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Therapeutic options after surgical failure in Cushing's disease: A critical review

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Cushing's disease (CD) is the most common etiology of Cushing's syndrome (CD) due to corticotroph pituitary adenoma, which are in most cases small (80–90% microadenomas) and in about 40% cannot be visualized on imaging of the sella. First-line treatment for CD is transsphenoidal surgery (TSS) with the aim of complete adenoma removal and preservation of pituitary gland function. As complete adenoma resection is not always possible, surgical failure is a common problem. This can be the case either due to persistent hypercortisolism after first TSS or recurrence of hypercortisolism after initially achieving remission. For these scenarios exist several therapeutic options with their inherent characteristics, which will be covered by this review.

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Introduction

Cushing's syndrome (CS) is a condition caused by excessive levels of glucocorticoids leading to a characteristic phenotype, increased morbidity and mortality. With a percentage of 70–80% Cushing's disease (CD) is the most common etiology of CS due to corticotroph pituitary adenomas producing excessively adrenocorticotropic hormone (ACTH) [1]. About 80–90% of these adenomas are microadenomas (<1 cm) [2], which cannot be visualized in around 40% on magnetic resonance imaging (MRI) of the sella region [3]. First-line therapy for CD is transsphenoidal surgery (TSS) with selective resection of the adenoma (adenomectomy) with the aim of complete adenoma removal and preservation of normal pituitary gland function [4]. In some cases complete resection of the causative adenoma is not possible. This is the case when the adenoma is invasive into the sinus cavernosus and dura, has a large extrasellar expansion or when it simply cannot be identified intraoperatively despite careful exploration of the pituitary gland. Therefore, surgical failure is a relatively common problem: either due to persistent hypercortisolism after first TSS or due to recurrence of CD after initially achieving remission. Recurrent CD can be often diagnosed biochemically before clinical symptoms re-develop. Treatment should be initiated in hypercortisolemic patients before full-blown re-appearance of the Cushing phenotype. There exist several therapeutic options for recurrent CD which will be covered in this review. Since pharmacological treatment has evolved as an important bridging and long term treatment option, we will provide at the end of the manuscript a flowchart from our tertiary referral center representing the personal view and practice of the authors.

Prevalence of surgical failure for CD after first TSS

Rates for initial remission and recurrence after first TSS were reported with a great variability. The same accounts for the criteria defining remission and recurrence [5]. According to a meta-analysis from 2016 with a large heterogeneity in compared studies, Abu Darbh et al. reported, that after first TSS initial remission can be achieved in 76% of cases [6]. This number is very close to another large meta-analysis by Petersenn et al. reporting a remission rate of 78% [5]. Microadenomas and positive ACTH-staining in immunohistochemistry on tumor tissue were significant positive predictors of achieving remission whereas macroadenoma or negative ACTH-staining predicted unfavorable outcome [6]. Honegger et al. reported in a systematic literature search a positive (but not significant) correlation between remission rates and the center's annual number of TSS procedures. Also, the range of remission rates in high volume centers was more narrow compared to low volume centers, an indirect indication for better outcome rates by more experienced neurosurgeon [7]. In contrast to microadenomas, both macroadenomas and non-detectable adenomas are associated with a lower remission rate. Regarding the technique of TSS, a meta-analysis of 2018 found no differences between microscopic and endoscopic TSS for the remission and recurrence rates of microadenomas. Macroadenomas treated with endoscopic TSS had an better outcome compared to microscopic TSS [8]. Low early morning cortisol (<50 nmol/L, 2 μg/dl) after first TSS is a hallmark of remission, although recurrence of CD can still be observed in patients with undetectable cortisol levels after TSS [9]. Morning baseline cortisol levels between 50 and 140 nmol/L (2–5 μg/dl) are in favor of remission, whereas cortisol levels above 140 nmol/L indicate persistent disease and further testing is required. Although recurrence rates have been reported to range from 8% to 66% [10], the meta-analysis of Abu Darbh et al. and Petersenn et al. showed a quite low recurrence rate of 10% [6] and 12% [5] 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 after TSS, but it can occur as late as several decades after surgery [11]. The duration of tertiary adrenal insufficiency, developing invariably after successful treatment for CD, is positively correlated with a lower risk for recurrence [12]. Salivary late night cortisol levels appear to be more sensitive in identifying early-on biochemical evidence of recurrence than dexamethasone suppression test and urinary free cortisol [13]. The same might account for the desmopressin test, which together with basal serum cortisol also might predict better long-term remission in CD after first TSS [14].

