: We suggest against the routine use of prophylactic pituitary radiation (fractionated or radiosurgery) to prevent corticotroph tumor progression. In cases of invasive macroadenomas with incomplete resection concomitant radiotherapy should be discussed by an interdisciplinary team before BADX.

Radiation therapy of CTP-BADX/NS

Radiation therapy can be used as a primary treatment option in pituitary adenomas, or secondary when surgical failure is evident. In general, the outcome of radiation therapy for CTP-BADX/NS is less favorable compared to other forms of pituitary adenomas. Radiation therapy is mainly divided into conventional radiotherapy (CRT) and stereotactic radiosurgery (SRS). Table 4 summarizes the outcomes of radiation therapy and its complications and side effects in patients with CTP-BADX/NS. None of these studies reported rates for peri and post procedural mortality.

Conventional radiotherapy (CRT)

CRT is based on an external photon source to radiate the targeted volume in 20-30 sessions and was used mainly in earlier years for the treatment of CTP-BADX/NS, although in total only 6 studies (1980-2019) with 58 patients have reported on its outcome (19, 62, 69, 71-73). Moreover, most of the studies focused on clinical and biochemical outcomes and lack data on radiological

outcomes and possible side effects of CRT. Comparison to more recent studies is difficult, as often radiation of the whole sellar region was performed and therefore radiotherapy-induced hypopituitarism was common. In addition, earlier studies used different ACTH assays, and imaging with MRI was not available. Howlett *et al.* studied 15 patients with CTP-BADX/NS treated with CRT (72). In 7 of them, CT scans were available demonstrating an empty sella after CRT in all (7/7, 100%). Kemink *et al*. reported tumor control in 5 of 6 patients (83%) (62). ACTH normalization was reported in 50%-60% of patients (62, 71). Two studies with 6 and 15 patients reported on new-onset hypopituitarism (5/6, 83%; and 2/15, 13%)(62, 72). As reported above, the largest study on the long-term outcome was recently published by Fountas *et al*., reporting retrospectively on 22 patients treated from 1969-2018 in 13 UK pituitary centers by "radiotherapy" (19 with CRT, 2 with gamma knife surgery, 1 with cyber-knife surgery)(69). At 10-year follow up, 52% of these patients showed tumor progression-free survival compared to 81% of patients treated by pituitary surgery together with radiotherapy and 80% of subjects treated by surgery alone. However, no further information on radiotherapy (target volume, used dose) and imaging technique nor on side effects was given.

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) uses a very high dose of radiation (considered lethal to cells) applied from different angles (3D) to a precisely defined target volume. Its rationale is that by concentrating radiation on the biological target, more normal surrounding tissue can be preserved. It is usually applied in a single-session, but is sometimes split up into 5 sessions. For SRS different

683 technologies, sources of radiation and computer systems are used, but they all
684 fulfill the above-mentioned characteristics: gamma-knife surgery (GKS) is the
685 most frequently used technique, using gamma rays from a cobalt-60 source.
686 Radiosurgery from linear accelerator systems (LINAC) uses accelerated electrons
687 colliding with a target and therefore generating photons as the radiation source.
688 Finally, proton-based SRS uses accelerated protons with favorable physical
689 characteristics, but the technology is expensive and not widely available. As
690 movement of the patient must be restricted, the patient's head gets fixed with
691 either an invasive metal frame (in GKS) or a non-invasive mask (in LINAC).
692
693 Our systematic literature search identified 11 studies with outcome data on 179
694 patients (GKS: 7 studies with 150 patients (74-80); proton-based SRS: 2 studies
695 with 15 patients (81, 82); LINAC: 2 studies with 14 patients (83, 84).
696 Different definitions of outcome were applied, most of them focused on
697 biochemical and radiological remission, as defined by a decline or normalization
698 of ACTH and stable or decreasing volume of the adenoma. The main therapeutic
699 aim was tumor growth control. Information on pre- and post-treatment status
700 was not reported in all studies, and interpretation of these results has to be
701 handled with caution, because a high percentage of patients treated with
702 radiosurgery was previously treated with multiple operations and CRT for CTP-
703 BADX/NS. Therefore, the isolated effect of radiosurgery might be overestimated.
704
705 *Gamma knife surgery (GKS): efficacy*
706 The majority of the studies reported excellent tumor growth control rates,
707 ranging from 82% to 100%. Since the studies had a mean follow-up of >50

months, and some even 85-144 months (77, 78), this indicates good long-term tumor control rates. In parallel, ACTH stabilization or an ACTH decrease was documented in 66 to 100% of the patients. The target volume was in the range of 1-2 ml. Post-radiation tumor volume shrinkage by 33% and 32% was documented in two studies (77, 79). In patients who achieved ACTH normalization, time from GKS to normalization was 115 and 162 months in two studies (77, 78). A shorter interval between transsphenoidal surgery and GKS was associated with a better endocrine remission (80).

