Влияние предоперационной терапии аналогами соматостатина на исход хирургического лечения СТГ-продуцирующих макроаденом гипофиза: критический анализ

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Тридцать лет назад была выдвинута гипотеза, согласно которой уменьшение размера макроаденом гипофиза, продуцирующих соматотропный гормон (СТГ), под действием аналогов соматостатина (АС) может улучшить исход хирургического лечения. С тех пор множество ретроспективных нерандомизированных исследований, а также четыре современных проспективных рандомизированных исследования были проведены для проверки истинности этой гипотезы. Они критически разобраны в этой статье.

За исключением единичных ретроспективных исследований, преобладающее большинство работ не подтверждают эту гипотезу. Также, хотя все проспективные исследования указывают на улучшение хирургического исхода через 3 мес после операции при проведении предоперационной подготовки АС, различия между пациентами, получавшими лечение до операции, и нелеченными пациентами из группы контроля исчезают через 6–12 мес.

Таким образом, предоперационная терапия макросоматотропином АС с целью достижения полного удаления опухоли не оправдывает ожиданий и не может быть рекомендована.

Ключевые слова: *акромегалия, СТГ-продуцирующая аденома гипофиза, трансназальная аденомэктомия, аналоги соматостатина.*

Preoperative treatment of growth hormone (GH) producing macroadenomas with somatostatin receptor ligands (SRLs) to improve surgical outcome: a critical analysis

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Thirty years ago, a hypothesis stating that preoperative shrinkage of growth hormone (GH) producing macroadenomas with somatostatin receptor ligands (SRLs) may improve surgical outcome was put forward. Since then, multiple retrospective, non-randomized studies as well as four contemporary prospective, randomized studies have been performed to evaluate the validity of that hypothesis and are critically reviewed in this manuscript.

With the exception of an occasional retrospective study the great preponderance of evidence could not confirm this hypothesis. Similarly, while all prospective studies suggested better surgical outcome for SRL-pretreated tumors 3 months post surgery, the differences in outcomes between pretreated and untreated control patients disappeared after 6–12 months.

Thus, preoperative treatment of macrosomatotropinomas with SRLs should not be relied upon as a means to achieve complete tumor removal and cannot be recommended.

Key words: *acromegaly, growth hormone-secreting pituitary adenoma, octreotide, treatment outcome.*

Introduction

The greatest majority of cases of acromegaly are due to the formation of a growth hormone (GH) producing pituitary tumor. Less than 1% of the totality of cases are due to ectopic production of a GH-releasing hormone (GHRH), hypothalamic or pituitary GHRH-producing gangliocytomas, GH-producing tumors of the ectopic pituitary glands or to ectopic production of GH by a non- pituitary malignancy. Thus, the focus of this review is dedicated to the most frequent etiology of acromegaly, i.e. the pituitary somatotropinoma.

Upon its release from the pituitary, somatotrophs GH acts on virtually all organs and tissues and they in turn produce Insulin-like Growth Factor-1 (IGF-1), which is the true growth – promoting hormone. In addition, GH has IGF-1 independent metabolic effects. It augments the rate of lipolysis which in turn increases insulin resistance and promotes protein conservation. The two branches of GH action are mediated by different components of the GH secretory profile: the rate of lipolysis and, consequently, the other metabolic parameters are increased by the pulsatile component of GH secretion, whereas induction of IGF-1 synthesis is regulated by the interpulse, baseline GH concentrations [1]. Indeed, baseline GH values maintained at a constant level as low as 0.2–0.3 ng/ml are sufficient to increase IGF-1 synthesis and secretion into an “acromegalic” range [2, 3]. That raises the surgical bar: if even small tumor remnants are left behind and continue to release small amounts of GH in a constant fashion, the operation will fail to achieve biochemical remission of acromegaly.

