

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

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96 **Title:**

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

99

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116 progression

117

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119 pituitary corticotroph adenoma, tumor growth, Nelson's tumor, radiation,
120 transsphenoidal surgery, hypopituitarism

121

122 **Abbreviations:**

123 ACTH: Adrenocorticotrophic hormone

124 BADX: bilateral adrenalectomy

125 Cushing's disease: CD

126 Cushing's syndrome: CS

127 Glucocorticoid: GC

128 MRI: magnetic resonance imaging

129 Nelson's syndrome: NS

130 Computed tomography: CT

131 Magnetic resonance imaging: MRI

132 Transsphenoidal surgery: TSS

133 Conventional radiotherapy: CRT

134 Stereotactic radiosurgery: SRS

135

136 **Summary**

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

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

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

151 CONCLUSIONS: We endorse the definition of CTP-BADX/NS as radiological
152 progression or new detection of a pituitary tumor on thin-section MRI. We
153 recommend surveillance by MRI after 3 months and every 12 months for the first
154 3 years after BADX. Subsequently, we suggest clinical evaluation every 12
155 months and MRI at increasing intervals every 2-4 years (depending on ACTH and
156 clinical parameters). We recommend pituitary surgery as first-line therapy in
157 patients with CTP-BADX/NS. Surgery should be performed before extrasellar
158 expansion of the tumor to obtain complete and long-term remission.
159 Conventional radiotherapy or stereotactic radiosurgery should be utilized as
160 second-line treatment for remnant tumor tissue showing extrasellar extension

161 **Introduction**

162 Cushing's disease (CD) is caused by a pituitary corticotroph adenoma producing
163 sustained levels of adrenocorticotrophic hormone (ACTH), leading to excessive
164 glucocorticoid secretion. The treatment of choice is transsphenoidal surgery
165 (TSS) with selective removal of the adenoma tissue. Rates for persistence of CD
166 or recurrence after initial remission were reported with a great variability
167 depending on the ratio of micro-/macroadenoma, the experience of the surgeons
168 and the definition for persistence and recurrence (1, 2). Based on meta-analyses
169 the rates for persistence and recurrence after initial TSS ranged from 22% to
170 24% (persistence) (3-5) and 10-12% (recurrence), (4) respectively. Studies with
171 a longer follow-up showed higher recurrence rates. Although the highest risk for
172 recurrent disease is observed in the first five years (6), it can occur as late as
173 several decades after surgery and lifelong surveillance for recurrence is
174 essential. Second-line treatments in persistent and recurrent CD include repeat
175 transsphenoidal surgery, fractionated pituitary radiation and radiosurgery,
176 medical therapy targeting ACTH and cortisol excess, and bilateral adrenalectomy
177 (BADX). BADX is highly effective but leads to permanent adrenal insufficiency
178 requiring life-long steroid replacement therapy with the risk of life-threatening
179 adrenal crisis. Therefore, BADX is generally considered the *ultima ratio* in CD
180 treatment used when all other treatment options have failed. The use of BADX is
181 highly variable between centers.

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

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

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

195

196 **Methods of Literature Search and Consensus**

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

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

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

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

221

222 **History, Terminology and Key Features**

223 In 1958 Don H. Nelson published the first description of a progressive ACTH-
224 producing pituitary tumor following BADX; a case of deep pigmentation after
225 BADX had already been recognized by Dr. Allan W. Spence at London’s St
226 Bartholomew’s Hospital in 1957 (8). The syndrome, initially coined “post
227 adrenalectomy syndrome”, was characterized by hyperpigmentation, elevated
228 ACTH and an expanding sellar mass (9). One year later in 1959, Robert M.
229 Salassa reported the first series of 5 patients with a progressive corticotroph
230 tumor after bilateral adrenalectomy (10). Over time, the terminology “Nelson’s
231 syndrome” was more widely used than “Nelson-Salassa syndrome” as indicated
232 by the number of references in the scientific domain (Pubmed search: 598 hits vs
233 5 hits, April 2020).

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

246

247 **Consensus Recommendation 1:** We suggest amending the terminology from
248 “Nelson’s syndrome” (NS) to “Corticotroph Tumor Progression after bilateral
249 adrenalectomy/Nelson’s syndrome” (CTP-BADX/NS, no grading).

