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# Corticotroph tumor progression after bilateral adrenalectomy: data from ERCUSYN

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## Abstract

Corticotroph tumor progression after bilateral adrenalectomy/Nelson's syndrome (CTP-BADX/NS) is a severe complication of bilateral adrenalectomy (BADX). The aim of our study was to investigate the prevalence, presentation and outcome of CTP-BADX/NS in patients with Cushing's disease (CD) included in the European Registry on Cushing's Syndrome (ERCUSYN). We examined data on 1045 CD patients and identified 85 (8%) who underwent BADX. Of these, 73 (86%) had follow-up data available. The median duration of follow-up since BADX to the last visit/death was 7 years (IQR 2–9 years). Thirty-three patients (45%) experienced CTP-BADX/NS after 3 years (1.5–6) since BADX. Cumulative progression-free survival was 73% at 3 years, 66% at 5 years and 46% at 10 years. CTP-BADX/NS patients more frequently had a visible tumor at diagnosis of CD than patients without CTP-BADX/NS ( $P < 0.05$ ). Twenty-seven CTP-BADX/NS patients underwent surgery, 48% radiotherapy and 27% received medical therapy. The median time since diagnosis of CTP-BADX/NS to the last follow-up visit was 2 years (IQR, 1–5). Control of tumor progression was not achieved in 16 of 33 (48%) patients, of whom 8 (50%) died after a mean of 4 years. Maximum adenoma size at diagnosis of CD was associated with further tumor growth in CTP-BADX/NS despite treatment ( $P = 0.033$ ). Diagnosis of

## Key Words

- ▶ Cushing's disease
- ▶ Nelson's syndrome
- ▶ bilateral adrenalectomy
- ▶ corticotroph adenoma

CTP-BADX/NS, older age, greater UFC levels at diagnosis of CD and initial treatment predicted mortality. In conclusion, CTP-BADX/NS was reported in 45% of the ERCUSYN patients who underwent BADX, and control of tumor growth was reached in half of them. Future studies are needed to establish effective strategies for prevention and treatment.

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## Introduction

Transsphenoidal surgery (TSS), the treatment of choice for Cushing's disease (CD), is not always curative (Nieman *et al.* 2015). Persistent hypercortisolism due to incomplete removal of an adrenocorticotrophic hormone (ACTH)-producing adenoma has been reported in approximately 20% of patients (Valassi *et al.* 2010, Petersenn *et al.* 2015, Abu Dabrh *et al.* 2016). Prevalence of recurrence, which is roughly 2% per year and peaks in the first 5 postoperative years, may also occur decades after remission, the cumulative risk being almost 30% on long-term follow-up (Alexandraki *et al.* 2013, Roelfsema *et al.* 2018, Braun *et al.* 2020). Second-line treatments for persistent or recurrent hypercortisolism include re-operation, radiation therapy, pharmacological treatment and bilateral adrenalectomy (BADX). In contrast with the other options, BADX almost invariably leads to permanent correction of cortisol excess and, although it is associated with lifelong primary adrenal insufficiency, may be recommendable in patients with severe, symptomatic hypercortisolism who did not adequately respond to multimodal treatments (Oßwald *et al.* 2014).

BADX can be followed by subsequent progression or new occurrence of a corticotroph tumor, which has traditionally been defined as 'Nelson's syndrome' (NS) (Barnett *et al.* 1983, Kasperlik-Zaluska *et al.* 1983, Littley *et al.* 1990, McCance *et al.* 1993, Kemink *et al.* 1994, Misra *et al.* 1994, Jenkins *et al.* 1995, Sonino *et al.* 1996, Pereira *et al.* 1998, Nagesser *et al.* 2000, Kasperlik-Zaluska *et al.* 2006, Assié *et al.* 2007, Gil-Cardenas *et al.* 2007, Smith *et al.* 2009).

While tumor growth may occur as a consequence of lack of cortisol feedback after adrenalectomy, it may also reflect an intrinsic aggressiveness of some of these adenomas, which could have been present from the beginning (Fountas *et al.* 2020).