The combination of growth-promoting and metabolic effects of GH results in a typical clinical picture of acromegaly: overgrowth of facial features and extremities at the expense of both soft tissue and the bones and seen as coarsening of face features with deep facial furrows, prognathism, large tongue, widely separated teeth, increase in hand and shoe size, carpal tunnel syndrome, sleep apnea, left ventricular hypertrophy, arthropathy, increased perspiration, and glucose intolerance up to the point of developing true diabetes mellitus. Additionally, the tumor itself may result in visual problems, most often bitemporal hemianopsia if it grows upwards and compresses the optic chiasm, or ophthalmoplegia if it invades the cavernous sinus. Compression of the healthy pituitary may cause hypopituitarism. All this leads to significant morbidities and augments the mortality risk.

This combination of clinical features dictates a two-pronged strategy of treatment: elimination of mass effects of the tumor and normalization of GH/IGF-1 milieu.

Unfortunately, in the majority of cases the diagnosis of acromegaly is delayed by at least 5–10 years; by the time of diagnosis most tumors are already at the stage of macroadenoma (>10 mm), and many of them are obviously grossly invasive.

Current therapies of acromegaly include surgery, radiation therapy (conventional external radiotherapy and different forms of radiosurgery, such as Proton Beam, Gamma Knife, Cyber Knifes and LINAC), somatostatin receptor ligands (SRLs) such as octreotide, lanreotide and pasireotide, all of which are available in long-acting forms requiring monthly injections, dopamine agonist cabergoline (Dostinex) and GH-receptor antagonist pegvisomant (Somavert). More recently, an interest in the use of oral estrogens or Selective Estrogen Receptor Modulators (SERMs) has been rekindled [4]. All modalities have their advantages and disadvantages.

Surgery constitutes the first line of therapy in the majority of cases and only patients who are medically unfit for anesthesia or those who refuse surgery are subjected to non-surgical modalities. Surgery offers rapid abolition of the mass effects of the tumor, carries a promise of biochemical remission of the disease, and has very low morbidity and mortality rates. In a long run, it is by far the cheapest form of treatment of acromegaly. In the past, transcranial approach to the tumor dominated the field, but it was superseded in the great majority of cases by the microscope-assisted transsphenoidal approach. More recently, the latter gave way to an endoscope-assisted transsphenoidal surgery. Its advantage over the microscopic surgery is a wider exposure of the tumor with excellent visibility of its lateral expansion allowing tumor removal from the previously unapproachable

locations such as lateral of carotid arteries. It requires a wide resection of the sellar floor and the adjacent skull base with a subsequent closure of the opening by a mucosal flap, patient's own fat and tissue glue. Infrequent GH-producing microadenomas can be removed equally well by either approach, but an ~80% incidence of macroadenomas in acromegalic patients is dealt with significantly more efficiently by the endoscopic approach.

The success of surgery, as measured by the normalization of IGF-1 is determined largely by two factors:

1. the size and extent of the tumor;
2. the technical expertise of the operator.

The definition of the former is simple and straightforward: the smaller and the more contained the tumor, the higher the likelihood of its total removal. Indeed, in typical studies coming from highly-experienced pituitary surgical groups, 75–90% of patients with microadenoma, 40–73% of patients with non (or minimally) -invasive macroadenoma between 11–20 mm in diameter, but only 10–20% of those with macroadenomas larger than 20 mm (thus, obviously invasive) achieved remission based on normalization of IGF-1 [5, 6]

The second point is still an issue of debate, but a recent statement of the Pituitary Society suggests a track record of at least 50 pituitary surgeries per year as a criterion of the operator's proficiency [7]. A study from Birmingham demonstrated a dramatic improvement in the postoperative levels of GH when local neurosurgeons agreed to refer all their acromegaly cases to a single surgeon [8]. Moreover, a study by Ciric [9] demonstrated a 2–4 times lower incidence of surgical complications among dedicated pituitary surgeons. Thus, creations of specialized Pituitary Centers concentrating patients from large patient populations and increasing surgical volume in a single institution seems to be unarguably beneficial for the patients and the society as a whole [7].