Before decision on secondary treatments is made, a repeat high-resolution MRI scan of the pituitary should be used to visualize a recurrent adenoma. In addition essential documents to be reviewed include the neurosurgical (intraoperative findings/localization/invasion of adenoma?) and the

histopathology report (ACTH staining in immunohistochemistry? complete resection? Crooke cells?) from first TSS. We recommend that any therapeutic decisions should be based on the review of clinical, biochemical and imaging data by a multidisciplinary endocrine tumor board.

Second transsphenoidal surgery (TSS)

Second TSS poses an effective treatment option for persistent or recurrent CD possibly achieving long term remission, although outcome/remission rates are lower for both persistent and recurrent CD compared to first TSS and the risk for new hypopituitarism is higher (due to a more radical surgery in these situations, e.g. hypophysectomy). In most studies —original and reviews - outcome for repeat TSS is reported together for both persistent and recurrent CD. Such practice can be disputed because the two scenarios represent different situations with inherent complexities and therefore need to be reviewed separately. Table 1 shows the results of individual studies reporting on second/repeat TSS for each of these two scenarios: mean remission rate was 54% in persistent CD, and 64% in recurrent CD. The lower remission rates of TSS in recurrent CD versus first TSS can be explained by the presence of invasive adenomas. Many neurosurgeons favor in the setting of persistent CD an early repeated TSS (after weeks-2 months), as less scar tissue has developed and the surgeon is more aware of anatomical details of the given patient or when pathological studies confirm an ACTH-expressing adenoma, but no complete resection of it [15]. The outcome data have to be interpreted with caution, as these studies are mainly retrospective and come from different geographical regions with different experiences among the neurosurgeons. In addition, the indication for repeat TSS and the extent of the surgery were not always stated. Commonly, neurosurgeons performed in a repeat TSS a more extensive operation aiming at total or hemi-hypophysectomy in instances when after an exploratory approach no selective adenomectomy is possible. As remission rates after hypophysectomy are not higher than those of selective adenomectomy, but morbidity is increased through higher rates of (pan-)hypopituitarism [12,16,17], we recommend against this strategy and recommend termination of surgery at this point. Similar to first TSS a detectable adenoma on preoperative MRI or the intraoperatively finding of an adenoma are associated with higher remission rates. As the recurrent adenoma is usually localized in the area of the initial adenoma [18,19], second TSS should be performed by the same experienced neurosurgeon.

Radiation

Radiation therapy is an effective treatment option for CD in order to achieve biochemical remission. In general two different types of radiation can be distinguished: conventional (stereotactic/fractionized) radiotherapy (RT) and (unfractionated) stereotactic radiosurgery (SRS). RT uses ionizing x-rays, which are nowadays administered stereotactically, but fractionized over 20–30 sessions. SRS applies a very high energy on a precisely targeted volume in one session. SRS uses different sources of radiation: Gamma-rays from a Cobalt source (GammaKnife) or a linear accelerators (LINAC, Cyberknife) or radiation with heavy particles like protons. Using conventional RT a review reported biochemical remission rates in 68% (range 46–89%) with a mean time to remission of 15–24 months (with very different definitions of remission) [20]. 38% developed new hypopituitarism. Remission rates for SRS with Gammaknife were 66% (mean time to remission 17 months), with protons 66% (mean time to remission 22 months), and with LINAC 46% (mean time to remission 24 months) [20]. Remission rates of RT are therefore comparable to that of SRS, which is also true for the risk of new hypopituitarism. SRS using Cyberknife was used in seven patients with persistent or recurrent CD with sinus cavernosus invasion, reporting a remission rate 57% and no recurrence after a median follow-up of 4 years and 7 months (55 months) [21].

Recently, in 2017 and 2018 the group around Jason Sheehan from the International Gamma Knife Research Foundation published their results from a large, international and multicenter retrospective analysis for patients with CD treated with Gamma Knife. In this analysis they reported also on results for upfront Gamma knife SRS (GKRS) as first-line therapy, repeated GKRS for patients who failed after first GKRS and whole-sella GKRS vs. adenoma-targeted GKRS. In 278 patients with CD treated with GKRS (indications: 23 (8%) primary treatment, 221 (79%) residual tumor, 34 (12%) recurrent tumor) initial biochemical remission was achieved in 80% at 10 years after GKRS. A limitation of this study is

Table 1
Studies reporting on outcome of second TSS for persistent or recurrent CD. N.a., not available; UFC, urinary free cortisol; DI, diabetes insipidus.