There is broad variability in the criteria used to diagnose this potential complication of BADX. Because tumor growth may be associated with ACTH rise and skin hyperpigmentation, these concomitant features have also been included, alone or in combination, to define NS in the past, making comparison between studies challenging (Fountas & Karavitaki 2020). A recent consensus

recognized the presence of an expanding adenoma on imaging as the most accurate diagnostic criterion of NS and, accordingly, proposed the definition of 'corticotroph tumor progression after bilateral adrenalectomy/Nelson's syndrome' (CTP-BADX/NS), also based on the original work by Assié *et al.* (Assié *et al.* 2007, Reincke *et al.* 2021). Studies on management and follow-up strategies are sparse and limited by suboptimal design and small sample size. A multicenter, retrospective study from the UK recently described management strategies and outcomes in 68 patients who received the diagnosis of CTP-BADX/NS over a mean follow-up of 13 years (Fountas *et al.* 2020). However, large studies on long-term outcomes of BADX, which characterize the subgroup of patients experiencing CTP-BADX/NS and identify potential clinical differences between them and their counterparts without corticotroph adenoma progression, are still lacking. Data on long-term survival in patients with CTP-BADX/NS are also scanty.

The aims of this study were to (i) assess the prevalence of CTP-BADX/NS in the large cohort of patients with CD included in the European Registry on Cushing's Syndrome (ERCUSYN) and (ii) investigate risk factors for adverse long-term outcomes including mortality of CTB-BADX/NS.

## Methods

At the time of the analysis, the ERCUSYN database comprised 1564 Cushing's syndrome (CS) patients entered between January 1, 2000, and January 31, 2017, from 57 centers in 26 European countries. For this study, we analyzed data of the 1045 patients with pituitary-dependent CS (PIT-CS) to identify those who had undergone BADX. Eighty-five patients received BADX. Information on the general characteristics of these patients, locally measured hormone levels at diagnosis and treatment received were obtained from the 'Diagnosis', 'Therapy' and 'Follow-up visits' sections in the register, as previously described (Valassi *et al.* 2011). Centers where BADX patients had been followed were also asked to provide additional information through the completion of a survey containing specific questions for each patient. In particular, participants were required to describe

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hormone levels and maximum adenoma size at the time of BADX, and whether hypopituitarism was present. Centers were also asked to indicate whether and when CTP-BADX/NS occurred after BADX. In cases of CTP-BADX/NS, participants were asked to report ACTH levels and maximum tumor size at diagnosis as well as whether hyperpigmentation, hypopituitarism and cranial nerve palsy were found. They were also required to describe the treatments performed (medical or radiation therapy), and whether control of progression was achieved; information on length of follow-up and survival at the last follow-up visit was also collected.

Following the recommendations of a recent consensus, CTP-BADX/NS was defined as the evidence of (i) a new-onset corticotroph adenoma or (ii) an increase in size by at least 1 mm of a preexisting corticotroph adenoma, either detected on pituitary MRI at post-BADX follow-up evaluations (25).

### Statistical methods

Statistical analyses were performed using IBM® SPSS® Statistics, version 26. Categorical variables are presented as number and percentages. Normally distributed continuous variables are presented as mean  $\pm$  S.D. and non-normally distributed as median (range). For comparison between two groups, we used unpaired *t*-test or Mann–Whitney *U* test as appropriate. For proportions, Pearson’s chi-square or Fisher’s exact test was used. Kaplan–Meier plot was used to illustrate tumor progression-free and progression-survival curves. The mean cumulative progression-free and progression-survival rate at 3, 5 and 10 years was based on Kaplan–Meier estimates. The influence of several factors on tumor progression (age at diagnosis, gender, baseline hormone levels, modes of treatment of CD before BADX, hypopituitarism, tumor characteristics at baseline and time elapsed since diagnosis of CD and BADX) and mortality (age at diagnosis and at progression, gender, tumor characteristics at diagnosis and progression, hormone levels and relative delta between ACTH at progression and baseline ( $\Delta\%$ ), hypopituitarism, nerve palsies and hyperpigmentation at progression, modes of treatment of CTP-BADX/NS) was assessed using Cox-regression analysis and calculation of Hazard ratio (HR) with 95% CIs or log-rank test.

Stepwise logistic regression was used to identify clinical variables (age, modes of treatment, maximum adenoma size, macroadenoma/microadenoma, hypopituitarism) that may predict control of tumor growth after treatment of CTP-BADX/NS.

We used the chart ‘log-log(Sf) vs log (time)’ to verify that the effects of the variables evaluated were constant over time.

Two-sided *P* values  $\leq$  0.05 were considered evidence of statistical significance.