However, an alternative idea that if one could by some means shrink the tumors, bringing them into an easily surgically-approachable operating field and thereby improving the success rate is tantalizing.

In 1988 [10], we published a study systematically evaluating the microscopic appearance and the rate of tumor shrinkage in 10 invasive pituitary somatotropinomas treated with short-acting octreotide. To our surprise, 8 pretreated patients achieved mean 24 h plasma GH <4.6 ng/ml and normal IGF-1 postoperatively, but only 5 of 16 untreated patients with tumors of a similar size and operated by the same neurosurgeon during the preceding 5 years achieved random GH <5 ng/ml (p = 0.021). The shortcomings of that study were obvious: no IGF-1 measurements were done in the untreated group, the nascent GH and IGF-1 assays had limited sensitivity, the size and the invasiveness of the tumors were estimated by a less accurate CT scanning, there was a bias of improved surgical expertise with time, and the patients were not randomized. Nevertheless, that study opened the gates to many other investigators attempting to answer the question whether preoperative shrinkage of somatotropinomas might be surgically beneficial.

Thus, we shall review the available information on the value of preoperative shrinkage of GH-producing macroadenomas as a means of improving surgical efficiency and potentially resulting in postoperative biochemical control. Since the pharmacological tumor-shrinking effect is largely limited to SRLs, only the drugs belonging to that group will be discussed.

Efficacy of SRLs as somatotropinoma-shrinking agents

The ability of short-acting octreotide to shrink pituitary somatotropinomas was demonstrated almost immediately upon its introduction in clinical trials. Subsequent studies confirmed their efficacy with long-acting forms of SRLs. The unified contemporary criterion of the tumor-shrinking efficacy for the latter studies was the MRI- calculated decrease of tumor volume by >20%.

In a meta-analysis of 41 studies, Octreotide LAR (Sandostatin LAR) decreased tumor size in 66% of 748 patients, by a mean of 50.6% [11]. Although in individual cases the degree of shrinkage may be very dramatic, the 95% confidence interval calculated in the meta-analysis was very tight, between 42.7–58.4%

In a prospective 48 week-long study PRIMARYS in 90 (64 completed) patients with macroadenomas who were newly-diagnosed

and somatostatin-naïve, Lanreotide Autogel at a dose 120 mg monthly achieved tumor shrinkage by more than 20% in 54.1% of the patients at 3 months and in 62.9% at 6 months (95% CI 52.0–72.9%) [12]. No quantification of the average degree of tumor shrinkage was reported. In a similar study [13] 29 patients with untreated acromegaly were given Somatuline Autogel 90 mg monthly with titration to either 60 or 120 mg monthly after 3 months. Twenty one of the 27 responders decreased their tumor volume by >20% (range 21–82%) and the remaining 6 decreased tumor volume by <20%. In 2 patients who were obvious SRL non-responders based on unchanged levels of GH and IGF-1 the tumors grew noticeably. Overall, median tumor shrinkage was 39% volume – wise.

Pasireotide is the newest SRL with wide receptor affinity has approximately 30-, 11-, and 158-fold higher functional activity than octreotide on somatostatin receptors (sstr) sstr1, sstr3, and sstr5, respectively, but seven-fold lower activity on sstr2 [14, 15].

Colao et al. [16] performed a head-to-head superiority study in somatostatin-naïve patients with acromegaly comparing long-acting pasireotide (Signifor LAR) and octreotide (Sandostatin LAR). From baseline to month 12, mean tumor volume decreased by 40% and 38% in the pasireotide LAR and octreotide LAR groups, respectively (p = 0.838). A significant (⩾20%) tumor volume reduction was achieved by 80.8% and 77.4% of pasireotide LAR and octreotide LAR patients; 1 patient experienced a ⩾20% increase in tumor volume in the octreotide LAR arm. A similar magnitude of tumor volume reduction was observed in the postsurgery and in the de novo groups.