250

251 **Definition and Diagnosis of CTP-BADX /NS**

252 *Corticotroph tumor progression in pituitary imaging*

253 In early publications, skull radiographs were used for diagnosing sellar masses
254 (13-25). The assumption of pituitary tumor progression was based on findings of
255 sellar enlargement, and distortion or thinning of the dorsum sellae. Also, clinical
256 signs of tumor infiltration such as loss of vision were used for diagnosis. Since
257 the 1980s pituitary tumors have been diagnosed with tomographic techniques
258 (CT and later MRI, (11, 26-42)). Although CT allowed more accurate description

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

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

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

277

278 *Hyperpigmentation*

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

284 presence of MC1R genetic variants might also affect the degree of skin
285 darkening, as previously reported for primary adrenal insufficiency (43).
286 However, hyperpigmentation has served as a diagnostic criterion in several
287 studies and has been documented in many publications. In earlier studies,
288 before tomographic imaging was widely available, hyperpigmentation after
289 BADX was more prevalent than expanding pituitary tumors (13-24, 26, 28, 30,
290 32, 35, 36). Interestingly, a recent study showed that a considerable number of
291 patients with tumor progression on MRI had no obvious hyperpigmentation,
292 indicating that tumor progression on MRI imaging might precede
293 hyperpigmentation in some cases (42).

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

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

304

305 *ACTH elevation*

306 ACTH as a tumor marker for CTP-BADX/NS has been measured and evaluated in
307 most studies. Systematic comparisons between reports are difficult and limited
308 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*

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

335

336 *Conclusions*

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

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

355

356 **Cumulative incidence** of CTP-BADX/NS

357 *Cumulative incidence* of Nelson's syndrome in adults

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

361

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

367

368 In studies published from 1990 onwards, CT and MRI have been mainly used for
369 pituitary imaging. The mean **cumulative incidence** of CTP-BADX/NS in these
370 studies was 29%, ranging from 8% to 53%. The large variability was due to the
371 fact that the diagnostic criteria for CTP-BAD/NS were still heterogeneous (11,
372 26-42, 48). As an example, the lowest **cumulative incidence** of CTP-BADX/NS
373 (8%) was observed in a study where CTP-BADX/NS was defined by the need for
374 intervention for a pituitary tumor (39). A more consistent definition was
375 introduced from 2007 onwards, with CTP-BADX/NS mainly defined by the new
376 occurrence or significant corticotroph tumor progression on CT or MRI scans.
377 The mean prevalence of CTP-BADX/NS in these studies was 43% (28-53%) (11,
378 38, 41, 42).

379

380 *Predictive factors*

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

383 the first year after BADX seemed to be predictive of CTP-BADX/NS (11, 21, 28,
384 34, 48). Patients with an obvious adenoma (33, 34) or larger tumor size before
385 BADX (6mm vs. 1mm (42)) had an increased **cumulative incidence** of CTP-
386 BADX/NS after BADX. Additionally, young age at BADX was positively associated
387 with the appearance of CTP-BADX/NS. Patients younger than 35 years at BADX
388 seem to have a particularly increased risk (22, 29, 37, 42). Cushing's disease has
389 a female preponderance and more female than male patients undergo BADX. In
390 11 studies, specification of gender allowed calculation of the gender-related risk
391 of CTP-BADX/NS (15-17, 21, 22, 29, 34, 36, 38, 42, 48). The majority of BADX
392 patients were female (394 of 500). The mean proportion of female patients who
393 developed CTP-BADX/NS was equivalent to the proportion of female patients in
394 the group that was not diagnosed with CTP-BADX/NS (77.7 % vs. 78.4 %). While
395 CD has higher preponderance in females, the **cumulative incidence** of CTP-
396 BADX/NS is not sexually discordant. **The effect of pregnancy on CTP-BADX/NS**
397 **has been investigated in 11 women who became pregnant at a median time**
398 **interval of 3.5 years after BADX by serial pituitary MRI bevor, during and after**
399 **pregnancy. Interestingly, pregnancy did not accelerate corticotroph tumor**
400 **progression (50).**

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

403

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

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

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

425

426 *Cumulative incidence of Nelson's syndrome in childhood*

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

433

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

435 The mean time interval between BADX and diagnosis of CTP-BADX/NS was 5.3
436 years (9-11, 13-22, 56). However, the occurrence of CTP-BADX/NS has been
437 reported from as little as 2 months up to 27 years after BADX (18, 38). In more
438 recent studies, using CT or MRI imaging and more consistent criteria for CTP-
439 BADX/NS, the time between BADX and CTP-BADX/NS was 2.5 years (0.2-8) (11,
440 38, 41, 42). A previous study reported a median growth rate of 3 mm/year (0.5-
441 21 mm) ³⁸: From these data, surveillance by tomographic imaging every 12
442 months for the first 3 years seems reasonable.

