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The effects of pre-operative somatostatin analogue therapy on treatment cost and remission in acromegaly

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Abstract

Purpose To investigate the effects of preoperative somatostatin analogue (SSA) treatment on the annual cost of all acromegaly treatment modalities and on remission rates.

Methods The medical records of 135 patients with acromegaly who were followed at endocrinology clinic of Cerrahpasa Medical Faculty for at least 2 years after surgery between 2009 and 2016 were reviewed.

Results The mean follow-up time was 50.9 ± 25.7 months. Early remission was defined according to 3rd month values in patients who didn't achieve remission, and 6th month values in patients who achieved remission at the 3rd month after surgery. The early and late remission rates of the entire study population were 40% and 80.7%, respectively. The early remission of the preoperative SSA-treated group (61.5%) was significantly higher than SSA-untreated group (31.2%) (p = 0.002). The early remission of the preoperative SSA-treated patients with macroadenomas (52.2%) was also significantly higher than the SSA-untreated group (23.5%) (p = 0.02). In the subgroup analysis; this difference was much more pronounced in invasive macroadenomas (p = 0.002). There were no differences between the groups in terms of late remission.The median annual cost of all acromegaly treatment modalities in study population was €3788.4; the cost for macroadenomas was significantly higher than for microadenomas (€4125.0 vs. €3226.5, respectively; p = 0.03). Preoperative SSA use in both microadenomas and macroadenomas didn't alter the cost of treatment. The increase in the duration of preoperative medical treatment had no effect on early or late remissions (p = 0.09; p = 0.8).

Conclusions Preoperative medical treatment had no effect on the costs of acromegaly treatment. There was a benefical effect of pre-operative SSA use on early remission in patients with macroadenomas; however, this effect didn't persist long term.

Keywords Acromegaly · Preoperative treatment · Cost · Somatostatin analogue

Introduction

Acromegaly is a rare endocrine disease caused by the hypersecretion of growth hormone (GH), generally from a pituitary adenoma. Excessive GH secretion leads to the hypersecretion of insulin-like growth factor-1 (IGF-1), which is the main cause of the comorbidities and premature mortality associated with acromegaly [1].

The therapeutic goals of treatment in acromegaly are to resect the tumor and to achieve hormonal remission, thereby reducing disease-related comorbidities, improving patient quality of life, and decreasing the rate of mortality. The treatment modalities of acromegaly include neurosurgery, radiotherapy, medical therapy with SSA, dopamine agonists, and the GH receptor antagonist pegvisomant. Although various treatment options exist, acromegaly is still a disease with

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substantial mortality and economic burden [2–4]. Therefore, early diagnosis and control of the disease are crucial in acromegaly [3, 4]. Currently, transsphenoidal surgery is the accepted first-line treatment modality in acromegaly [1, 5, 6]. In experienced centers, the surgical remission rates approach 80–85% for microadenomas, whereas they are still in the 40–50% range for macroadenomas [7–9].

Medical therapy is the modality of choice if transsphenoidal surgery fails or if the patient is a poor candidate for surgery [10]. Long-acting SSAs are the mainstay drugs as the adjuvant therapy of acromegaly [1]. Recently, there have been several studies investigating the effects of SA therapy in the preoperative period in order to improve the remission rates for surgery, but the results have been conflicting [11–19]. It was shown that SSA pretreatment could lead to tumor shrinkage, softening of the tumor [20–22], and also improved surgical remission rates, especially for macroadenomas [12, 18, 19]. Some studies suggested the use of preoperative SSA treatment to alleviate the symptoms of acromegaly and to reduce the risk of complications during surgery [23]. However, there have also been studies that failed to demonstrate any benefits of preoperative medical treatment [11, 16, 17]. There is a lack of certainty in the literature about whether preoperative treatment improves the control of acromegaly because of the different study designs [24–27]. Only a few studies investigated the cost-effectiveness of SSA pretreatment [28, 29]. Current guidelines do not recommend the routine use of SSA pretreatment prior to surgery in acromegaly, but the effect of pre-operative SSA therapy on post-operative acromegaly treatment cost, which has a high economic burden, may affect a phsysician's acromegaly management.

In light of these findings, we aimed to investigate the effects preoperative SSA treatment on the annual cost of all acromegaly treatment modalities (medical, surgical and radiosurgical treatments), and also the effects on early and late remission rates in patients with acromegaly.

Subjects and methods

Subjects and study design

The medical records of 210 patients with acromegaly who were being followed at our clinic between 2009 and 2016 were retrospectively reviewed. One hundred thirty-five patients who had been followed up for at least 2 years after surgery were assessed.