Thus, overall, all 3 available SRLs have comparable efficacies in terms of somatotropinoma shrinkage.

The tempo of this effect had been first studied by our group in 1988 [10] using short-acting octreotide. Major reduction of tumor volume was achieved after ~3 months of therapy, with only a minor decrease thereafter. This was fully confirmed by Bevan et al. [17]. However, these results cannot be applicable to long-acting SRLs whose pharmacokinetics demands at least 3-4 monthly injections for the inhibitory effect of the drug to fully manifest. Also, the routine 3 daily injections of short-acting octreotide allow the tumor to escape from the inhibitory effect of the drug [18]. A combination of these differences likely explains the continuous tumor-shrinking effect of long-acting preparations that may reach its full potential as late as 12 months post initiation of therapy [16] as well as their additional shrinking effect on the already shrunken tumors pretreated with the short-acting galenic form [17].

To summarize, all available SRLs may induce shrinkage of somatotropinomas, but the responses are heterogeneous: 20–30% of the tumors do not exhibit tumor volume reduction, and the responding populations decrease their tumor volume by ~40%, although dramatic responses may occasionally be seen. Long-acting SRL formulations appear to be more effective than the older, short-acting ones.

Recently, the correlation between the responsiveness of somatotropinomas to the SRLs and their radiological appearance was studied [19–21]. All studies have reached the same conclusion: tumors with T2- weighted hypointense signal were dramatically more sensitive to both hormonal and morphological effects of the SRLs. As an example, Potorac et al. [19] have shown that the T2-hypointense tumors had an average of 88% reduction of random GH (vs. 24% in isointense and 36% in hyperintense ones), 59% reduction in IGF-1 (vs. 20% in isointense and 33% in the hyperintense ones), and their percent volume reduction was 38% (vs. 8% in isointense and 3% in hyperintense ones). T2-weighted signal correlated negatively with tumor granularity and T2 hyperintense tumors tend to have sparse granularity [21], which in turn is known to confer poor responsiveness to somatostatin [22, 23]. Thus, these data may suggest that selective inclusion of patients with T2-hypointense tumors into a study of pre-operative tumor shrinkage (thus, weeding out the likely non-responders) might increase the tumor shrinking rate of SRLs. However, more careful reading of the study by Potorac et al. [19] does not support this hypothesis. Among 84 T2-hypointense tumors, 82% achieved tumor shrinkage by >20%, but in the total sample of 120 tumors the same effect was achieved in 63%, a modest

difference. This was due to a relatively minor (30%) contribution of T2-iso and hyper-intense tumors in the total sample, and only 82% of significant tumor shrinkage rate among the purportedly sensitive T2-hypointense ones. Whether pre-selecting potentially good responders to SRLs with a view to increasing the tumor shrinkage rate is likely to bring about better surgical outcomes was not addressed by these investigators and will be discussed separately.

Cellular effects of SRLs on somatotropinomas

Having reviewed the gross effects of SRLs on the secretory activity and the volume of somatotropinomas, the next question is what morphologic changes within the tumors underwrite these dynamics?

To this end, we [10] have studied 10 somatotropinomas pre-treated with short-acting octreotide for 3-30 weeks before surgery, with the last injection given on the morning of surgery. Plasma GH levels were suppressed from 8.5–40.9 ng/ml to <1–4.9 ng/ml (all normal for the then-used RIA) in 9 patients, and from 66.7 to 27.3 ng/ml in the remaining one. Plasma IGF-1 also became normal or near-normal in the same patients (358–752 ng /ml to 14–179 ng/ml; nl. < 178). In a patient with only partial GH suppression IGF-1 declined from 740 to 630 ng/ml. Thus, our group has achieved better than average biochemical tumor control in this group, with the proviso that performance of the assays was at the nascent state.