443

444 *Conclusions*

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

455

456 **Consensus Recommendation 3.1:** We recommend close surveillance in
457 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 adenectomy*

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 adenectomy (58, 59). For example, in 1980
482 a study reported tumor control in 4 of 19 tumors by selective adenectomy,

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

487

488 *Transsphenoidal versus transcranial approach*

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

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

509

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

517

518 *Remission rates of surgery*

519 The most relevant studies reporting on the outcome of pituitary surgery in
520 patients with CTP-BADX/NS are summarized in Table 3. Remission rates after
521 surgery ranged between 17% and 80%: Outcome was mainly influenced by
522 tumor volume and the degree of extrasellar extension. However, different
523 criteria of remission have been used over the years. All authors agree that a more
524 favorable prognosis with fewer complications after neurosurgery occurs in
525 microadenomas and intrasellar macroadenomas, whereas large tumors with
526 cavernous sinus invasion have a low chance of complete tumor excision (62).
527 Intrasellar tumors have been reported to be in remission after neurosurgery in
528 70-80% of the cases, leading also to a more pronounced reduction of plasma
529 ACTH levels (60, 66, 67). The best surgical outcome in those patients treated at
530 an early stage was documented in a large cohort of 30 patients with CTP-
531 BADX/NS(37). Wilson and coworkers reported that none of the 10 patients with

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

540

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

548

549 *Long-term follow-up after surgery*

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

557 pigmentation, plasma ACTH levels less than 200 pg/ml (44 pmol/l) and no
558 visible pituitary tumor in 6 of 13 patients with CTP-BADX/NS (61). In a small
559 cohort of 6 patients with intrasellar CTP-BADX/NS, only one had a recurrent
560 ACTH elevation after 10 years follow-up, without evidence of tumor regrowth
561 (60).

562 Recently, a large retrospective study assessed the outcome of patients with CTP-
563 BADX/NS followed for a median of 13 years (69). Of 68 patients with CTP-
564 BADX/NS, 28 underwent pituitary surgery (n=10 surgery only; n=18 surgery
565 plus radiotherapy), 22 radiotherapy alone, 2 were treated with pasireotide and
566 16 were observed without treatment. The 10-year tumor progression-free
567 survival was higher in patients treated with pituitary surgery, either alone or in
568 combination with radiotherapy, attaining a figure of ~80% (69).

569

570 *Side effects of surgery*

571 Pituitary surgery in CTP-BADX/NS is associated more frequently with side
572 effects than primary TSS, since patients are more often subjected to repeated
573 interventions. Still, cerebrospinal fluid leak (CSF) and meningitis have been
574 rarely reported as complications (61, 65). Hypopituitarism or the onset of new
575 pituitary deficits is reported in 5%-30% of cases (58, 60, 62, 64, 65).
576 Exceptionally, Kelly *et al.* described hypopituitarism after surgery in a higher
577 percentage (69%) (61). However, a total hypophysectomy was performed in all
578 13 patients. Permanent diabetes insipidus has been reported in 18-38% of cases
579 (61, 62, 65). Mortality has been described as direct consequence of tumor
580 progression, pituitary apoplexy or metastasis rather than a surgical complication

581 (37, 59, 62, 65, 69). Death shortly after pituitary surgery has been reported in
582 few patients (37, 69).

583

584 *Conclusions*

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

593

594 **Consensus Recommendation 4.1**

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

598

599 **Consensus Recommendation 4.2**

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

602

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

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

607

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

609 The available literature on this subject is sparse, many studies are based on data

610 sources from previous decades and all data are retrospective. Several studies

611 have evaluated the effect of radiotherapy on the risk of developing CTP-

612 BADX/NS. However, most studies have not clearly distinguished between

613 prophylactic radiotherapy or therapeutic radiation of a corticotroph tumor prior

614 to BADX. Additionally, the absence of a control group in several studies and the

615 low number of patients receiving radiation limits interpretation.