The pre-operative use of SSA of these 135 patients was determined. Patients who had taken SSA for less than 3 months were excluded from the study. These patients received a dose of 20 mg of octreotide LAR or 90 mg of lanreotide autogel every 28 days at the initiation of preoperative SSA treatment and titrated as needed until surgery. Preoperative treatment was given to patients with comorbid diseases that needed to be treated before surgery or those whose surgery would be delayed. Also we start pre-operative SSA treatment in patients with the expected operation time exceeding 1 month, without distinction of the tumor size. The length of the preoperative medical treatment was also recorded. The surgery was planed in all pretreated medical group. The surgical decision wasn't made according to the normalization of IGF-1 or patients decision.

The clinical characteristics of patients and biochemical data were recorded. The pathologic data were evaluated and Ki-67, p53, and mitosis indices were determined. The pretreatment magnetic resonance imaging (MRI) of patients were assessed. Adenomas were classified by Knosp classification. Tumors were considered as invasive if they had adenomas with Knosp 3–4 [30].

GH levels during a 75-g oral glucose tolerance test (OGTT) of < 1 ng/mL, and age and sex-adjusted IGF-1 levels in the normal range at the 3rd post-operative month were accepted as early remission, whereas among patients who took pre-op treatment, the early remission was assessed at the 6th post-operative month in order to exclude the potential residual effects of pre-operative SSA use.

The GH and IGF-1 levels at the most recent visit were accepted as 'late remission.' The current regimen and dosages of medical treatment, the number of surgeries, and whether the patient had received radiotherapy were recorded. The options of medical therapy, re-operation or radiotherapy usage were tailored according to current guidelines [1, 3].

The combined costs of medical therapy (SSA, Cabergoline, Pegvisomant), transsphenoidal surgery and radiotherapy (Gammaknife, Cyberknife), of all patients from the time of the diagnosis of acromegaly till the last visit were calculated. For the patients who had received preoperative medical therapy, the cost of SSA therapy administered in the preoperative period was added to the total cost. For patients who received no preoperative medical therapy, the duration of follow-up was considered to be the period of time between the date of the transsphenoidal surgery and the last visit. For patients who received preoperative SSA treatment, the duration of follow-up was considered as the duration of preoperative medical therapy plus the time between the date of the transsphenoidal surgery and the last visit. The cost of all treatments used for acromegaly (medical, surgery, radiotherapy) expensed in Euros.

Statistical analyses

The data were statistically analyzed using the Statistical Package for the Social Sciences for Windows version 21.0 (SPSS, Chicago, IL) statistics program. The normality of distribution was determined using the Kolmogorov–Smirnov

Table 1 Demographic characteristics, biochemical parameters, pathologic and radiologic indices of the patients according to preoperative SSA treatment

	Preoperative SSA-treated group (n = 39)	Preoperative SSA-untreated group (n = 96)	p value
Sex (F/M)	21 (53.8)/18 (46.2)	56 (58.3.)/40 (41.7)	0.2
Age at diagnosis	39 [27–62]	43 [19–68]	0.2
Preoperative IGF-1 (ng/mL)	656.0 [442.2–1600.0]	750,6 [385.7–4020.0]	0.1
Preoperative GH (ng/mL)	8.6 [2.7–32.1]	10.3 [3.6–26.9]	0.1
Tumor size (Micro/macroadenoma)	16 (41.0)/23 (59.0)	15 (15.6)/81 (84.4)	**0.001**
Invasion status (Non-invasive/invasive)	25 (64.1)/14 (35.9)	54 (56.3)/42 (43.8)	0.4
Ki-67 score (< 3%/≥ 3%)	36 (92.3)/3 (7.7)	57 (59.4)/39 (40.6)	**< 0.001**
p53 (< 1%/≥ 1%)	31 (79.9)/8 (20.5)	64 (66.7)/32 (33.3)	0.1
Mitoses (< 1%/≥ 1%)	36 (92.3)/3 (7.7)	85 (88.5)/11 (11.5)	0.5

Bold values indicate statistical significance ($p < 0.05$)

Data are expressed as number and percentages or median and interquartile ranges

SSA somatostatin analogue, *p* p-value, *n* number, *F* female, *M* male, *GH* growth hormone, *IGF-1* insulin-like growth factor-1

Table 2 Knosp classification of study population

		Preoperative SSA-untreated group (n = 96) n (%)	Preoperative SSA-treated group (n = 39) n (%)	p
Knosp classification	0	10 (10.4)	9 (23.1)	0.2
	1	20 (20.8)	7 (17.9)	
	2	24 (25.0)	9 (23.1)	
	3	28 (29.2)	12 (30.8)	
	4	14 (14.6)	2 (5.1)	

Data are expressed as number and percentages

test. Variables that had normal distribution were assessed using an independent *t* test; the results are presented as mean and standard deviation. For variables that did not have normal distribution, nonparametric tests (Mann–Whitney U test for the comparison of two groups) were used and the results are presented as median and interquartile range (IQR). Categoric variables were assessed using the Chi square test or Fisher's exact test where appropriate. P values of 0.05 were considered statistically significant.