Light microscopy showed that all treated tumors exhibited perivascular and interstitial fibrosis, and immunochemically all stained intensely for GH. Electron microscopy demonstrated densely-granulated pattern in all tumors studied; in two of them the so-called “fibrous bodies”, a pathognomonic sign of sparsely-granulated tumors, was seen. This indicates that these two examples were converted from a sparsely-granulated into a densely-granulated pattern. Morphometric studies revealed parallel shrinkages of the total cell area, cytoplasmic area and nuclear area by ~30–40% each. Overall, these finding were consistent with anti-proliferative effect of octreotide coupled with inhibition of secretion, but not the synthesis of GH.

Subsequently, Kovacs’ group [24] utilized he materials of a multicenter trial [24] and was able to study 86 acromegalic tumors (43 pretreated and 43 naïve). Due to stringent protocol conditions individual octreotide titration was not possible and only ~ half of octreotide-treated patients reached normal GH and IGF-1 levels. Nevertheless, there were close similarities with our earlier study: lower cell morphometry, intense GH staining, increased granularity and fibrosis in the octreotide-treated group.

Overall, both studies showed identical results fully consistent with known effects of somatostatin on the somatotroph proliferation, GH synthesis and secretion.

Now we are in a position to review the results of several studies designed to answer the question posed at the beginning of this discussion:

Does preoperative shrinkage of GH-producing macroadenomas improve surgical cure rate?

Multiple surgical series have shown that the success of surgery for acromegaly depends largely on the tumor size and invasiveness. The smaller the tumor, the higher is the likelihood of its complete removal by an experienced operator. Also, one could put forward a hypothesis that even a less experienced general neurosurgeon may be capable of successfully removing pituitary macroadenomas that were “pre-shrunk” by one of the SRLs. That would obviate the need of referring the patient to a faraway specialized center, thus greatly improving the efficiency of the health delivery system.

Since 1988 there were several studies addressing this issue. Most of them were uncontrolled and retrospective (with the exception of study by Kristof [26]) and employed early and insufficiently sensitive and specific GH and IGF-1 assays, thus carrying significant interpretation biases. Most importantly, the timing of outcome ascertainment was not consistent and not specified in the majority of the reports (Table 1).

Thus, in retrospective non-randomized studies there was no difference in the surgical control rate between SRL- pretreated and untreated patients. Only two studies reported statistically significant improvement in the

Table 1. Retrospective and non-randomized studies

Author [Ref]	Pre-treated/total (%)	Untreated controls/total (%)	P value
Barkan [10]	(8/10 (80%)	5/16 (31%)	0.02
Lv [25]	17/38 (45%)	28/62 (45%)	NS*
Kristof [26]	6/17(35%)	9/19 (47%)	NS
Biermasz [27]	10/29 (34%)	15/34 (44%)	NS
Losa [28]	81/143 (57%)	91/143 (64%)	NS
Abe [29]	62/90 (69%)	44/101 (44%)	NS
Stevenaert [30]	46/64 (72%)	63/108 (58%)	NS
Plockinger [31]	18/24 (75%)	18/24 (75%)	NS
Colao [32]	12/22 (54%)	11/37 (30%)	<0.05
Petersenn [33]	63/93 (68%)	372/559 (67%)	NS
Total	323/530 (61%)	656/1103 (59 %)	NS

Table 2. Prospective randomized studies utilizing strict remission criteria in patients with macroadenomas

Author [Ref]	Pretreated /total (%)	Untreated control/ total (%)	P value (3 months)
Mao [35]	24/49 (49%)	9/49 (18%)	0.001
Li [36]	11/24 (46%)	5/25 (20%)	<0.05
Shen [37]	6/19 (32%)	1/20 (5%)	<0.05
Carlsen [38]	13/26 (50%)	4/25 (16%)	0.017

surgical control rate [10, 32], but the baseline (SRL untreated) control rate was markedly lower than in the rest of the studies. Stevenaert [30] reported no overall difference between SRL-treated and untreated groups, but found higher remission rates in SRL-pretreated enclosed adenomas, including microadenomas, a finding that is difficult to explain.