First author	Year	Center	N	Indication of TSS	Definition of Persistence	Remission	Recurrence	New Hypopituitarism
Ram [48]	1994	Single-center (Bethesa, NIH)	17	Persistence	N.a.	12/17 71%)	3/12 (25%)	New Hypopituitarism: 41%
Knappe [49]	1996	Single-center (Hamburg)	16	Persistence	N.a.	9/16 (56%)	N.a.	N.a.
Locatteli [50]	2005	Single-center (Charlottesville)	12	Persistence	Cortisol >2 μg/dl	8/12 (67%)	N.a.	New Hypopituitarism: 11/11 (100%) Panhypopituitarism: 8/11 (73%) (Total hypophysectomy, 10/12, subtotal hypophysectomy 2/12)
Hofmann [51]	2008	Single-center (Erlangen)	15	Persistence	N.a.	3/15 (20%)	N.a.	N.a.
Wagenmakers [52]	2009	Single-center (Nijmegen)	6	Persistence	Cortisol >2 μg/dl	3/6 (50%)	0%	Both persistent and recurrent: New Hypopituitarism: 9/14 (64%)
Honegger [53]	2012	Single-surgeon (Freiburg & Tübingen)	6	Persistence	N.a.	5/6 (83%)	N.a.	4/6 (67%), 4/6 patients had at least hemi-hypophysectomy
Hameed [54]	2013	Single-center (Portland)	10	Persistence	No remission	7/10 (70%)	N.a.	Transient DI: 3/10 (30%)
Valderrábano [55]	2013	Single-center (Madrid)	11	Persistence	Increased UFC in the immediate postsurgical evaluation	4/11 (36%)	¼ (25%)	Both persistent and recurrent: New Hypopituitarism: 7/19 (37%), Transient DI: 9/26 (35%)
Chandler [56]	2015	Single-center (Ann Arbor)	33	Persistence	Continuation of elevated cortisol and UFC levels	15/33 (45%)	N.a.	N.a.
Mayberg [57]	2017	Single-center (Seattle)	23	Persistence	Cortisol >2 μg/dl	78%	N.a.	N.a.
Espinosa-de-los-Monteros [58]	2017	Single-center (Mexico-City)	8	Persistence	N.a.	(3/8) 38%	1/3 (33%)	Transient DI 27.7%, Permanent DI 5.5%, Arachnoid tear 38.8%, Hypopituitarism 11.1%
Brichard [59]	2018	Single-center (Brussels)	10	Persistence	No remission (mainly Cortisol level <5 μg/dL	4/13 (31%)	N.a.	Not stated separately for second TSS
Recurrence								
Nakane [60]	1984	Single-center (Tokyo)	8	Recurrence	N.a.	7/8 (88%)	N.a.	N.a.
Knappe [49]	1996	Single-center (Hamburg)	24	Recurrence	N.a.	17/24 (71%)	N.a.	N.a.
Hofmann [61]	2006	Single-center (Erlangen)	16	Recurrence	Elevated cortisol after 2 mg dexamethasone	6/16 (38%)	0% (5 patients received additional radiation treatment)	N.a.
Hofmann [51]	2008	Single-center (Erlangen)	35	Recurrence	N.a.	13/35 (37%)	N.a.	N.a.
Patil [19]	2008	Single-center (Virginia)	36	Recurrence	Elevated UFC and clinical symptoms	22 (61%)	2/22 (9%)	7 panhypopituitarism (19%, 5 patients total hypophysectomy), other not stated

Table 1 (*continued*)

First author	Year	Center	N	Indication of TSS	Definition of Persistence	Remission	Recurrence	New Hypopituitarism
Wagenmakers [52]	2009	Single-center (Nijmegen)	8	Recurrence	Re-occurrence of hypercortisolism (clinical symptoms and elevated cortisol after 1 mg dexamethasone) after 12 months of remission	7/8 (88%)	0%	Both persistent and recurrent: New Hypopituitarism: 9/14 (64%)
Valderrábano [55]	2013	Single-center (Madrid)	26	Recurrence	Elevated UFC after remission	8/15 (53%)	6/8 (75%)	Both persistent and recurrent: New Hypopituitarism: 7/19 (37%) Transient DI: 9/26 (35%)
Shirvani [62]	2016	Single-center (Teheran)	17	Recurrence	Re-occurrence of hypercortisolism after 12 months of remission.	12/17 (71%)	N.a.	N.a.
Espinosa-de-los-Monteros [58]	2017	Single-center (Mexico-City)	10	Recurrence	N.a.	(9/10) 90%	5/9 (56%)	Transient DI 27.7%, Permanent DI 5.5%, Arachnoid tear 38.8% Hypopituitarism 11.1%
Brichard [59]	2018	Single-center (Brussels)	10	Recurrence	Re-occurrence of hypercortisolism after 12 months of complete remission. Persistence & Recurrence	7/10 (70%)	N.a.	Not stated separately for second TSS
Friedman [63]	1989	Single-center (Bethesa, NIH)	31	Persistence & Recurrence	high dose of the Liddle DST & CRH-test, selective IPSS	24 (73%)	3/24 (13%)	New Hypopituitarism 1/20 in selective adenomectomy, 6/12 in (sub-)total hypophysectomy
Chee [64]	2001	Single-surgeon (Newcastle)	13	Persistence (n = 9) & Recurrence (n = 4)	Re-occurrence of hypercortisolism after 12 months of remission.	5/13 (39%)	N.a.	N.a.
Shimon [65]	2002	Single-center (Tel Hashomer)	13	Persistence (n = 10) & Recurrence (n = 3)	N.a.	8/13 (62%)	N.a.	N.a.
Benveniste [66]	2005	Single-center (New York, Mt. Sinai)	44	Persistence & Recurrence	N.a.	57%	25%	Not specifically stated for CD
Alexandraki [12]	2013	Single-center (London)	22	N.a.	N.a.	11/22 (50%)	4.5%	N.a.
Berker [67]	2013	Single-center (Ankara)	25	Persistence (n = 21) & Recurrence (n = 4)	Remission: serum cortisol level <1.8 μg/dl after low-dose dexamethasone	19/25 (76%)	N.a.	Not stated separately for second TSS
Dimopoulou [11]	2014	Multi-center (Munich Metropolitan Region)	36	Persistence & Recurrence	UFC > ULN or cortisol >5 μg/dl after low-dose dexamethasone with clinical symptoms of CD	15/36 (42%)	6/15 (40%)	Not stated separately for second TSS
Nankova [68]	2018	Single-center (Sofia)	33	Persistence & Recurrence	N.a.	36%	N.a.	Not stated separately for second TSS