The study was approved by the local ethics committee of Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpasa and was conducted in accordance with the Declaration of Helsinki.

Results

A total of 135 patients were evaluated. The total mean follow-up time was 50.9 ± 25.7 months. Thirty-nine (28.8%) of the 135 patients had used preoperative SSA; 19 patients octreotide LAR, 20 patients lanreotide autogel. The mean duration time of preoperative SSA therapy was 8 ± 8.2 months. Ninety-six (71.2%) of 135 patients did not use preoperative SSA.

Demographic characteristics, biochemical parameters, pathologic and radiologic indices for preoperative SSA-treated and untreated patients are shown in Table 1. There was no statistically significant difference between the SSA-treated and untreated group in sex distribution, age at diagnosis, and preoperative GH and IGF-1 levels ($p > 0.05$). The SSA-treated group had more microadenoma than the SSA-untreated group (41% vs. 15.6% respectively; $p = 0.001$). In addition, the Ki-67 score of the tumors were higher in the SSA-untreated group ($p < 0.001$, respectively). In the subgroup analysis, according to adenoma size, Ki-67 scores were lower in preoperative SSA-treated patients than in the SSA-untreated group (87% vs. 51.9% respectively, $p = 0.002$) with macroadenomas. There were no differences between the patient groups with microadenomas in terms of proliferative indices. The Knosp classification of adenomas were compared between preoperative SSA-treated and untreated patients (Table 2). In addition, there was no differences between preoperative the SSA-treated and untreated groups with macroadenomas in terms of invasion status.

In SSA treated group; the mean IGF-1 levels before SSA treatment was 710.1 ± 361.1, the mean IGF-1 levels after SSA treatment—before surgery was 546.2 ± 253.8. There was a statistically significant decrease after SSA treatment

Table 3 The early-late remissions and cost of acromegaly treatment per year according to preoperative SSA treatment status

	Preoperative SSA-treated group (n = 39) (Microadenoma = 16) (Macroadenoma = 23) (Noninvasive macroadenoma = 9) (Invasive macroadenoma = 14)	Preoperative SSA-untreated group (n = 96) (Microadenoma = 15) (Macroadenoma = 81) (Noninvasive macroadenoma = 39) (Invasive macroadenoma = 42)	p value
Early remission rate*			
Total n (%)	24 (61.5)	30 (31.2)	**0.002**
Microadenoma n (%)	12 (75.0)	11 (73.3)	1.0
Macroadenoma n (%)	12 (52.2)	19 (23.5)	**0.02**
Noninvasive macroadenoma n (%)	7 (77.8)	17 (43.6)	0.06
Invasive macroadenoma n (%)**	5 (35.7)	2 (4.8)	**0.002**
Late remission rate			
Total n (%)	30 (76.9)	79 (82.3)	0.6
Microadenoma n (%)	16 (100)	14 (93.3)	0.5
Macroadenoma n (%)	14 (60.9)	65 (80.2)	0.1
Noninvasive macroadenoma n (%)	9 (100)	39 (100)	1.0
Invasive macroadenoma n (%)**	5 (35.7)	26 (61.9)	0.09
Treatment cost/year €[a]			
Total	3960.4 (481.9–7098.3)	3731.8 (315.8–15184.7)	0.4
Microadenoma	3282.8 (481.9–5672.1)	1934.3 (315.8–14155.1)	0.4
Macroadenoma	4124.9 (744.0–7098.3)	4117.3 (403.8–15184.7)	0.5
Noninvasive macroadenoma n (%)	4495.1 (792.5–7098.3)	3644.3 (403.8–12959.8)	0.2
Invasive macroadenoma n (%)**	4815.3 (744.0–6724.1)	3946.1 (703.9–15185.7)	0.07

Bold values indicate statistical significance ($p < 0.05$)

Data are expressed as number and percentages or median and interquartile ranges

*Early remission defined according to 3rd month values of patients who are under remission at 3rd month after surgery. Early remission defined according to 6th month values of patients who are not under remission at 3rd month after surgery

**Adenomas were classified by Knosp classification. Tumors were considered as invasive if they had adenomas with Knosp 3–4

[a]Annual cost of all acromegaly treatment modalities (medical, surgical and radio-surgical treatments) of patients with acromegaly

($p < 0.001$). However none of these patients had biochemical remission and all patients had surgery after SSA treatment.