However, one could point out the limitations of these studies: many of them were performed using simplified GH assessment and imperfect IGF-1 assays, some used historical controls, which might have introduced a bias of time-improved surgical expertise, etc. The sheer volume of observations likely compensated for these deficiencies, but the hypothesis would still has to be tested in a study of strict epidemiological design.

Recently, four such prospective randomized studies were published. All employed contemporary GH and IGF-1 assays, utilized strict Cortina criteria for remission [34], used long-acting octreotide and lanreotide preparations for at least 3 months prior to surgery and included only patients with macroadenomas (5 micro-adenomas in the pretreated and 5 in the control group in the study by Carlsen [38] have been removed from final analysis). Biochemical parameters were tested 3 months after surgical intervention, an interval thought to be sufficient for a wash-out of SRL-induced effects (Table 2).

These four studies, appearing in rapid succession, seemed to overthrow the negative conclusions of the earlier uncontrolled reports on the role of pre-surgical treatment of GH-producing macroadenomas. Indeed, dramatic improvements in the biochemical control rate strongly suggested that, indeed, decreasing the tumor size prior to surgery offers marked improvement in the outcome.

However, more careful analysis of the data revealed some disturbing doubts on the validity of such a conclusion. First, the control (untreated) groups all had unusually low surgical remission rates compared with the routinely observed ones coming from specialized pituitary centers (see Table 1). However, another study from China [25] reported remission rate in non-pretreated patients that was equal to those reported by the three Chinese groups in pre-treated subjects. Whereas all 3 studies from China came from single institutions, the Norwegian cohort [38] was operated by their community general neurosurgeons. Most

importantly, even in the original study by Shen et al. [37] the higher biochemical remission rate in the pre-treated group was seen at 3 and 6 months follow-ups, but the difference disappeared after that (p = 0.13).

In 2014 Fougner et al. [39] published the results of a long-term follow-up of the patients reported in the study by Carlsen [38]. In the original study, the 3 months postoperative evaluation identified a clear advantage of preoperative Sandostatin LAR treatment upon surgically-induced biochemical remission (50% vs. 16% in untreated). However, between that point and a 1 year follow-up, 8 purportedly controlled patients in the pretreated group required additional treatments (8 were given acromegaly medications, 1 of them also had radiation therapy and 1 had repeat surgery). If we remove those 8 obviously uncured patients from the list of the allegedly" cured " ones, the pretreated group will have 5 "cured" and 21 noncured patients, and their percentage "cure" will drop to 19% as compared to 16% in the untreated group (p = NS). This study also provided an answer to the question whether preoperative shrinkage of the tumor might enable a general neurosurgeon to remove it completely. Similar percentages of biochemical control in pretreated and untreated patients in the final analysis strongly vouch against it.

Thus, at least in 2 of the 4 above studies the seeming advantage of SRL pretreatment was a pharmacological artefact whereby long-acting octreotide continued to exert its suppressive effect on GH secretion by the still present tumor tissue 3 months after its last injection. The long-term follow-up of patients reported by Mao et al. [35] and Li et al. [36] is, unfortunately, not yet available.

Will SRL treatment with specific targeting of somatostatin-sensitive tumors result in a better surgical control rate?