## Results

### Baseline characteristics and treatment modalities at diagnosis of CD in patients who subsequently underwent BADX (*n* = 73)

Eighty-five of 1045 (8%) PIT-CS patients included in ERCUSYN underwent BADX, and 73 of them (86%) had follow-up data available. The participating centers with the highest rates of BADX were from Athens (9.1%), Oldenburg (8.9%), Marseilles (8.7%) and Zagreb (7.1%). The median duration of follow-up since diagnosis of CD until the last follow-up visit or date of death was 10 years (IQR 8–13). Information on the indications to perform BADX was available in 56 (77%) patients. Thirty-two (57%) of them underwent BADX due to intolerance/resistance to medical treatment, 19 (34%) due to severe disease and 5 (9%) due to desire for pregnancy.

Patients were classified based on subsequent occurrence of CTP-BADX/NS. Baseline characteristics of both groups are shown in [Table 1](#).

CTP-BADX/NS was reported in 33 (45%) patients, whereas 40 (55%) had no CTP-BADX/NS.

At diagnosis of CD, patients who subsequently developed CTP-BADX/NS more frequently had a visible pituitary adenoma as compared with noCTP-BADX/NS patients (20 (61%) vs 12 (29%); *P*=0.017). Hormone levels before BADX were available in 55 patients (30 CTP-BADX/NS and 25 noCTP-BADX/NS). Concentrations of ACTH, serum cortisol and urinary free cortisol (UFC) were not different between the two groups, but normal ranges were not provided in most of the cases.

Overall, one TSS was performed in 54 (74%) patients, of whom 32 (59%) subsequently developed CTP-BADX/NS and 22 (41%) who did not experience CTP-BADX/NS (*P*<0.01) ([Table 1](#)). A second TSS was performed in 15 patients who subsequently developed CTP-BADX/NS (45%) and in 7 (18%) noCTP-BADX/NS patients (*P*<0.01). A third TSS was performed in three CTP patients and one noCTP-BADX/NS (*P*=0.31). A fourth TSS was only performed in two patients who subsequently developed CTP-BADX/NS patients.

Radiotherapy was performed in 16 of 73 (22%) patients, all of whom had undergone at least 1 TSS

**Table 1** Baseline characteristics at diagnosis of CD and length of follow-up in patients with bilateral adrenalectomy and corticotroph tumor progression (CTP-BADX/NS) and patients without corticotroph tumor progression (noCTP-BADX/NS).

Variable	CTP-BADX/NS (n = 33)	noCTP-BADX/NS (n = 40)	P value
Gender (F/M)	25/8	32/8	0.77
Age	38.6 ± 15.7	41 ± 15	0.53
Visualization of an adenoma on MRI (%)	20 (61)	12 (30)	<b>0.017</b>
Macroadenoma/microadenoma *	11/9	4/8	0.29
Maximum tumor size*	11.9 ± 6.8	8 ± 4.6	0.067
Pituitary surgery (at least one TSS) (%) (n = 54)	32 (59)	22 (41)	<b>&lt;0.01</b>
Ki67**	4.6 ± 2.5	3.7 ± 1.9	0.64
Negative p53**	4 (67%)	7 (100%)	0.26
Radiotherapy (n = 16)	12 (75)	4 (25)	<b>&lt;0.01</b>
Hypopituitarism***	11 (33)	8 (30)	0.78
Timeframe since diagnosis of CD to last visit (years)	10 (7–12)	10 (8–12)	0.61
Timeframe since diagnosis of CD to BADX (years)	4 ± 3	3 ± 5	0.54

Data are expressed as (mean (±s.d.)), except 'Timeframe since diagnosis of CD to last visit' which is expressed as median (IQR).

\*Information on adenoma size was available in 32 patients; \*\*Information on Ki67 was available in 22 patients (13 CTP-BADX/NS and 9 noCTP-BADX/NS); information on p53 was available in 13 patients (6 CTP-BADX/NS and 7 noCTP-BADX/NS); \*\*\*Information on the prevalence of hypopituitarism was available in 60 patients. Hypopituitarism may be a consequence of previous treatment.

Bold indicates statistical significance,  $P < 0.05$ .

CD, Cushing's disease; CTP, corticotroph tumor progression; NCTP, without corticotroph tumor progression; TSS, transsphenoidal surgery; BADX, bilateral adrenalectomy.

previously. Twelve patients of 16 (75%) were in the CTP-BADX/NS and 4 (25%) were in the noCTP-BADX/NS group ( $P < 0.01$ ) (Table 1). Fractionated radiotherapy (FRT) was performed in 6 of 12 (50%) CTP-BADX/NS (mean dose (±s.d.) 51 ± 1.6 Gy) and 3 of 4 (75%) noCTP-BADX/NS (mean dose, 51.6 ± 2 Gy). Radiosurgery was performed in 5 (42%) CTP-BADX/NS at the mean dose of 23.9 ± 7.2 Gy, and in 1 noCTP-BADX/NS patient at the dose of 30 Gy.