that complementary medical treatment to control hypercortisolism was applied in 31 patients, but information on continuous use beyond 10 years was missing. Recurrence occurred in 35 patients (18%) with a recurrence free-survival rate of 70% after 10 years Total durable control of hypercortisolism was achieved in 64% at 10 years after GKRS. New hypopituitarism occurred in 25% patients, although this could be underestimated as not all non-ACTH axes of the pituitary were systematically recorded in every participating center [22]. In 21 patients who were treated with GKRS as first line therapy for CD biochemical remission was achieved in 81% at 5 years follow-up. Two patients experienced recurrence with median time to recurrence of 6.2 years, 5 patients (24%) developed new hypopituitarism [23]. Twenty patients, who did not achieve biochemical remission after first GKRS, were treated with repeated GKRS (with a median time from initial to repeat GKRS of 3 years) [24]. Biochemical remission was achieved in 12 patients (60%) with a median time to remission of 6 months. Two of 12 patients developed a recurrence, therefore durable remission was 50%. New hypopituitarism was difficult to assess since 14 patients had pre-existing hypopituitarism. Of the remaining 6 patients with normal pituitary function at baseline, 2 (33%) developed new hypopituitarism, although it is unclear whether it is related to first or second GKRS. One patient suffered from a persistent left cranial nerve III palsy and another one from a temporary left arcuate visual field deficit 1 week after SRS. It is stated that dose to the optic apparatus was 3.6 Gy in the second SRS and 7 Gy in the first SRS. Generally maximal doses to the optic apparatus were kept below 8–12 Gy [24]. Ultimately published from this group was a retrospective analysis of 68 patients with CD who received whole-sella radiation with GKRS (indication: either no visible adenoma (13 patients) or invasion of the dura and/or sinus cavernosus (55 patients)). 43 patients (63%) experienced remission, in 9 of these (21%) recurrence occurred. Surprisingly, although this radiosurgical procedure applied a dose aiming at “total hypophysectomy”, only 15 patients (23%) developed new hypopituitarism. No differences in remission or hypopituitarism rates were seen in comparison to adenoma-targeted GKRS [25].

As therapeutic effect of radiation for CD is delayed, medical therapy appears to be mandatory for “bridging” patients until remission is achieved. Patients need active endocrine surveillance to detect newly developing hypopituitarism and to titrate interim medical therapy controlling hypercortisolism.

Bilateral adrenalectomy (BADX)