Pituitary somatotropinomas are morphologically and functionally heterogeneous: densely-granulated adenomas respond better to SRL than sparsely-granulated ones. As discussed earlier, T2 sequences of the MRI images are capable of separating SRL responsive of densely –granulated T2-hypointense tumors from the poorly responsive sparsely-granulated T2- hyperintense ones. Thus, there is a theoretical possibility that selecting only densely-granulated T2-hypointense tumors for SRL pretreatment may uncover major differences in the surgical control rates since the non-responsive tumors would not be included in the general analytical pool. Dogansen et al. [40] have recently published a study addressing this point. They reviewed results of SRL treatment on surgical control rates in 78 patients with acromegaly and different T2 images of their pituitary tumors. Twenty two of the 42 patients with T2-hypointense tumors achieved biochemical remission (52%), as opposed to 4 out of 15 (27%) in T2 –isointense tumors and 9 out of 21 (42%) in T2- hyperintense tumors (p = NS). When all the patients were analyzed as a single group, 35 out of a total of 78 patients (45%) achieved biochemical remission, not different from the results obtained in exclusively T2-hypointense tumors. That was despite better shrinkage of the T2-hypointense tumors vs. the hyperintense ones (66 ± 33% hypointense, 64 ± 36% isointense, 23 ± 17% hyperintense; p = 0.029). These negative results were further strengthened by the fact that T2-hypointense tumors were from the beginning markedly smaller than the hyperintense ones (14 ± 8 mm hypointense, 17 ± 7 mm isointense, 24 ± 14 mm hyperintense; p = 0.007), and had lower rates of cavernous sinus invasion (8% hypointense, 11% isointense, 30% hyperintense; p = 0.05), thus, having surgically more advantageous presentation. Despite multiple shortcomings of that study [retrospective design, incomplete data sets, uncertain timing of ascertainment of biochemical remission, etc.] its results cast doubt on the assumption that better responsivity to SRLs may translate into higher surgical control rates.

Conclusions

Thus, at the present time we still do not have any confirmation that preoperative SRL therapy improves surgical outcome in patients with GH–producing macroadenomas. On the contrary, the entire body of evidence is tilted toward a negative answer.

There are several reviews and Consensus Statements addressing this issue.

Pita-Gutierrez et al. [41] advocated using SRL pretreatment in centers with poor surgical results prior to surgical intervention (ironically, presumably by the same inexperienced surgeons). Based on their reading of the 4 randomized trials but not addressing the longer term data by Shen [37] and not able to see the results by the study of Fougner [39], Jacob and Bevan [42] joined their Spanish colleagues in support of such a tactic. The Consensus Statement of the Polish Society of Endocrinology [43] also supported preoperative SRL treatment, although for different reasons: "…biochemical improvement, reduced risk of disease's complications, perioperative risk reduction, inhibition of tumor growth." Ferone et al. [44] joined this position, carefully avoiding the issue of absent surgical benefits and stressing "…more general clinical outcome of the patients and, perhaps, also the general cost of the illness, including multimodality treatment". These rather nebulous endpoints suggested by the latter 2 groups have never been shown to play a significant role on the outcome of surgical intervention and the apparent absence of surgical benefits [39] makes their importance unlikely. Losa (who published an earlier paper [28] strongly advocating against pre-surgical therapy) and Bollerslev (a co-author of the Carlsen's study [38]) called for yet another controlled study, this time with pasireotide, in a hope that it would finally show an advantage of pre-surgical SRL therapy [45], even though this drug does not differ from octreotide in its tumor-shrinking ability [16]. Finally, Fleseriu et al. [46] authored a Concensus Statement of the American Association of Clinical Endocrinologists in which they state that "…. the data are insufficient to support general use of a SRL prior to surgery in order to improve post-surgery biochemical outcomes", but do not oppose such therapy in patients with severe cardiac or anesthetic problems to reduce peri-operative morbidity. Even though this is an extremely rare scenario, it is unquestionably reasonable, similar to the use of cortisol synthesis inhibitors or mifepristone in patients with debilitating hypercortisolism, but it has nothing to do with the surgical outcome.

Thus, the preoperative shrinkage of pituitary macroadenomas with SRLs in hope of improving surgical outcomes cannot be recommended. As it so often happens in science, a beautiful hypothesis seems to have been slain by ugly facts.

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