Nineteen (26%) patients did not undergo TSS, of whom 5 (26%) received medical therapy. Patients who did not undergo TSS were older than those who underwent TSS (48 ± 5 vs 38 ± 16 years;  $P = 0.004$ ) and less frequently had a visible tumor on baseline MRI (2/19 (11%) vs 30/54 (56%);  $P = 0.01$ ). CTP-BADX/NS was more frequent in patients who underwent at least one TSS as compared with those who did not undergo any pituitary surgery (32/54 (59%) vs 1/19 (5%);  $P < 0.001$ ).

### Progression-free survival and predictors of mortality in patients undergoing BADX

Cumulative progression-free survival was 73% at 3 years, 66% at 5 years and 46% at 10 years. Median progression-free survival was 10 years (95% CI, 4.8–15.2) (Fig. 1). No predictors of progression could be identified based on our data.

Median time elapsed since BADX to last visit or date of death was 7 years (IQR, 2–9).

The estimated cumulative survival rate was 95% at 3 years, 93% at 5 years and 79% at 10 years (Fig. 2A). Eight of 33 (24%) CTP-BADX/NS and 1 of 40 (3%) noCTP-BADX/NS

patients were deceased at the end of follow-up ( $P = 0.003$ ). The diagnosis of CTP-BADX/NS and having received combined treatment with both surgery and radiotherapy as initial treatment of CD predicted mortality (Log-rank,  $P = 0.019$  and  $P = 0.009$ , respectively) (Fig. 2B and C). Older age at diagnosis of CD (HR, 1.096 (95% CI 1.029–1.166,  $P = 0.004$ )), higher UFC concentrations at diagnosis of CD (HR, 1.002 (95% CI 1–1.005,  $P = 0.049$ )) and older age at diagnosis of CTP-BADX/NS (HR, 1.154 (95% CI 1.016–1.311,  $P = 0.027$ )) also predicted mortality in our patients.

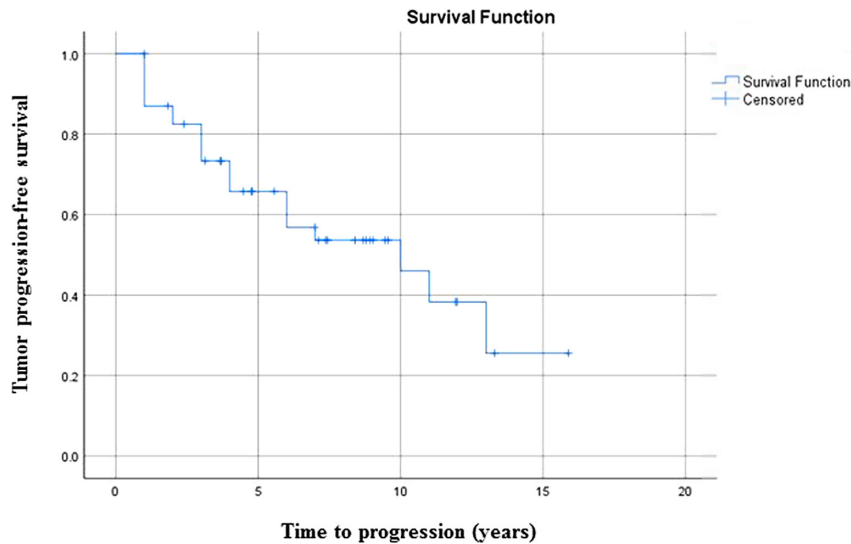
Cause of death was known in two CTP-BADX/NS patients; one patient died due to the occurrence of an epileptic status related to a growing meningioma, while another developed complete blindness, spinal stenosis and terminal intracranial hypertension related to corticotroph tumor growth. One patient who did not develop CTP-BADX/NS died due to an unknown reason.

### Patient's characteristics at diagnosis of corticotroph tumor progression (CTP-BADX/NS) (n = 33)

CTP-BADX/NS was documented in 33 patients, 6 years (IQR, 4–8) after the diagnosis of CD and 3 years (1.5/6 years) after BADX.