BADX is a definite and effective treatment for CD, which is generally performed when other therapies (TSS and radiation) have failed or cannot be used. When chances for achieving remission through repeated TSS or radiation is low, and risk for hypopituitarism is high, or if medical treatment is not well tolerated, has to be stopped due to complications, or is ineffective, BADX should be performed without further delay. In case of life-threatening complications of hypercortisolism BADX can be used as ‘emergency treatment’ with excellent results [26]. We showed in a meta-analysis of 23 retrospective studies, that surgical mortality was low (3%), clinical remission of CS could be achieved in more than 95% and health related quality of life (HRQoL) improved in 82–89% [27]. Analysis of our own Munich cohort documented an excellent long-outcome [28]: Of 36 patients studied 11 years after BADX 100% of patients were in biochemical remission and hypercortisolism associated co-morbidities (i.e. diabetes, osteoporosis, hypertension) had improved. Long-term mortality in CD was excellent in this study, with 94% long-term survival at last follow-up after 25 years. Recently, Sarkis et al. reported on 34 patients from two French centers that HRQoL was significantly lower in the BADX group (17 patients) compared to a heterogeneous CD group (17 patients) receiving other treatments (mainly TSS) [29]. A simple explanation for this difference might be the longer exposure time to hypercortisolism, and the higher number of unsuccessful procedure preceding BADX. Obvious consequence of BADX is life-long dependency on gluco- and mineralocorticoids substitution and being at risk for Addison's crisis. The risk of corticotroph adenoma progression (so-called Nelson's syndrome) requiring additional pituitary-directed therapies ranges from 0–50% (median 21%) [30].

Medical therapy

Medical therapy poses an effective, emerging treatment for CS by lowering cortisol levels through different mechanisms of action. In the past mainly used as “bridging therapy” awaiting the effects of

radiation it gets more and more popular as a long-term therapy for hypercortisolism in different kind of situations: long-term treatment after failure of TSS or radiation therapy or in patients who are not candidates for surgery, as emergency treatment in severe and life threatening hypercortisolism or preoperatively before TSS in order to reduce perioperative morbidity. Medical therapy for CD can be classified as pituitary-directed therapy aiming at ACTH release of the corticotroph adenoma or as steroidogenesis inhibitor effective in all causes of CS. The currently approved drugs in Europe are pasireotide (targeting the somatostatin receptor 5) as a pituitary-directed therapy, and ketoconazole, metyrapone, etomidate and mitotane as steroidogenesis inhibitors (Table 2).

Ketoconazole, formerly used as an anti-fungal therapy, induces at higher doses adrenal insufficiency due to blocking different enzymes of the steroidogenesis. Recently, a retrospective, multi-center study from 14 French centers and 200 patients showed that normalization of the UFC was achieved in 49%, and significant reduction of UFC > 50% in additional 26% [31]. Its effectiveness might be higher, if maximum doses would be applied in uncontrolled patients which was not the case in this study. Increase of liver enzymes is commonly seen during treatment with ketoconazole and have to be controlled accordingly. An increase of more than threefold above upper normal range required reduction or cessation of therapy. Life-threatening liver failure requiring liver transplantation is usually not observed [32].

Contrary to ketoconazole, metyrapone blocks one enzyme of the steroid biosynthesis, 11beta-hydroxylase. Therefore, reduced cortisol production, but also an increase of the mineralocorticoid and androgen precursors is observed, leading in females to hirsutism, acne and edema. In the so far largest study with 195 patients treated with metyrapone, Daniel et al. showed that eucortisolaemia (defined by normalized morning cortisol profiles) was achieved in 55% [33]. In a single-center study with 91 patients treated with metyrapone targeted cortisol levels were achieved in 70–83% of patients [34]. According to a review normalization of hypercortisolism was achieved by metyrapone monotherapy in 75% of 200 cases [35]. Currently, an ongoing prospective multicenter trial is assessing the efficacy and safety of metyrapone treatment in patients with endogenous CS (PROMPT; https://clinicaltrials.gov/ct2/show/NCT02297945). When the effectiveness of metyrapone is monitored in a given patient by cortisol measurement, it is important to note, that assays have to be used, which are not cross-reacting with 11-deoxyxcortisol, which is increased following 11beta-hydroxylse inhibition by metyrapone leading to false high measured levels.

Etomidate is an anesthetic drug, which also inhibits mainly the 11β-hydroxylase blocking dose-dependently cortisol production. It has to be administered intravenously in low doses beyond the threshold required for anesthetic use. Etomidate is a potent and very fast inhibitor of steroid synthesis, which is mainly used in case of life-threatening complications of CS (such as severe infection) according to compassionate use. Because of its potential sedative effect it requires surveillance in an intensive care unit.

Mitotane is an adrenolytic drug mainly used for adrenocortical carcinoma due to its cytotoxic effect an adrenocortical cells. Due to its inhibition of several enzymes of the steroid biosynthesis it can be used to control hypercortisolism, usually in a lower dose than needed for cytotoxic effects, but still with severe side effects. In a French single-center study with 67 patients, clinical and biochemical remission was achieved in 72% [36].

Treatment with steroid synthesis inhibitors can be performed by a titration schedule until biochemical control is achieved or by a “block and replace” regimen with fully blockage of cortisol synthesis and hydrocortisone replacement. For many drugs, especially ketoconazole and metyrapone an escape phenomen has been described in CD, due to increased corticotroph adenoma ACTH secretion. Therefore, regular monitoring has to be performed (when a stable state is achieved, in our institution every 3 months).

