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PROGETTO DI RICERCA:

PREVALENZA DELL'IPOPITUITARISMO SECONDARIO AD IPOFISITE INDOTTA DA IMMUNO CHECK-POINT INHIBITORS NEI PAZIENTI CON MELANOMA AVANZATO: VALUTAZIONE ORMONALE E RADIOLOGICA

TUTOR **CANDIDATO**

Prof.ssa Annamaria Colao **Dott.ssa Elisabetta Scarano**

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1. INTRODUCTION

Immunotherapy is wide spreading in the field of innovative cancer therapy. In particular, immune checkpoint inhibitors are approved for treatment of advanced melanoma (unresectable stage III and IV metastatic melanoma) (1). Blocking CTLA-4 (cytotoxic T lymphocyte-associated protein 4) by ipilimumab is the first systemic treatment in 30 years of intensive clinical research to show improved overall survival (OS) in stage IV melanoma patients in phase 3 trials (2,3). Currently, six immune checkpoint inhibitors (ICI) have been approved for the treatment of different advanced solid tumors: the CTLA-4 inhibitor ipilimumab; 2 PD-1 (programmed cell death protein 1) inhibitors, nivolumab and pembrolizumab; and 3 PD-L1 (programmed cell death 1 ligand 1) inhibitors, atezolizumab, avelumab, and durvalumab (4). Additionally, combination therapy of ipilimumab plus nivolumab has been approved for treatment of advanced melanoma (1). To understand how ICI manage to have such efficacy as antitumor therapies, it is necessary to know that Immune checkpoint molecules have an important function in regulating immune response: after binding to their ligands, these proteins can initiate either inhibitory or stimulatory pathways that modulate T-cell function (5). These novel antibodies release the brakes of the immune system and potentiate antitumor immune responses through the inhibition of receptors on immune and cancer cells such as CTLA-4 or PD- 1 and its ligand, PD-L1, whose function is to maintain self-tolerance (6). In particular, CTLA-4 was the first molecule to be identified as a co-inhibitory molecule and it is the counterpart of the co-stimulatory B7–CD28 axis (7,8). Following activation, T cells up-regulate surface expression of CTLA-4 that binds B7 with a higher avidity, and thus outcompetes

CD28's positive co-stimulatory signal. This dominance of negative signals results in reduced T cell proliferation and decreased IL-2 production (7,9). The PD-1/PD1-L1 pathway is not involved in initial T-cell activation: it regulates inflammatory responses in peripheral tissues sustained by already activated effector T-cells. Activated T-cells up-regulate PD-1 , inflammatory signals in the tissue and induce the expression of PD1-L1s, which downregulate the activity of T-cells, protecting normal tissues from collateral destruction; this mechanism is also used by tumor cells to evade the immune system response (10).

Blocking CTLA- 4, and thus freeing B7 for interaction with the co-stimulatory molecule CD28, results in the rejection of tumors and induced immunity to a secondary tumor challenge (11). At the same manner, PD1/PD1-L1 inhibition increases cytotoxic T-cell activity by expanding T-cell activation and proliferation (10).

Therefore, according to these mechanisms, ICI can at the same time induce T cells to fight cancer and bring the onset of autoimmune-like manifestations in different organ systems. Among these immune-related adverse events (irAEs), **endocrine dysfunctions** are the most common reported in clinical trials. All endocrine sites could be involved, thyroid (hypothyroidism, hyperthyroidism), pituitary (hypophysitis, Hypopituitarism), adrenal glands (primary adrenal insufficiency (PAI)) and pancreatic beta cells (insulin-deficient diabetes (IDD)) (12,13).

Other systems and organs involved are: **skin** (rash/inflammatory dermatitis; bullous dermatoses; Stevens-Johnson syndrome; toxic epidermal necrolysis; drug rash with eosinophilia and systemic symptoms syndrome; drug-induced

hypersensitivity syndrome; acute generalized exanthematous pustulosis; alopecia areata; vitiligo; psoriasis), **gastrointestinal system** (colitis; hepatitis; pancreatitis), **lung** (pneumonitis), **musculoskeletal system** (arthritis; polymyalgia-like syndrome; myositis; vasculitis), **kidney** (nephritis), **cardiovascular system** (myocarditis; pericarditis; arrhythmias; heart failure; vasculitis; venous thromboembolism), **nervous system** (Guillain-Barré syndrome; myasthenia gravis; peripheral neuropathy; autonomic neuropathy; aseptic meningitis; encephalitis; transverse myelitis), **hematologic system** (autoimmune hemolytic anemia; acquired thrombotic thrombocytopenic purpura; hemolytic uremic syndrome; aplastic anemia; lymphopenia; immune thrombocytopenia; acquired hemophilia), **eye** (uveitis; iritis; episcleritis; blepharitis) (14) .

In particular, hypophysitis has an overall incidence of 12% in patients treated with anti-CTLA-4 antibodies and 0.5% in patients treated with anti-programmed death 1 (PD1) antibodies (4,15). The pathogenesis of anti-CTLA-4 antibody-induced hypophysitis involves type II and IV hypersensitivity, as well as the humoral immune response. This has been suggested by histopathological findings of patients with hypophysitis following treatment with Ipilimumab (alone or in combination with Nivolumab or Pembrolizumab), evidence of pituitary antibodies in the serum of these patients, association with specific human leucocyte antigens, and animal models of anti-CTLA-4-induced hypophysitis (16-21).