The early and late remission rates according to preoperative SA treatment use are shown in Table 3. The early and late remission rates of the entire study population were 40% and 80.7% respectively. The early remission rate of the preoperative SSA-treated group (61.5%) was significantly higher than in the SSA-untreated group (31.2%) ($p = 0.002$). Additionally, the early remission rate of the preoperative SSA-treated patients with macroadenomas (52.2%) was also significantly higher than in the SSA-untreated group (23.5%) ($p = 0.02$). In the subgroup analysis, according to invasion status of macroadenomas, this difference was much more pronounced in invasive macroadenomas (preoperative SSA treated patients; 35.7% vs. preoperative SSA untreated patients; 4.8% respectively, $p = 0.002$). The early remission rate was higher in preoperative SSA-treated patients than in the SSA-untreated patients (77.8% vs. 43.6% respectively; $p = 0.06$) with noninvasive macroadenomas. However, this difference was not statistically significant. There were no differences between the groups in terms of late remission.

The durations of preoperative SSA treatment were different among our study population (range, 3–32 months). The increase in the duration of preoperative medical treatment did not related to an increase in early or late remission rates in the entire study population ($p = 0.09$; $p = 0.8$).

The costs of all treatment strategies used in acromegaly are shown in Table 4. The median annual costs of all acromegaly treatment modalities (medical, surgical and radiosurgical treatments) in the entire study population was €3788.4 (IQR: €315.8–€15184.7). The median annual cost of treatment for macroadenomas was significantly higher than for microadenomas (€4125.0 vs. €3226.5 respectively; $p = 0.03$). The costs of acromegaly treatment per year in those who

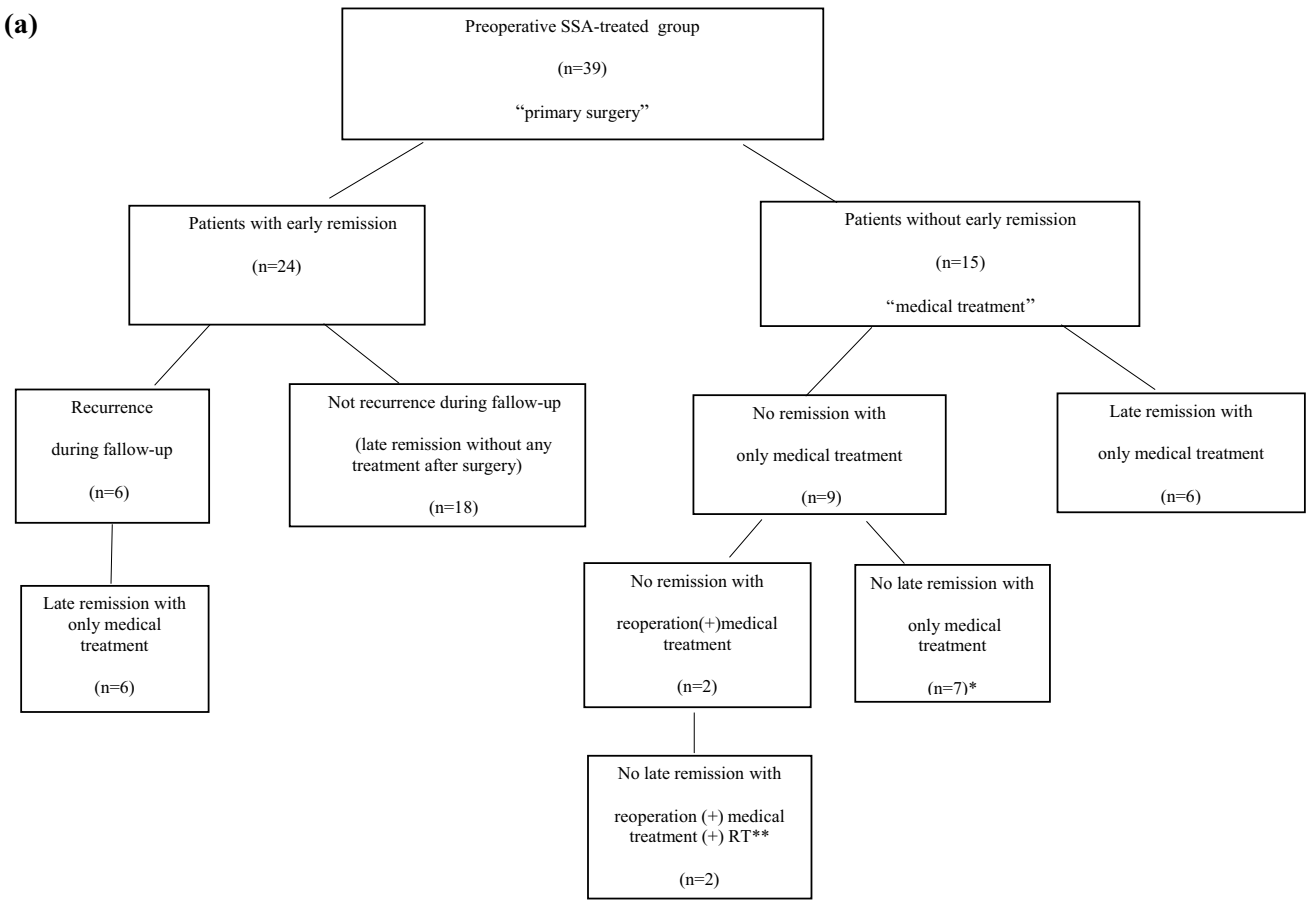
Table 4 The costs of all treatment strategies of acromegaly