Pituitary-directed therapies are aiming to decrease ACTH secretion and taking advantage of cell membrane receptors expressed by the corticotroph adenoma cells. One type of these receptors are the somatostatin receptors (SSTR). Mainly type 2 (SSTR2) and type 5 (SSTR5) are expressed by corticotroph cells, which represent a main target. However, first generation somatostatin analogues used in the treatment of acromegaly or neuroendocrine tumors (such as octreotide and lanreotide, mainly acting on the SSTR2) did not lead to reduced ACTH secretion. Pasireotide is a somatostatin analogue with a high affinity for SSTR5. In the first randomized, double-blind, clinical trial for CD, it was shown that

Table 2
Medical therapy for Cushing's disease. GI, gastrointestinal; IM, intramuscular; IV, intravenous; LAR, long-acting release; SC, subcutaneous; UFC, urinary free cortisol; ULN, upper limit of normal.

Drug	Dose rate	Efficacy (UFC normalization)	Side effects	Special issues
Pituitary-directed drugs				
Pasireotide	2 × 0.6 −0.9 mg/d SC	-Phase-III-study [37]: 20%, better efficacy when UFC <2-fold UN	Hyperglycaemia, GI disturbances, cholelithiasis	Awareness of hyperglycaemia
Pasireotide LAR	Starting 10 mg every 28 days IM (max. 40 mg)	Phase-III-study [39] (ULN UFC 1.5−5.0): 40%	See above	See above
Cabergolin	Starting: 1 −2 mg/week, Maximum: 7 mg/week	Aprox. 40% [44]	Dizziness, nausea, GI disturbances	
Steroidogenesis inhibitors				
Metyrapone	Starting: 3-4x 250 mg/d Maximum: 4 × 1500 mg/d	Aprox. 75% [35]	Androgen- & mineralocorticoid-excess: hirsutism, edema, hypokalaemia	- Intake with milk improves GI disturbances - interaction with 11-desoxycortisol in immunoassays (false high measurement of cortisol) - higher dose in evening/night
Ketoconazole	Starting: 2 × 200 mg/d Maximum: 3 × 400 mg/d	Aprox. 50% [31]	Liver toxicity	Monitor liver enzymes, increase >3-fold of ULN: reduction or cessation
Etomidate	Starting: 0.03 mg/kg/h IV	Almost 100% (no studies available)	Anaesthetic drug: somnolence, nausea; Symptoms of adrenal insufficiency	-Only parenteral, continuous administration -Lower doses needed than for anaesthesia -monitoring of cortisol levels every 4−6 h (complete block leads to adrenal insufficiency) -considered as emergency therapy
Mitotane	Starting: 1−2 g/d	Aprox. 72% [36]	GI disturbances, nausea, neurological toxicity	- monitoring of plasma drug levels -Used as cytotoxic drug, severe adverse events
Emerging drugs				
Osilodrostat (LCI699)	Starting 10 mg/d, Maximum: 60 mg/d	Phase-II-study: 79% [69] Two ongoing phase-III-studies: LINC-3: NCT02180217; LINC-4: NCT02697734	Nausea, diarrhea, asthenia, and adrenal insufficiency. In females hirsutism and acne.	Inhibitor of 11β-hydroxylase (similar to metyrapone)
Levoketoconazole	400 mg/d	Two ongoing phase-III-study: NCT01838551; NCT03277690	Less liver toxicity expected compared to ketoconazole	
Glucocorticoid receptor antagonists				
Mifepristone	1 × 300 −1200 mg/d	Clinical response: 88% [46]	Severe hypokalemia, hypertension. Symptoms of adrenal insufficiency.	- Increase of ACTH and cortisol (no biomarker of effective therapy) - concerns about tumor progression - not approved in Europe

pasireotide (either 600 or 900 μg twice daily SC) achieved UFC normalization in 20% and UFC reduction >50% in approximately half of the 162 patients treated. 12 months after initiation of treatment UFC remained normal in up to 25% [37]. After 24 months of treatment a large number of patients remained controlled [38]. It was shown, that UFC normalization was achieved more often, when hypercortisolism

was rather mild. Main side effect of pasireotide is a high rate of hyperglycemia compared to other somatostatin analogues in approximately 75% of patients. Recently, a LAR (long acting release) formula of pasireotide (every 4 weeks intramuscular injection) was approved. 24-hour UFC normalization was 41.9% in the 10 mg LAR group, and 40.8% in the 30 mg LAR group, higher than in the study using the subcutaneous formulation. The higher efficacy is likely due to the pre-selection of patients with mild to moderate CS (UFC 1.5 to 5 times upper limit of normal). Accordingly, UFC normalization was highest (52%) in the group of patients with very mildly elevated UFC (1.5–2.0 upper limit of normal) [39].