Individual characteristics of patients at progression are shown in Supplementary Table 1 (see section on supplementary materials given at the end of this article). Hyperpigmentation was reported in 20 of 24 (83%) patients with data available. The mean relative ACTH delta was 3984 ± 9958% at progression. No difference in





**Figure 1**

Cumulative progression-free survival was 73% at 3 years, 66% at 5 years and 46% at 10 years. Median progression-free survival was 10 years (95% CI, 4.8–15.2).

Number at risk

45                      22                      6                      0

the relative ACTH delta was found between patients with hyperpigmentation as compared with those without.

In patients without a visible adenoma at diagnosis of CD, maximum adenoma size at progression was not different as compared with that in patients with a visible adenoma at diagnosis of CD ( $17.7 \pm 12.5$  vs  $18.5 \pm 11$  mm,  $P=0.94$ ).

Four CTP-BADX/NS patients of 28 (14%) with data available had oculomotor nerve palsy, 3 (11%) abducens nerve palsy and 7 (25%) opticus nerve palsy.

Ten CTP-BADX/NS patients of 28 (36%) with data available had central hypothyroidism, 11 (39%) had central hypogonadism, 6 (21%) had growth hormone deficiency (GHD) and 2 (7%) had diabetes insipidus.

### Treatment of CTP-BADX/NS patients

TSS was performed in 9 (27%) CTP-BADX/NS patients; 1 of them underwent 3 TSS. Sixteen (48%) patients received radiotherapy, 10 of whom as a primary treatment and 6 as a secondary treatment after surgery. Information on mode of radiotherapy was available in 14 patients; 8 (57%) patients received FRT (mean dose,  $49.8 \pm 2.6$  Gy) and 6 (43%) stereotactic radiosurgery (mean dose,  $20.6 \pm 2.9$  Gy). Nine patients (27%) received pharmacological treatment, of whom three (33%) temozolomide alone, and three (33%) temozolomide combined with cabergoline, pasireotide or bevacizumab. Two patients received pasireotide alone and another patient was treated with an unspecified agent. Four patients received medical therapy alone, two patients

received medical therapy after radiotherapy, one patient after surgery and another combined with surgery and radiotherapy (Supplementary Table 1).

### Control of tumor progression in CTP-BADX/NS patients

The median time elapsed since diagnosis of CTP-BADX/NS to the last follow-up visit or date of death was 2 years (IQR 1–5).

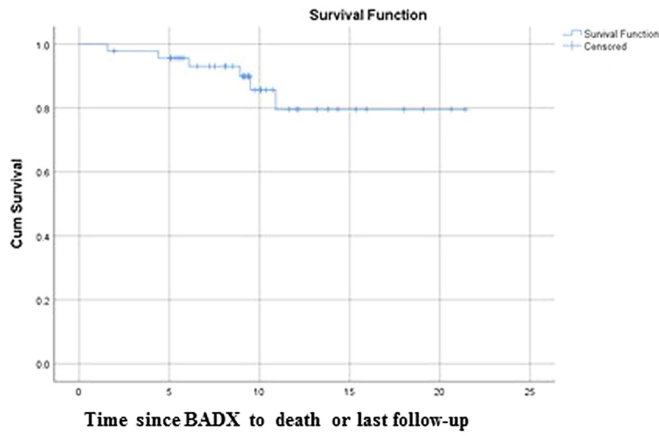
At the last follow-up visit, control of tumor progression was achieved in 17 of 33 (51%) CTP-BADX/NS patients (Supplementary Table 1). Of these patients, 6 (35%) had received radiotherapy alone, and 4 (24%) had received radiotherapy and surgery. Two patients had undergone surgery alone and two had received medical therapy (one alone and one in combination with radiotherapy). An expectant management was elected in three patients.

CTP-BADX/NS patients who experienced further tumor growth despite treatment had a larger pituitary adenoma at diagnosis of CD ( $15 \pm 5$  vs  $8 \pm 4$  mm;  $P=0.012$ ) and more frequently developed hypopituitarism after initial treatment (55 vs 16%;  $P=0.027$ ), as compared with patients in whom further tumor growth did not occur.

Maximum adenoma size at diagnosis of CD was associated with further tumor growth despite treatment (HR=1.30 (95%CI 1.02–1.66),  $P=0.033$ ).