GKS: Side effects

Adverse effects were reported in 6 of 7 studies. The most common adverse effect was new-onset hypopituitarism in 7%-40% of patients (22% in the largest series with 27 patients) (80). In some patients, the anti-tumor effect of GKS has led to improvement of pituitary function and tapering of replacement therapy (79). Visual field deficits and cranial nerves palsies (CNP; transitory and permanent) were reported in 19% and 14%, respectively (77, 78). It has to be noted, however, that many of the patients had received CRT before GKS, potentially increasing radiation-induced neuropathy. A single study reported that 10% of the patients had seizures (80). Additional radiation side effects, such as apoplexy and asymptomatic temporal lobe radiation necrosis, occurred in a small number of patients. (74, 77). One case of glioblastoma multiforme occurred 15 years after GKS in a brain area exposed to no more than 1 Gy which lead the authors to the conclusion that this event was probably not related to the procedure (79).

Proton based SRS and SRS from LINAC

Proton-based radiation has been suggested to have advantages over other forms of radiation as an even more precise and normal tissue sparing radiation might be possible. This so-called Bragg-peak effect allows protons to deposit almost all their energy in the targeted volume. So far, just two studies from 2008 and 2014 reported on 11 patients treated with proton-based SRS (81, 82). Stabilization of tumor growth was reported in both studies as 100%, ACTH normalization in 75% and 100%: 52% of patients developed new hypopituitarism (81).

Two studies including 14 patients reported outcome of LINAC radiosurgery (83, 84). Tumor control was achieved in 60% and 88% (83, 84) and new hypopituitarism developed in 20% (83).

Other forms of radiation

Early studies (1976, 1977) reported outcomes in 28 patients treated by radiation with heavy particles (910 MeV alpha), leading to improvement of hyperpigmentation and decline of ACTH (85, 86); one study from 1976 used the implantation of Yttrium-90 and Gold-198 seeds into the pituitary, by which also improvement and an ACTH decline could be achieved (87).

Conclusions

Radiation therapy is commonly used in CTP-BADX/NS. In earlier years, CRT was widely used, with poorly documented outcome data. More recently, SRS with GKS has been used, leading to high tumor growth control rates of >90%. However, outcome data and side-effect rates of GKS have to be treated with caution, as most patients received CRT prior to GKS, the studies were retrospective, and essential data are often missing. Another major caveat is that

recent technical advances in conventional as well as stereotactic radiotherapy limit the transferability of earlier outcome data to modern radiotherapy. In summary, although of low quality, these data support the concept that radiation therapy can be safely used for CTP-BADX/NS. In general, small tumor volumes are more suitable for SRS, whereas larger tumors may be more suitable for fractionated CRT.

Recommendation 5.2: We recommend radiation therapy for CTP-BADX/NS in patients with tumors not safely accessible by surgery or when complete tumor resection is not possible by surgery. An interdisciplinary tumor board should govern the indication for treatment, the choice of treatment and radiation technique considering clinical, radiological and pathological characteristics.

Outcome of medical treatment in CTP-BADX/NS

Medical therapy in CTP-BADX/NS has been reported in a limited number of studies. Early studies focused on plasma ACTH levels as the outcome indicator, since CTP could not be followed-up because of a lack of accurate imaging techniques (CT and MRI).

Medical therapy with a focus on plasma ACTH

A few studies have investigated the effect of medical therapy on plasma ACTH as a surrogate marker of tumor growth. No effect was reported for either MSH release-inhibiting factor (MIF) or rosiglitazone (88-91). Reports on the efficacy of cyproheptadine, sodium valproate and dopamine agonists (bromocriptine and cabergoline) were heterogeneous. Whereas Krieger *et al*. reported an effect in 3 of 4 patients with CTP-BADX/NS treated with cyproheptadine 24 mg/day orally for 3-5 months, Cassar *et al*. observed no effect on ACTH levels in 3 patients receiving cyproheptadine 24 mg/per day orally for 6 weeks and 40 mg/day for 7 weeks (92, 93). Similarly, a single dose of 5 mg bromocriptine in 9 patients led to lowering of ACTH in one case, whereas a single dose of 2.5mg bromocriptine caused a significant decrease in plasma ACTH levels in 6 patients according to Mercado-Asis (94, 95). A few single case reports showed improvement of ACTH values and control of tumor growth with cabergoline, but larger studies are lacking (96). Sodium valproate 1200mg per day for 3 days resulted in lowered ACTH levels in 3 patients with CTP-BADX/NS (97). However, long-term therapy of 6 patients with sodium valproate 600mg per day for one year showed no significant effect on ACTH levels (98). In summary, these early studies do not

provide evidence for consistent pharmacological effect of any of the investigated medications.