616 Five of the studies (total n=149 patients with BADX of which 91 patients

617 received radiation) reported a potential beneficial effect of radiation in reducing

618 the cumulative incidence of CTP-BADX/NS (13, 21, 32, 38, 70). Conventional

619 radiotherapy was used in 4 studies (30-50 Gy, fractionated). Two of these studies

620 had control groups, showing a reduction in CTP-BADX/NS from 50% to 25% and

621 50% to 0 % in treated patients (32, 38). Radiosurgery was used in the most

622 recent analysis with a remarkably low cumulative incidence of CTP-BADX/NS

623 (5%) (70) after prophylactic gamma knife radiation.

624

625 In contrast to these publications, two studies (n=208 patients with BADX, of

626 which 45 patients received radiation) could not confirm a risk reduction for CTP-

627 BADX/NS by radiotherapy (15, 42). Another investigation found a high

628 cumulative incidence of CTP-BADX/NS despite low dose pituitary radiation in a

629 small group of patients (26). Together, the data are not sufficient for a general

630 recommendation of prophylactic radiation, and the question whether

631 radiotherapy can prevent CTP-BADX/NS remains unanswered. In particular, the

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

634

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

640

641

642 **Radiation therapy of CTP-BADX/NS**

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

651

652 *Conventional radiotherapy (CRT)*

653 CRT is based on an external photon source to radiate the targeted volume in 20-
654 30 sessions and was used mainly in earlier years for the treatment of CTP-
655 BADX/NS, although in total only 6 studies (1980-2019) with 58 patients have
656 reported on its outcome (19, 62, 69, 71-73). Moreover, most of the studies
657 focused on clinical and biochemical outcomes and lack data on radiological

658 outcomes and possible side effects of CRT. Comparison to more recent studies is
659 difficult, as often radiation of the whole sellar region was performed and
660 therefore radiotherapy-induced hypopituitarism was common. In addition,
661 earlier studies used different ACTH assays, and imaging with MRI was not
662 available. Howlett *et al.* studied 15 patients with CTP-BADX/NS treated with CRT
663 (72). In 7 of them, CT scans were available demonstrating an empty sella after
664 CRT in all (7/7, 100%). Kemink *et al.* reported tumor control in 5 of 6 patients
665 (83%) (62). ACTH normalization was reported in 50%-60% of patients (62, 71).
666 Two studies with 6 and 15 patients reported on new-onset hypopituitarism (5/6,
667 83%; and 2/15, 13%)(62, 72). As reported above, the largest study on the long-
668 term outcome was recently published by Fountas *et al.*, reporting retrospectively
669 on 22 patients treated from 1969-2018 in 13 UK pituitary centers by
670 “radiotherapy” (19 with CRT, 2 with gamma knife surgery, 1 with cyber-knife
671 surgery)(69). At 10-year follow up, 52% of these patients showed tumor
672 progression-free survival compared to 81% of patients treated by pituitary
673 surgery together with radiotherapy and 80% of subjects treated by surgery
674 alone. However, no further information on radiotherapy (target volume, used
675 dose) and imaging technique nor on side effects was given.

676

677 *Stereotactic radiosurgery*

678 Stereotactic radiosurgery (SRS) uses a very high dose of radiation (considered
679 lethal to cells) applied from different angles (3D) to a precisely defined target
680 volume. Its rationale is that by concentrating radiation on the biological target,
681 more normal surrounding tissue can be preserved. It is usually applied in a
682 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

708 months, and some even 85-144 months (77, 78), this indicates good long-term
709 tumor control rates. In parallel, ACTH stabilization or an ACTH decrease was
710 documented in 66 to 100% of the patients. The target volume was in the range of
711 1-2 ml. Post-radiation tumor volume shrinkage by 33% and 32% was
712 documented in two studies (77, 79). In patients who achieved ACTH
713 normalization, time from GKS to normalization was 115 and 162 months in two
714 studies (77, 78). A shorter interval between transsphenoidal surgery and GKS
715 was associated with a better endocrine remission (80).

716

717 *GKS: Side effects*

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

731

732 *Proton based SRS and SRS from LINAC*

733 Proton-based radiation has been suggested to have advantages over other forms
734 of radiation as an even more precise and normal tissue sparing radiation might
735 be possible. This so-called Bragg-peak effect allows protons to deposit almost all
736 their energy in the targeted volume. So far, just two studies from 2008 and 2014
737 reported on 11 patients treated with proton-based SRS (81, 82). Stabilization of
738 tumor growth was reported in both studies as 100%, ACTH normalization in
739 75% and 100%: 52% of patients developed new hypopituitarism (81).
740 Two studies including 14 patients reported outcome of LINAC radiosurgery (83,
741 84). Tumor control was achieved in 60% and 88% (83, 84) and new
742 hypopituitarism developed in 20% (83).