Eight CTP-BADX/NS (50%) patients with uncontrolled tumor growth died  $4 \pm 3$  years after the diagnosis of progression. Of six patients with data

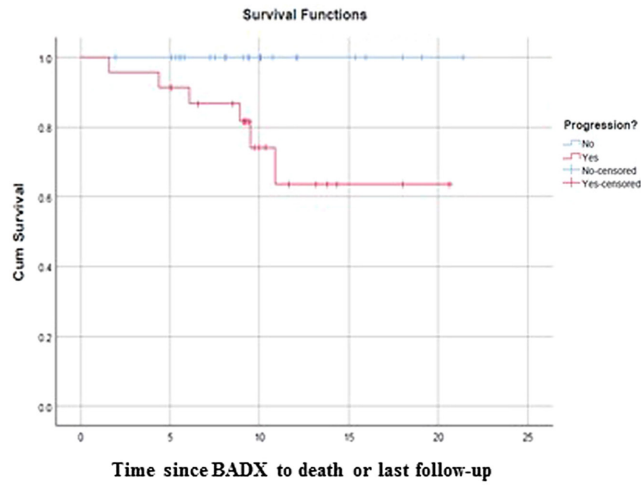
A



Number at risk

45      42      17      6      1

B

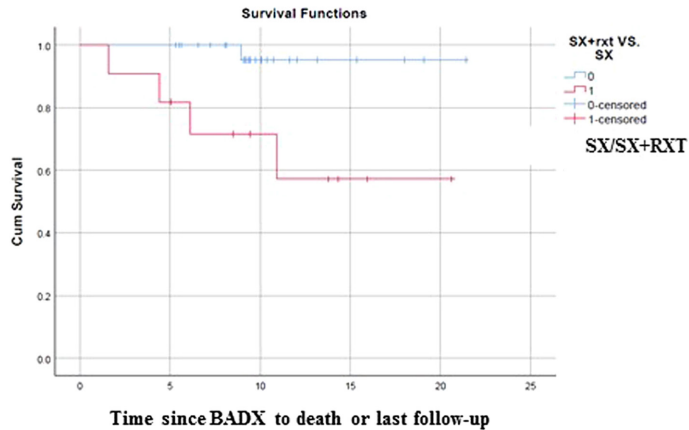


Number at risk

No  
Yes

22	21	9	4	1
20	20	9	1	0

C



Number at risk

Sx  
Sx+Rxt

27	27	10	4	1
10	8	4	1	0

**Figure 2**

(A) Estimated cumulative survival rate was 95% at 3 years, 93% at 5 years and 79% at 10 years; (B) Mortality rate was greater in CTP-BADX/NS as compared with noCTP-BADX/NS patients (Log-rank  $P = 0.019$ ); (C) Mortality was greater in patients who received surgery (SX)+ radiotherapy (RXT) at the diagnosis of CD as compared with those who only received SX (Log-rank  $P = 0.009$ ).

available, five had received medical therapy, of whom two had medical therapy alone (temozolomide), one combined with radiotherapy, one combined with surgery and another combined with both radiotherapy and surgery. Another patient received radiotherapy alone. Death occurred  $18 \pm 16$  months after the start of medical therapy,  $75 \pm 47$  months after the start of radiotherapy and  $53 \pm 6$  after surgery.

## Discussion

We examined the prevalence, risk factors and outcome of CTP-BADX/NS in a large cohort of patients with CD included in the ERCUSYN database. The main findings of our study are two-fold: First, these ERCUSYN data show that CTP-BADX/NS, defined as evidence of progression or new detection of a pituitary tumor, occurs in 45% of CD patients who underwent BADX, after a median of 3 years since the intervention. Based on this definition, a similar prevalence of 43% was recently reported in a systematic review of the literature, which was spanning a time period of 60 years (Reincke *et al.* 2021). The patients of the ERCUSYN database, however, reflect treatment modalities of the last two decades. This implies that despite recent advances in treatment of pituitary diseases, CTP-BADX/NS remains a serious and frequent complication. Second, our data also demonstrate that once CTP-BADX/NS has occurred, the long-term outcome is considerably worse compared to noCTP-BADX/NS patients.

Fountas *et al.* recently published a retrospective cohort study including 68 patients who already received the diagnosis of CTP-BADX/NS, aimed at investigating potential risk factors of further tumor progression despite treatment (Fountas *et al.* 2020). In our study, we evaluated 73 patients who underwent BADX in order to establish the incidence of CTP-BADX/NS and identify predictors of both tumor progression and mortality. Our analysis was mainly based on the direct comparison between the patients who developed CTP-BADX/NS and those who did not have this complication during the follow-up period.