	Cost €*
Octreotide LAR (10 mg, 1 blister)	117.4
Octreotide LAR (20 mg, 1 blister)	229.9
Octreotide LAR (30 mg, 1 blister)	342.8
Lanreotide Autogel (60 mg, 1 prefilled syringe)	307.7
Lanreotide Autogel (90 mg, 1 prefilled syringe)	372.4
Lanreotide Autogel (120 mg, 1 prefilled syringe)	453.5
Pegvisomant (10 mg, 30 blister)	715.4
Pegvisomant (15 mg, 30 blister)	1071.9
Pegvisomant (20 mg, 30 blister)	1409.1
Cabergoline (0.5 mg, 8 tablets)	12.0
TSS operation	2053.1
Gamma knife radiosurgery	362.3
Cyberknife radiosurgery	483.0

*The costs of all treatment strategies of acromegaly

were and were not treated with SSA were €3960.4 [IQR: €481.9–€7098.3] and €3731.8 (IQR: €315.8–€15184.7), respectively (p = 0.4) (Table 3). There were no differences between the groups in terms of treatment cost/year. In the subgroup analysis, according to adenoma invasion status, the median annual cost of treatment was higher in preoperative SSA-treated patients than in the SSA-untreated patients (€4815.3 vs. €3946.1 respectively; p = 0.07) with noninvasive macroadenomas. However, this difference was not statistically significant.

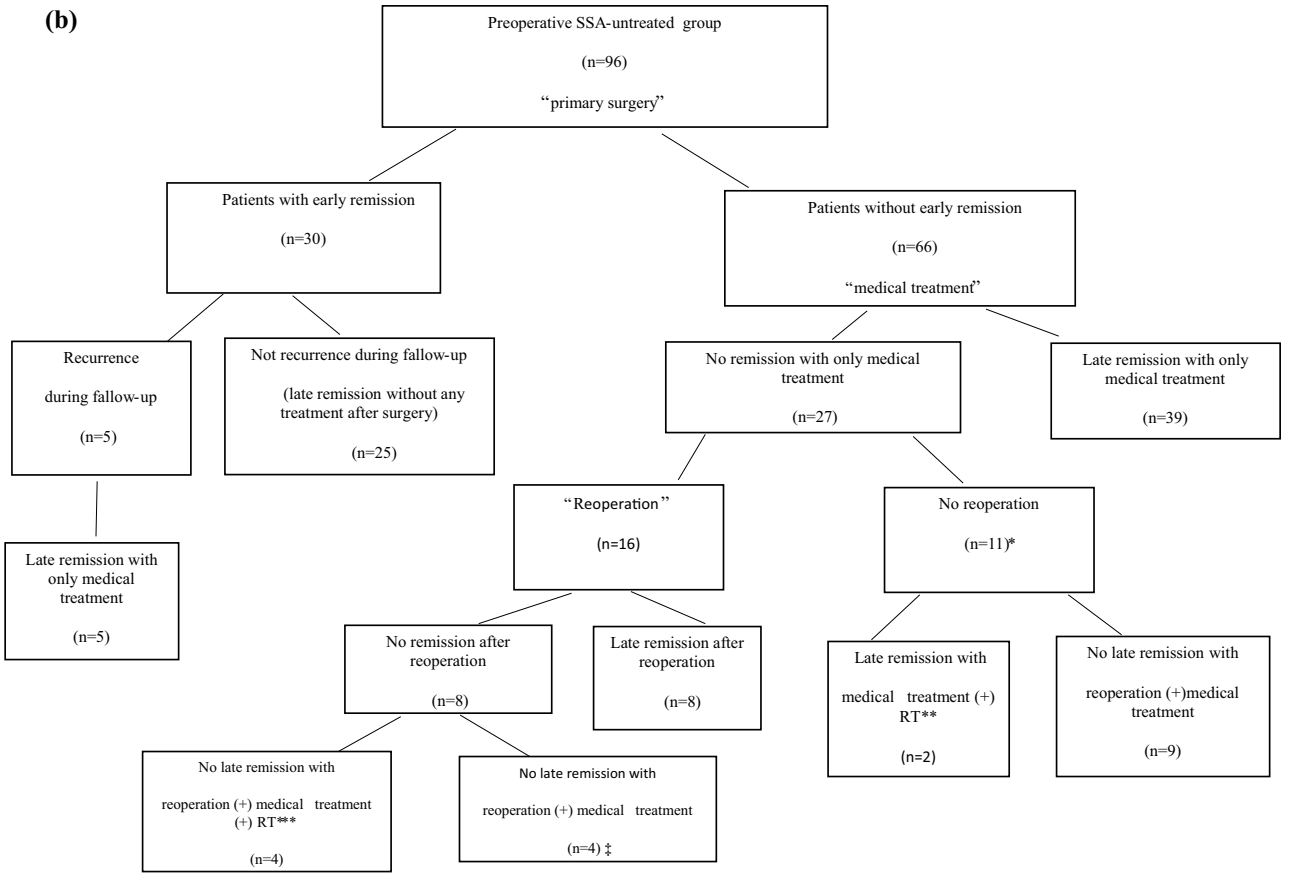
The flow charts of the patients according to preoperation SSA usage were shown in Fig. 1. The comparison of aggressive treatment, reoperation, and radiotherapy needs according to preoperative SSA use is shown in Table 5. The percentage of reoperation requirement or RT use was significantly higher in the preoperative SSA untreated group than in the treated group (p = 0.02). There were no statistically