Medical therapy focusing on tumor growth

The alkylating chemotherapeutic agent temozolomide has been used with limited efficacy. One patient with invasive CTP-BADX/NS received temozolomide 200 mg/m^2/day orally for 5 days of a 28-day cycle, leading to tumor shrinkage, improvement of headaches and lowering of ACTH levels after 4 cycles of treatment (99). Another case report of a patient with an invasive corticotroph tumor receiving temozolomide 150mg/m^2/day for 5 days every 28 days for 9 cycles resulted in marked clinical, biochemical, and radiological improvement. After stopping temozolomide tumor progression was observed after a 6-month period of remission, (100). Furthermore, there was a single case of stable disease (101) and a report of a lack of response in a patient despite absent MGMT expression (52, 102) receiving temozolomide for CTP-BADX/NS.

First-generation somatostatin analogues, acting on subtype-2 somatostatin receptors (SST2) were studied in a few patients: 100µg octreotide s.c. lowered ACTH levels and decreased tumor size in a patient with Nelson's syndrome (103); one patient received octreotide 300 µg/ day for a maximum of 2 years leading to lowered ACTH levels and tumor shrinkage (104); in another patient receiving the same regiment, visual field defects normalized (105). The somatostatin analogue pasireotide is a second-generation somatostatin receptor multi-ligand mainly acting on subtype 2 and 5 receptors (SST2, SST5). The

effects of pasireotide on corticotroph tumor growth are discussed controversially(106). A recently published study reported dose and time dependent reduction of tumor volume with pasireotide in patients with CD (107). Daniel *et al.* studied in an open-labeled multicenter longitudinal trial the effect of pasireotide in CTP-BADX/NS (49). Seven patients with subcutaneous treatment demonstrated a significant reduction in morning plasma ACTH of around 50%. This effect was maintained in 5 patients receiving long-acting pasireotide. An acute response to a test dose predicted outcome to long-term treatment in 4 of 5 patients. No significant change in tumor volumes was observed (1.4 ± 0.9 vs. 1.3 ± 1.0, $p = 0.86$). Four patients withdrew during the study. Hyperglycemia occurred in 6 patients. Besides lowering plasma ACTH levels, pasireotide had no major effects on tumor growth in patients with CTP-BADX/NS. Based on their study in 60 corticotroph adenomas, Hayashi *et al*. concluded that the presence of *USP8* mutations may predict favorable responses to pasireotide, whereas non-mutated aggressive tumors might respond better to temozolomide because of their significantly weak expression of MGMT.(108)

The clinical effectivity of medical treatment options preventing corticotroph tumor progression after BADX remains to be investigated in future studies.

Recommendation 6: There is no established medical therapy for CTP-BADX/NS. In aggressive corticotroph tumors resistant to other treatment options, we suggest the use of temozolomide on an individual basis.

Declaration of interest

M Reincke has served on the advisory boards of Novartis and has received lecture fees and grants from Novartis, Ipsen, and Pfizer. I Bancos has served on the advisory boards of HRA Pharma and Corcept, and consulted for ClinCor. T Brue received consulting or speaker fees or grants from Novartis, Pfizer and Ipsen. He served as a board member or research investigator for Strongbridge, Pfizer, Ipsen and Recordati. O CHABRE received speaker fees from Novartis, has been an investigator in a clinical study financed by Novartis and is part of a board of HRA Pharma and Recordati. A Elenkova reports serving as the principal investigator/sub-investigator of clinical trials for Corcept Therapeutics and Novartis and receiving consulting honoraria from Novartis. Ashley Grossman has received lecture fees from Novartis, Ipsen, Pfizer and AAA. N Karavitaki has received educational grants from Novartis. A Lacroix received Clinical Trial Support from Novartis, GLWL Research Inc. and Corcept and served on advisory boards of Novartis, IPSEN and Pfizer. J Newell-Price has received research grants and consulting honoraria paid to the University of Sheffield from HRA Pharma, Novartis, Diurnal, and Ipsen. R Pivonello has been Principal Investigator of Research Studies for Novartis, HRA Pharma, Ipsen, Shire, Corcept Therapeutics, Cortendo AB; Co-investigator of Research Studies for Pfizer; received research grants from Novartis, Pfizer, Ipsen, HRA Pharma, Shire, IBSA; has been an occasional consultant for Novartis, Ipsen, Pfizer, Shire, HRA Pharma, Cortendo AB, Ferring and Italfarmaco; and has received fees and honoraria for presentations from Novartis and Shire. No conflict of interests that could be perceived as prejudicing the impartiality of this research reported. K Ritzel has

received lecture fee from Ipsen and served as investigator of clinical trials for Corcept. J Schopohl has received lecture fees from Novartis, Ipsen, and Pfizer. All the other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author's contribution