Cabergoline is acting as an agonist on dopamine D2 receptor, which are mainly expressed by lactotropes, but also by corticotroph adenoma cells. Both retrospective and prospective studies showed that treatment with cabergoline was able to achieve UFC normalization in about 40% of patients [40–42]. Although another prospective study with a follow-up of 6 weeks indicated much lower remission rate of 0–5% [43], a recent meta-analysis reported a mean remission rate of 39% for the monotherapy [44]. These effects are achieved by cabergoline doses of up to 7 mg/week, higher than those used in hyperprolactinemia [45]. No factors predicting responsiveness to cabergoline have been identified so far, and there are reports of escape in patients initially responding to cabergoline limiting its therapeutic potential. Nevertheless, because of its safety profile it can be administered in form of compassionate use on an individual basis and in pregnant patients with CD.

Another drug used in the treatment of CS is mifepristone, which is a glucocorticoid and progestogen receptor antagonist and showed to have a rapid clinical improvement. As levels of ACTH and cortisol rise during treatment, treatment is adjusted by clinical markers. Clinical response was 88% in the prospective SEISMIC study (study of the Efficacy and Safety of Mifepristone in the Treatment of Endogenous Cushing's syndrome) [46], which led to the approval of mifepristone in the USA, but not Europe. Adrenal insufficiency has to be monitored clinically and activation of mineralocorticoid receptor can lead to severe hypokalaemia and hypertension.

Summary

In recurrent and persistent CD after first TSS, the different scenarios possible require individualized therapeutic responses based on an interdisciplinary tumor board decision (see Fig. 1). While the necessary biochemical and imaging studies are planned and performed, it is in our view highly important to pursue in parallel control of hypercortisolism to avoid deterioration of the clinical conditions and prevent additional co-morbidities. We aim at achieving biochemical remission with the use of adrenostatic drugs within 4 weeks, addressing simultaneously consequences of uncontrolled hypercortisolism by rigorously treating comorbidities (such as hyperglycemia, hypertension, immunosuppression, myopathy, psychiatric co-morbidities).

When the tumor board decision has been taken and long-term medical treatment is required, our choice of drug depends on the biochemical activity of CD, pre-existing comorbidities such as hyperglycemia and remnant tumor tissue. In patients with mild CD (UFC $<$ 2 times ULN) and no hyperglycemia at baseline we start with pasireotide treatment and evaluate efficacy after 8 weeks. If a decrease, but not normalization of UFC is achieved, we add metyrapone or ketoconazole in order to obtain full biochemical remission. If initial UFC is above the threefold of ULN we usually start with metyrapone treatment and add ketoconazole if needed. Pasireotide can be used instead if remnant corticotroph tumor control is an issue. It is important to note, that medical treatment, if well tolerated, could be performed life-long, although in younger patients we tend to perform a definitive treatment.

Conclusions and recommendations

As reviewed here, there is unfortunately no optimal treatment option in CD after surgical failure. All mentioned treatment options have advantages and disadvantages and have to be discussed in the context of the individual patient. In general, when recurrent CD is biochemically diagnosed a new high-resolution MRI scan should be obtained. If an adenoma is visible, both second TSS and radiation therapy pose feasible treatment options, with the former having the advantages of rapid effectiveness and limited side effects,. If invasion of the sinus cavernosus is seen intraoperatively and hypercortisolism persists, radiation therapy should be initiated. In cases when no adenoma is visible, an explorative TSS