*7 patients→3 patients refused to be treted with RT or reoperation,; 4 patients were not suitable for reoperation or RT due to the tumor localization

** The time to last visit after RT was 8.1±3.4 months.

Fig. 1 The flow charts of the patients according to preoperation SSA usage; **a** preoperative SSA-treated group, **b** preopertive SSA-untreated group



*11 patients didn't go resurgery →1 patients refused reoperation,or RT therapy; 6 patients were not suitable for reoperation due to the komorbidities and 2 of these 6 patients were suitable for RT; 4 patients were in reproductive period, they were planning pregnancy recently, these 4 patients were not directed to RT or resurgery treatments.

** The time to remission after RT was 21.3±4.1 months. *** The time to remission after RT was 11.7±5.1 months. ‡ 4 patients were not suitable for reoperation or RT due to the tumor localization

Fig. 1 (continued)

Table 5 The comparison of aggressive treatment, reoperation, and radiotherapy requirement according to preoperative SSA use

n (%)	Preoperative SSA-treated group (n = 39) (Microadenoma = 16) (Macroadenoma = 23)	Preoperative SSA-untreated group (n = 96) (Microadenoma = 15) (Macroadenoma = 81)	p value
High dose SSA usage*	4 (10.3)	13 (13.5)	0.6
Microadenoma	0 (0)	1 (6.7)	0.3
Macroadenoma	4 (17.4)	12 (14.8)	0.8
PEG usage	3 (7.3)	9 (9.4)	0.8
Microadenoma	0 (0)	1 (6.7)	0.3
Macroadenoma	3 (13)	8 (9.9)	0.7
Reoperation/RT need	2 (5.1)	20 (20.8)	**0.02**
Microadenoma	0 (0.0)	2 (13.3)	0.1
Macroadenoma	2 (8.7)	18 (22.2)	0.1

Bold values indicate statistical significance ($p < 0.05$)

Data are expressed as number and percentages

SSA somatostatin analog, *PEG* pegvisomant, *RT* radiotherapy

*Octreteotide LAR 40–60 mg or Lanreotide Autogel 180 mg use

significant differences between other aggressive treatment options between the groups.

Discussion

In this study, we found that preoperative SSA treatment for at least 3 months had no effect on the costs of acromegaly treatment in long-term follow-up. We also found that although there was a benefical effect of pre-operative SSA use on early remissions in acromegalic patients with macroadenomas, this effect was not persistant in the long term. On the other hand, there was no significant effects of preoperative SSA treatment in terms of early or late remissions in patients with microadenoma. In addition, it was shown that the duration of preoperative medical treatment had no effect on early or late remissions.

Although various treatment options exist, acromegaly is currently a disease with substantial mortality, and remission rates are still low, especially in macroadenomas. Consequently, physicians are trying to find different treatment modalities, one of which is pre-operative SSA use. Several studies in the literature on pre-operative SSA use had conflicting results. Abe et al. showed that pre-operative treatment had no effect on either early or late remissions [11] A study from Carlsen et al. showed that preoperative SSA treatment did not improve surgical results in patients with microadenoma [12] Contrarily, in a large series Stevenaert and Beckers showed that disease control was significantly improved postoperatively for patients with both microadenomas and macroadenomas with preopertive treatment [13]. Similarly, Li et al. showed a decrease in tumor size and also higher early remission rates with pre-operative treatment [18]. There are other studies showing that preoperative SSA use, both with octreotide and lanreotide, increased the early remission rates only in macroadenomas [12, 19]. Duan et al. showed that preoperative SSA treatment improve the surgical curative rates in acromegalic patients with only invasive macroadenomas [31]. Various studies and meta-analyses that investigated both the short and long-term effects of pre-operative treatment showed that the beneficial effect on early remission did not persist in the long term [10, 17, 24]. As it can be seen, there is a lack of certainty in the literature about whether preoperative treatment improves the control of acromegaly because of the different study designs, and current guidelines do not recommend routine use of SSA prior to surgery in patients with acromegaly [24, 25]. In our study, we showed a benefical effect of pre-operative SSA use on early remission in acromegalic patients with macroadenomas. In the subgroup analysis, according to invasion status of macroadenomas, this difference was much more pronounced in invasive macroadenomas. But the benifical effect was not persistant in the long term, in both invasive and noninvasive macroadenomas. Because of the problems about the healthcare systems in our country, some delay could happen about the timing of the surgery. Therefore, we generally decide to start pre-operative SSA treatment in patients with the expected operation time exceeding 1 month, without distinction of the tumor size. Therefore, the number of patients with microadenoma was higher in the preoperative medical treatment group in our study.