743

744 *Other forms of radiation*

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

750

751 *Conclusions*

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

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

764

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

770

771

772 **Outcome of medical treatment in CTP-BADX/NS**

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

777

778 *Medical therapy with a focus on plasma ACTH*

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

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

798

799 *Medical therapy focusing on tumor growth*

800 The alkylating chemotherapeutic agent temozolomide has been used with
801 limited efficacy. One patient with invasive CTP-BADX/NS received temozolomide
802 200 mg/m²/day orally for 5 days of a 28-day cycle, leading to tumor shrinkage,
803 improvement of headaches and lowering of ACTH levels after 4 cycles of
804 treatment (99). Another case report of a patient with an invasive corticotroph
805 tumor receiving temozolomide 150mg/m²/day for 5 days every 28 days for 9
806 cycles resulted in marked clinical, biochemical, and radiological improvement.
807 After stopping temozolomide tumor progression was observed after a 6-month
808 period of remission, (100). Furthermore, there was a single case of stable disease
809 (101) and a report of a lack of response in a patient despite absent MGMT
810 expression (52, 102) receiving temozolomide for CTP-BADX/NS.

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

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

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

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

840

841 **Declaration of interest**

842 M Reincke has served on the advisory boards of Novartis and has received
843 lecture fees and grants from Novartis, Ipsen, and Pfizer. I Bancos has served on
844 the advisory boards of HRA Pharma and Corcept, and consulted for ClinCor. T
845 Brue received consulting or speaker fees or grants from Novartis, Pfizer and
846 Ipsen. He served as a board member or research investigator for Strongbridge,
847 Pfizer, Ipsen and Recordati. O CHABRE received speaker fees from Novartis, has
848 been an investigator in a clinical study financed by Novartis and is part of a
849 board of HRA Pharma and Recordati. A Elenkova reports serving as the principal
850 investigator/sub-investigator of clinical trials for Corcept Therapeutics and
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854 Support from Novartis, GLWL Research Inc. and Corcept and served on advisory
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859 Cortendo AB; Co-investigator of Research Studies for Pfizer; received research
860 grants from Novartis, Pfizer, Ipsen, HRA Pharma, Shire, IBSA; has been an
861 occasional consultant for Novartis, Ipsen, Pfizer, Shire, HRA Pharma, Cortendo
862 AB, Ferring and Italfarmaco; and has received fees and honoraria for
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864 perceived as prejudicing the impartiality of this research reported. K Ritzel has

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

869

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878

879 **Author’s contribution**

880 Martin Reincke: literature search, study design, data collection, analysis and
881 interpretation (systematic review), writing*. Adriana Albani: literature search,
882 study design, data collection, analysis and interpretation (systematic review),
883 writing*. Guillaume Assie: data interpretation, writing. Irina Bancos: data
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893 Lacroix: data interpretation, writing. Edward R. Laws: data interpretation,
894 writing. Marco Losa: data interpretation, writing. Masanori Murakami: data
895 interpretation, writing. John D. Newell-Price: data interpretation, writing.
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898 Rainey: data interpretation, writing. Silviu Sbiera: data interpretation, writing.
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902 interpretation, writing. Sabina Zacharieva: data. interpretation, writing. German
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904 interpretation (systematic review), writing*. Katrin Ritzel: literature search,
905 study design, data collection, analysis and interpretation (systematic review),
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- 1266
- 1267

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

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Table 1:

Summary of studies reporting on cumulative incidence of CTP-BADX/NS.

*mean or range

1274

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)*

1275 *statistically significant (p < 0.05)

1276 § regression model

1277

1278 **Table 2:** Potential predictors of CTP-BADX/NS in studies directly comparing risk
 1279 factors in patients with CD who developed CTP-BADX/NS vs. patients who did
 1280 not after BADX.

1281

1282 **Separately attached**

1283

1284 **Table 3:**

1285 Summary of studies reporting on outcome of pituitary surgery in patients with
1286 CTP-BADX/ NS.

1287

1288 **Table 4:**

1289 Summary of studies reporting the outcomes of radiation therapy in patients
1290 with CTP-BADX/NS.

1291