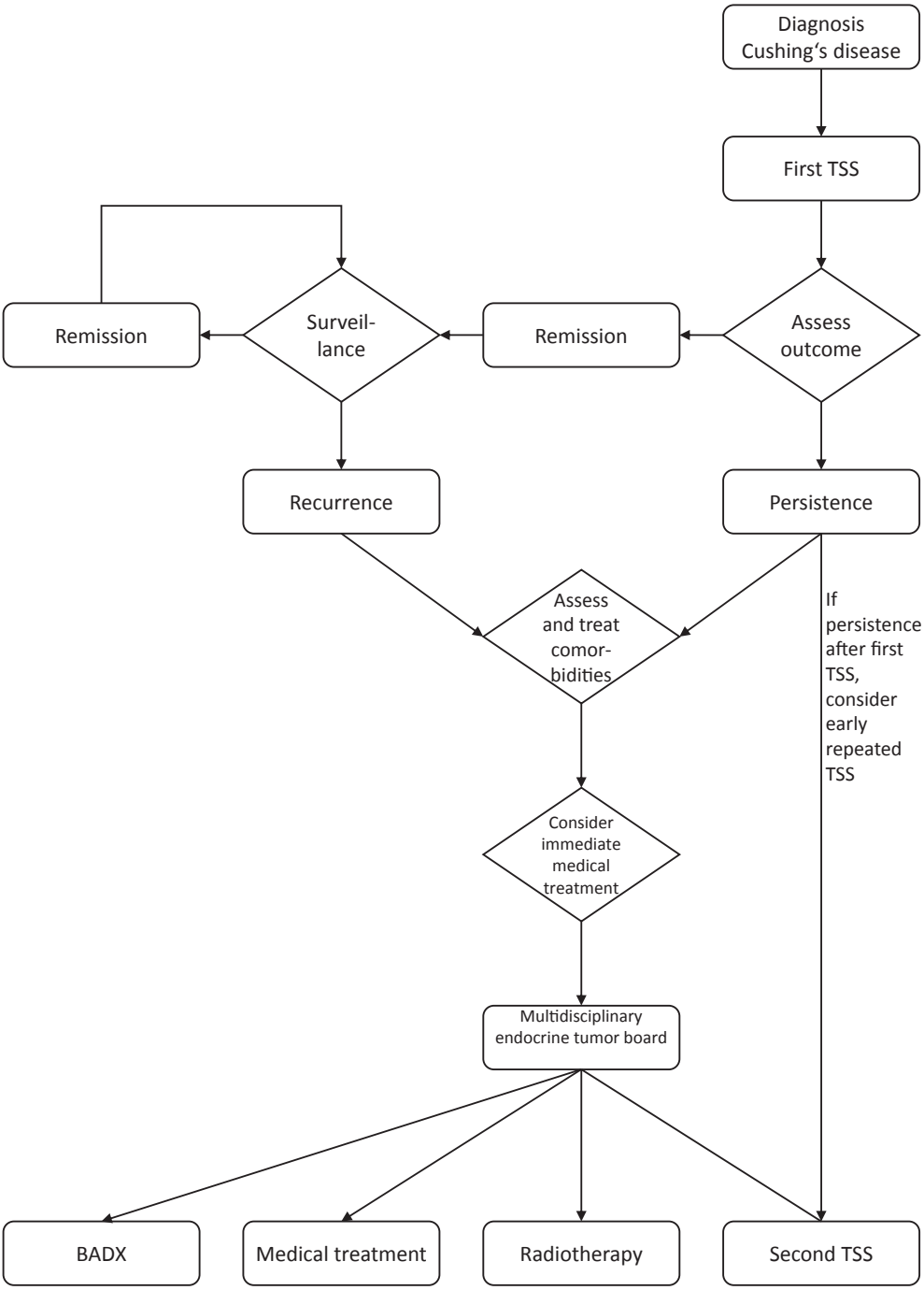

Fig. 1. Flowchart Treatment and Surveillance for Cushing's disease. TSS, transsphenoidal surgery; BADX, bilateral adrenalectomy.

can be performed with the aim to identify intraoperatively the adenoma. Recent studies suggested, that stereotactic radiosurgery of the whole pituitary does not cause more hypopituitarism than selective adenoma radiation. In the case of no visible adenoma, also medical therapy with either pituitary- or adrenal-directed therapies can be performed. If well tolerated, medical therapy can be performed even life-long. In such a scenario, repeat imaging studies during follow-up might be able to visualize corticotroph adenoma progression in initially imaging-negative patients, facilitating successful pituitary-directed therapies such as TSS or radiation. In long-term medically treated patients the pros and cons of continued medical therapy have to be weighted against those of BADX. BADX is definitively required, when no remission through TSS or radiation can be achieved and medical therapy has to be stopped due to side effects or complications. As there are many new drug for CS in development, the necessity for BADX will probably decrease in the future. Main therapeutic aim for CD remains achieving clinical and biochemical remission by first-line TSS. Possible improvement of the remission rates above 78% could come from preoperatively functional nuclear imaging or intraoperative MRI aiming to detect the very small adenomas [47].

Conflicts of interest

No potential conflict of interest was reported.

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Practice points

- Corticotroph adenoma responsible for CD are often not seen on MRI
- First-line therapy is transsphenoidal adenomectomy with the aim of complete adenoma removement and preserving pituitary function
- Surgery should be performed by experienced neurosurgeons
- Surgical failure (due to invasion or undetectable adenoma) is common
- A multidisciplinary endocrine tumor-board should review new sella MRI, surgical and histopathological report before deciding on second-line therapy
- Medical therapy can be used life-long, if well tolerated

Research agenda

- Visualizing corticotroph adenoma preoperatively
- Improvement of surgical effectiveness (intraoperative MRI)
- New medical agents

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