In contrast to the literature, a high level of preoperative SSA was given to patients with acromegaly with microadenoma (16 of 39 SSA-pretreated patients) in our retrospective study. However, patients with micro or macroadenoma were evaluated seperately in subgroup analyses. In concordance with other studies, we discovered that preoperative SSA treatment had no influence on either early or late remission in patients with microadenoma [18].

In the literature, the early remission was assessed at 3th post-operative month [12, 18]. In our study, in patients who took pre-op treatment, the early remission was assessed at 6th post-operative month in order to exclude the potential residual effects of pre-operative SSA use. This was important because as it is known that a potential prolonged effect of SSA in early-period post-operative evaluations causes false results; the period should be at least 6 months after SSA withdrawal in order to exclude any lingering effects of presurgical SSA treatment on the outcome [23, 25].

The duration of preoperative SSA treatment varies between 3 and 6 months in the literature despite optimal duration and dosages being uncertain [23]. Duan et al. showed that long-term use of pre-operative SSA (> 6 months) improved surgical curative rates [31]. In this context, in our study, we found no correlation between the duration of preoperative medical treatment and early or late remission rates.

In our retrospective study, the preoperative treatment group received octreotide LAR (20 mg IM every 4 weeks) or lanreotide autogel (90 mg IM every 4 weeks) at the initiation of preoperative SSA treatment and dose titration was performed if required until surgery. There is a lack of certainty in the literature about the appropriate dose for pretreatment SSA therapy. However, based on previous dose optimization studies, it is possible that a higher dose of SSA might have achieved better biochemical control overall [31, 32].

In previous studies, it was shown that the Ki-67 index of SSA-treated patients was significantly decreased, which suggests that SSA treatment might induce tumor shrinkage both by increasing apoptosis and decreasing cell proliferation in patients with acromegaly [33, 34]. Consistent with the literature, Ki-67 scores were lower in preoperative SSA-treated patients with macroadenomas than in the SSA-untreated group in our study.

Acromegaly is currently a disease with substantial mortality and economic burden [2–4]. Wilson et al. studied the costs of treatment in a total of 53 patients with acromegaly, with a mean follow-up of 49 months and found a mean annual cost per patient of $8111 [2]. Considering the studies in literature, medical treatment is the major contributor to the total cost of treatment in patients with acromegaly [2, 4, 35–37]. Treatment of patients with macroadenomas costs considerably more than for those with microadenomas, and the medications used in the treatment of acromegaly was the largest component (nearly 40%) of the overall cost of management [2]. In a study made by Roset et al., the mean annual cost of acromegaly was €9668 per patient; €2501 in patients who had surgery only and €9745 in patients who were treated medically [35].

Due to the high costs, management should be made according to the cost effectiveness of the treatment modalities [1, 6]. A systematic review performed by Moore et al. evaluated the economic burden of pegvisomant, which has the highest expenditure in acromegaly treatment, revealed its high level of clinical effectiveness, but also discovered that pegvisomant was not cost effective [37]. When other treatment options are considered, pegvisomant has much higher cost than cabergoline or SSA. However, as cited in studies; one should consider that costs of comorbidities in patients without remission were higher than those of controlled patients [36, 37]. Across our entire study population, the median annual costs of all acromegaly treatment modalities (medical, surgical and radiosurgical treatments) were €3788.4. In line with literature, the median annual cost of treatment for macroadenomas was significantly higher than for microadeadenomas. Compared with other studies, our annual treatment costs were found lower. The reason for this is that drug prices have been fixed in our country in the last ten years without changing with the exchange rate due to health fiscal policies, and the prices of medicines are lower than in other countries.