In our study, tumor progression occurred after a median of 10 years in half of the patients, with a progression-free survival of 73% at 3 years and 46% at 10 years.

To compare the estimates of tumor progression-free survival between published studies is difficult, due to differences in both the criteria used to define progression itself and in the frequency of monitoring. Sonino *et al.* showed an NS-free survival of 87% after 2 years and 71% after 10 years, based on a 'traditional' diagnostic paradigm

including clinical, biochemical and imaging parameters (Sonino *et al.* 1996). In another report on 53 patients from a single center where a strict imaging monitoring protocol was used, 39% of patients presented with tumor progression 3 years after BADX with a subsequent plateau at 47% after 7 years (Assié *et al.* 2007). Indeed, CTP-BADX/NS has been diagnosed, in the most recent series including our study, after a median of 2.5–3 years, the median growth rate being of 3 mm/year (Assié *et al.* 2007, Gil-Cardenas *et al.* 2007, Graffeo *et al.* 2017).

Overall, these data indicate that, although CTP-BADX/NS is more likely to occur early after BADX, a lifelong surveillance is warranted. Accordingly, the recent consensus on diagnosis and treatment of CTP-BADX/NS recommended post-surgical monitoring by MRI imaging 3 months after the intervention and subsequently every 12 months during the first 3 years (Reincke *et al.* 2021).

Several factors have been proposed as potential predictors of CTP-BADX/NS, including pre-BADX hormone levels or residual pituitary tumor, young age at the time of BADX and short duration of CD (Kemink *et al.* 1994, Sonino *et al.* 1996, Nagesser *et al.* 2000, Assié *et al.* 2007). We showed that CTP-BADX/NS patients more frequently had a visible tumor at diagnosis of CD as compared with patients who did not develop CTP-BADX/NS, but we could not relate any pre- or postoperative factors to a higher risk of tumor progression on survival analysis, likely due to the relatively small sample size.

Although TSS should be the first-line treatment, various modes of treatment have been applied to CTP-BADX/NS, consistent with the multiplicity of factors potentially influencing the therapeutic decision, including patient's conditions, tumor size and invasiveness, and availability of different options in each center (Reincke *et al.* 2021).

In our series, radiotherapy was the preferred treatment in most of the patients, being received by 51% of patients, regardless of the size of the tumor, whereas surgery (alone or in combination with other treatments) was performed in 35% of patients who reached control of tumor progression and 18% of those who had further tumor growth. While it may be that surgery was not feasible in some of the patients due to severe clinical conditions and/or tumor invasiveness, there could be space to more frequently consider neurosurgical approach in future cases, also in view of the growing technical advances in the field of pituitary surgery. Of note, no patients received prophylactic radiation therapy in an attempt to prevent tumor progression. Indeed, the real effectiveness of this strategy is still to be determined and evidence supporting its use is currently scarce (Reincke *et al.* 2021).



Interestingly, we have found that CTP-BADX/NS patients who experienced further tumor growth despite treatment had larger pituitary adenomas at diagnosis of CD and more frequently experienced hypopituitarism after initial TSS, suggesting that CTP-BADX/NS, which does not respond to therapy, may be due to a subtype of more aggressive and rapidly growing corticotroph tumors (Sonino *et al.* 1996, Nagesser *et al.* 2000, Fountas & Karavitaki 2020). Accordingly, Fountas *et al.* reported that patients who had received the most complex treatment schedule for their CD (i.e. surgery combined with radiotherapy and subsequent adrenalectomy), prior to the diagnosis of CTP-BADX/NS, had a greater risk of developing further growth despite specific therapy (Fountas *et al.* 2020).

As a matter of fact, we and others have shown that CTP-BADX/NS was more likely to occur in those patients who had larger or visible adenoma on MRI at diagnosis of CD which, again, may reflect a more aggressive behavior of the corticotroph tumor since the beginning (Sonino *et al.* 1996, Fountas & Karavitaki 2020). However, we did not find any differences in the pathology markers (Ki-67 and p53) of the corticotropinomas or in the proportion of worsening symptoms and/or tumor growth prior to BADX between the patients who experienced CTP-BADX/NS as compared with those who did not, although the small number of patients in whom these data were available may have contributed to this lack of significance. *In vitro* studies are warranted to investigate the histopathology and molecular characteristics of the subgroup of CTP-BADX/NS tumors and identify potential mechanisms promoting their progression (Salehi *et al.* 2010, Grossman 2017).