Martin Reincke: literature search, study design, data collection, analysis and interpretation (systematic review), writing*. Adriana Albani: literature search, study design, data collection, analysis and interpretation (systematic review), writing*. Guillaume Assie: data interpretation, writing. Irina Bancos: data interpretation, writing. Thierry Brue: data interpretation, writing. Michael Buchfelder: data interpretation, writing. Olivier Chabre: data interpretation, writing. Filippo Ceccato: data interpretation, writing. Andrea Daniele: data interpretation, writing. Mario Detomas: data interpretation, writing. Guido Di Dalmazi: data interpretation, writing. Atanaska Elenkova: data interpretation, writing. James Findling: data interpretation, writing. Ashley Grossman: data

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903 Rubinstein: literature search, study design, data collection, analysis and
904 interpretation (systematic review), writing*. Katrin Ritzel: literature search,
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First Author	year	Follow up (y)*	Age (y)*	n BADX (f/m)	n CTP-BADX (%)	Interval BADX CTP-BADX (y)
Orth	1971	8	NA	19	0 (0)	NA
Glenn	1972	10	NA	42	3 (7)	NA
Moore	1976	8	NA	120 (97/23)	9 (8)	7
Hopwood	1977	5	12	32 (16/16)	8 (25)	3
Cohen	1978	9	30	21 (19/2)	8 (38)	7
McArthur	1979	1-27	4-19	27 (10/17)	12 (44)	10
Sheeler	1980	NA	NA	17	6 (35)	NA
Tomita	1981	NA	NA	19	1 (5)	NA
Kelly	1983	10	NA	38	11 (29)	5
Barnett	1983	5	38	15 (13/2)	3 (20)	NA
Kasperlik-Zaluska	1983	12	42	50 (45/5)	14 (28)	5
Manolas	1984	11	40	65	14 (22)	NA
Thomas	1984	NA	8-17	6	4 (67)	8
Littley	1990	1-14	28	9 (9/0)	3 (33)	NA
Grabner	1991	13	NA	94	10 (11)	10
McCance	1993	5	46	26	9 (35)	NA
Misra	1994	2-10	36	18 (10/8)	2 (11)	NA
Kemink,	1994	10	16-55	48 (44/4)	8 (17)	7
O'Riordain	1994	5	NA	20	3 (15)	NA
Jenkins	1995	NA	39	38	11 (29)	1
Sonino	1996	9	NA	63	15 (24)	NA
Pereira	1998	8	32	30 (22/8)	14 (47)	5
Imai	2000	25	NA	16	4 (25)	NA
Nagesser	2000	19	40	44 (33/11)	10 (23)	NA
Kasperlik-Zaluska	2006	NA	NA	52	23 (43)	NA
Thompson	2007	4	42	36	3 (8)	NA
Gil-Cárdenas	2007	4	31	39 (32/7)	11(28)	1
Assie	2007	5	38	53 (45/8)	25 (47)	3
Smith	2009	5	45	40 (43/6)	13(33)	NA
Ding	2010	4	NA	34	6 (18)	NA
Oßwald	2014	11	NA	29	7 (24)	4
Prajapati	2015	3	NA	12	58 (42)	3
Graffeo	2017	16	NA	88	47 (53)	3
Cohen	2019	14	28	13 (9/4)	6 (46)	2

Table 1:
Summary of studies reporting on cumulative incidence of CTP-BADX/NS.
*mean or range

Author	n after BADX		Age at BADX		% female		ACTH after BADX (pg/ml)	
	CTP	no CTP	CTP	no CTP	CTP	no CTP	CTP	no CTP
Moore	9	111	30	35	88	75	NA	NA
Kelly	11	27	45	38	NA	NA	>240	60
Kemink,	8	40	26 ± 6 *	36 ± 11*	100	90	NA	NA
Pereira	14	16	31 ± 8	32 ± 8	63	86	1726 ± 668*	268 ± 236*
Nagesser	10	34	33	40	90	70	NA	NA
Gil-Cardenas	11	39	28	31	64	89	NA	NA
Assie	25	28	no predictor§		no predictor§		Predictor§	
Graffeo	47	41	35 ± 2*	49 ± 2*	79	73	690 ± 177	NA
Cohen	6	7	29 ± 12	27 ± 7	67	71	476 (240-1500)*	81 (48-330)*

*statistically significant ($p < 0.05$)
§ regression model

Table 2: Potential predictors of CTP-BADX/NS in studies directly comparing risk factors in patients with CD who developed CTP-BADX/NS vs. patients who did not after BADX.

Separately attached

Table 3:
Summary of studies reporting on outcome of pituitary surgery in patients with CTP-BADX/ NS.

Table 4:
Summary of studies reporting the outcomes of radiation therapy in patients with CTP-BADX/NS.