Few studies have investigated the cost effectiveness of pretreatment using SA in patients with acromegaly [28, 29]. A previous study evaluating preoperative SSA treatment performed by Framinan et al. revealed that preoperative treatment with SSA led to significant improvement in surgical results and was cost effective with an incremental cost effectiveness ratio (ICER) per patient/year one decade after surgery [28]. In this study, data were collected from three different centers, only macroadenoma patients were included and the treatment cost evaluated only with postoperative SSA and pegvisomant treatment. Postoperative evaluation periods were all different in the three mentioned meta-analyses. Another study by Duan et al. compared annual treatment costs of 11 patients with preoperative SSA treatment and 43 patients without preoperative SSA treatment who were diagnosed between 1994 and 2014 [29]. Postoperative long-term medical treatment costs in the preoperatively medically treated patient group were lower compared with the other patient group, but no evaluation for a statistical difference between the groups was performed. Secondly, the patients were followed up over a long period of time, as 1994–2014. Treatment options evolved considerably in that period; pegvisomant use was initiated in the 2000 s, which caused a major increase in treatment expenditure. Hence, this situation may have caused inequality and an iniquitus comparison about costs of treatment of the patients evaluated in the study. In our study, unlike other studies, the patients were diagnosed as having acromegaly between 2009 and 2016 and were followed and treated by a single center. Preoperative medical treatment costs in patients with both microadenoma and macroadenoma were compared. Different from the other two studies, we found that preoperative SSA treatment had no effect on the total costs of acromegaly treatment (medical, surgical and radiosurgical treatments) in long-term follow-up.

Transsphenoidal neurosurgery is the first-line treatment of acromegaly in the majority of patients. Outcome predictors include tumour size, cavernous sinus or dural invasion, pretreatment IGF-1/GH levels, and surgical expertise [1, 3]. Overall surgical remission rates are estimated as 75–90% for microadenomas and 10–60% for macroadenomas [3, 7, 8]. In our study, remission rates in patients with macroadenomas were low in concordance with the literature, and those of patients with macroadenomas were higher in the preoperative SSA-untreated group than in the SSA-treated group. This situation can influence both treatment costs and remission rates. Even though there was no significant difference in total treatment costs and late period remissions between both groups. In subgroup analysis, according to adenoma size, the percentage of reoperation requirement or RT use was also higher in preoperative SSA-untreated group with macroadenomas. However, this difference was not statistically significant. There were no statistically significant differences between other aggressive treatment options between the groups. When aggressive treatments applied that might affect late remission rates and treament costs were compared, there was no significant difference in high-dose SSA use and pegvisomant use, which are treatment modalities that increase treatment cost substantially. Nevertheless, reoperation and radiotherapy rates were significantly higher in the preoperative SSA-untreated group. When Table 4 is evaluated, which indicates the costs of all treatment strategies of acromegaly in our study, it can be seen that the costs of high-dose SSA for 3–4 months or PEG treatment of 1–2 months are equal to transsphenoidal surgery costs. Also, it is clear that PEG treatment of 1 month is more expensive than one session of RT (Gammaknife or Cyberknife therapy). In our study, despite the fact that the

number of patients who had macroadenomas was higher in the preoperative SSA-untreated group compared with the SSA-treated group, the increased late remission rates and lower treatment costs seem to be associated with aggressive treatments such as reoperation and radiotherapy. Owing to the substantial mortality and economic burden that remains with acromegaly, early diagnosis and control of the disease are essential [2–4]. As current guidelines suggest, in experienced centers, reoperation or radiotherapy in treatment-refractory patients can increase remission rates and diminish unnecessary high-dose medical treatment costs without any waste of time.

The study has some limitations. First, the study is retrospectively designed and the number of patients was small. In our study, we aimed to investigate the effects of preoperative SSA treatment on the cost of all acromegaly treatment modalities (medical, surgical and radiosurgical treatments), and also the effects on remission rates. However, the total cost of acromegaly treatment includes cost of diagnosis, treatment costs of complications after surgery or RT, and treatment costs of other disease-related complications such as medications for diabetes, and hypertension. We didn't include these costs. Nevertheless, preoperative SSA use in particular may have an effect on treatment costs of surgical complications. Thus, along with conflicting results in the literature, some studies indicate that SSA treatment decreases postsurgical complications and hospitalization duration [13].

In conclusion, according to the results of our study, preoperative medical treatment has no effect on the costs of acromegaly treatment. Although there is a benefical effect of preoperative SSA use on early remission in patients with acromegaly with macroadenomas, this effect does not persist in the long term. The benefical effect of preoperative SSA use on early remission was higher especially in invasive macroadenomas. Current guidelines do not recommend the routine use of SSA pretreatment prior to surgery in acromegaly, but the effect of preoperative SSA therapy on cost of illness in acromegaly, which has a high economic burden, may affect a clinician's management decision for acromegaly. Therefore, larger and prospectively designed studies are needed to investigate the effects of preoperative SSA therapy on cost of illness in acromegaly.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the local ethics committee of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Research involving human and animal participants This article does not contain any studies with animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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