Although BADX has been advocated as a last resort treatment after the failure of any other therapeutic options, it may be recommendable earlier in case of severe, life-threatening hypercortisolism or pregnancy desire in a female CD patient. However, treatment of CD should be established on an individual basis by a multidisciplinary team of experts in pituitary diseases after a thorough evaluation of the benefits and risk of all the options available (Fleseriu *et al.* 2021) after a thorough evaluation of the benefits and risk of each option by a multidisciplinary team.

In our series, 12% of patients who underwent BADX died after a median follow-up of 7 years, with a cumulative survival of 79% at 10 years. In a recent systematic review of data from 505 CD patients who underwent BADX, the mortality rate was 9% at a median follow-up of 4 years, with 43% of the deaths occurring within 12 months of surgery (Ritzel *et al.* 2013). Although we could not describe

the cause of death in most of our patients, those who developed CTP-BADX/NS more frequently deceased as compared with those without tumor progression after BADX, indicating that this complication is a prominent contributor to post-BADX mortality likely due to direct effects of an expanding tumor and its potential association with a more severe clinical picture since the initial diagnosis of CD. Indeed, we have observed that higher UFC levels at diagnosis of CD and having received surgery combined with radiotherapy (instead of surgery alone) as initial treatment were additional predictors of mortality in our series, consistent with other reports describing long-term outcomes after TSS (Lambert *et al.* 2013, Ritzel *et al.* 2013). It could be hypothesized that the number of treatments received to control hypercortisolism reflects the presence of an aggressive adenoma requiring multiple therapies (including BADX), which may have led to an increased risk of death in those who experienced CTP-BADX/NS. As a matter of fact, baseline UFC was also a predictor of mortality in our patients and the death rate was significantly greater in the ERCUSYN patients who received multimodal treatments including BADX as compared with those who received multimodal treatments without BADX (data not shown), again suggesting that the former might have had a more severe disease which required multiple treatments and influenced survival.

Interestingly, Clayton *et al.* demonstrated a clear association between a reduction in survival and increased number of treatments administered to reach remission of CD. In particular, the patients who had received surgery, radiotherapy and BADX had the highest mortality as compared with those who underwent only surgery alone or combined to radiotherapy, suggesting that multimodal treatment is indicative of the difficulty in controlling cortisol excess and may also reflect the severity of the disease (Clayton *et al.* 2016). We cannot exclude that previous RXT may have had a role in increasing the aggressiveness of the tumor although our data cannot address this point. One patient in our series who had received multimodal treatment died due to the occurrence of an epileptic status related to a growing meningioma. Whether RXT may have contributed to the meningioma occurrence and/or its growth is not known. Of note, Hamblin *et al.* recently showed that the risk of a second tumor after RXT is increased although lower than previously described with a cumulative probability of a second brain tumour of 4% for the irradiated patients and 2.1% for the controls at 20 years (Hamblin *et al.* 2022).

It should be emphasized that data on glucocorticoid replacement after BADX are lacking in our population,

which prevented us from evaluating the potential impact of suboptimal treatment of post-BADX adrenal deficiency (Ragnarsson *et al.* 2019).

ACTH elevation and skin hyperpigmentation were documented in the vast majority of our patients with CTP-BADX/NS, confirming that these features should be considered important clinical markers which may raise the suspect of corticotroph tumor progression (Reincke *et al.* 2021).

Our study has several limitations, including the data quality associated with the retrospective design and heterogeneity of the diagnostic and therapeutic approaches due to the multicentric study design. Also, normal ranges for hormone values measured in each center were not available, preventing us from performing some comparisons between the groups and establishing thresholds potentially related to tumor progression. Moreover, this study was not designed to monitor changes in ACTH concentrations after BADX and, therefore, we could not establish if ACTH variation over time may be an early marker of tumor progression. In addition, ACTH sampling may have been performed at different time points (before or after glucocorticoid replacement) at the participating centers, which could have influenced the results.

In conclusion, our study showed that almost half of the ERCUSYN patients with CD undergoing BADX have developed CTP-BADX/NS after a median of three years, especially those with a visible tumor at diagnosis. The mortality rate was elevated in CTP-BADX/NS and related to initial hormone status and therapeutic choices. These data indicate that CTP-BADX/NS is a frequent and serious complication after BADX for which close monitoring and early intervention are warranted to identify as early as possible this potentially lethal condition.

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#### Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/ERC-22-0074>.

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#### Declaration of interest

The 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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