Regarding the pathophysiology of anti-PD1/PD1-L1 antibody-induced hypophysitis there are no secure evidences, but it seems that immune response reactivation most likely targets ACTH-secreting cells because of the very frequent isolated ACTH deficiency (22). Moreover, a higher prevalence of anti-pituitary and anti-

hypothalamus antibodies in patients with cancer treated with anti-PD1/PD1-L1 agents has been found (23).

There are some differences between primary hypophysitis and ICI hypophysitis (16, 22, 24). ICI hypophysitis seems to be more frequently associated with hypopituitarism at diagnosis and more frequent male (16,25). In both ICI hypophysitis and primary hypophysitis there are initial deficits of ACTH, FSH/LH and TSH, but symptoms of adrenal insufficiency and confirmed ACTH deficiency are much more common in patients with immune checkpoint inhibitors induced hypophysitis (4, 15, 16). Central insipidus diabetes is extremely rare in immuncheckpoint induced hypophysitis. Morphological modifications and visual alterations are much more common in primary hypophysitis (16, 22).

According to the degree of symptoms and of the severity of the disease, there are four grades of immune checkpoint induced hypophysitis (26):

1. **Grade 1**: Asymptomatic or mild symptoms
2. **Grade 2**: Moderate symptoms, able to perform activity of daily living
3. **Grade 3**: Severe symptoms, medically significant consequences, unable to perform activity of daily living
4. **Grade 4**: Severe symptoms, life-threatening consequences, unable to perform activity of daily living

The last condition is death which is often considered as Grade 5.

In case of G1-G2 hypophysitis current guidelines suggest clinicians to consider continuing treatment and maintaining patient in a stabilized hormone replacement (14). Hypophysitis is often self-limiting and most of patients do not show progression of sella compression. Therefore, in case of G3-G4 grade

hypophysitis, an accurate decision, involving the possibility of a significant impact on the progression-free survival of the underlying malignancy, must be taken(14). In some cases of G3-G4 hypophysitis, high-dose corticosteroid therapy is required during the acute phase and it may result in inflammation reversal and ameliorate the compression of sella and parasellar structures. The impact of high dose glucocorticoids on antitumor effect of immune checkpoint inhibitors was investigated. Results are discordant: some studies suggest a neutral effect on survival (27-29) and others show reduced survival among patients with melanoma treated with high-doses glucocorticoids for Ipilimumab-induced hypophysitis (30,31).

Also, pituitary MRI is important for the differential diagnosis of other pituitary lesions, in particular metastases. In hypophysitis MRI major findings are: mild-to-moderate diffuse enlargement of the pituitary (up to 60-100% of the baseline size), homogeneous (more frequent) or heterogeneous enhancement (less frequent) post-gadolinium, empty sella (especially in the long term), extension into the cavernous sinus or above the sellar diaphragm (uncommon), suprasellar extension with compression and displacement of the chiasm (uncommon), thickness but not deviation of the pituitary and preservation of posterior pituitary signals (in most of cases) (32-36). Pituitary enlargement resolves in most cases over weeks/months. (33).

A common concern with immunotherapies is that their toxicity profile might diminish health-related quality of life (HRQoL), even when meaningful disease outcomes are observed. There is an increasing importance of considering HRQoL during treatment decision-making in oncology. Regarding considerations about

alterations in quality of life (QoL) of these patients, some studies support the evidence of unchanged parameters during follow up especially for nivolumab alone or ipilimumab+nivolumab treatment (37, 38,). Some worsening changings are reported for ipilimumab treatment (37). No specific data were reported in particular conditions of hypophysitis.

2. OBJECTIVES

The aim of our study was to evaluate prevalence of hypopituitarism secondary to hypophysitis in patients with advanced melanoma (unresectable stage III or IV melanoma) undergoing CTLA-4 (cytotoxic T lymphocyte-associated protein 4) inhibitors and PD-1 (programmed cell death protein 1) inhibitors at baseline and after 12 months of treatment.

The secondary aim of our study was to evaluate quality of life in all patients at baseline and after twelve months.

3. PATIENTS AND METHODS

The study was conducted in line with the Guidelines for Good Clinical Practice. All patients provided written informed consent before entering the study, with respect to study participation, and confidentiality statement of data collection according to the Italian privacy policy.

3.1 PATIENTS

In this study we evaluated 52 (34M, 18F, age 36-70 years, median 58.09±9.30) (**Table 1**) consecutive patients with advanced melanoma (unresectable stage III or IV melanoma) treated with CTLA4 (Ipilimumab) and PD 1 inhibitors (nivolumab) followed at the Oncological Endocrinology outpatient clinic of A*ORN dei Colli Ospedale Monaldi* in Naples, Italy from 2018 to October 2021.

The following exclusion criteria were considered: 1) patients with previous diagnosis of endocrine or neuroendocrine disease; 2) patients with previous treatment with others immune check-points inhibitors; 3) patients who underwent corticosteroid therapy during the two months before enrolment in the study. During the observation period of 12 months for each patient, 11 patients died because of the primary disease and no one of these patients developed hypopituitarism.

3.2 METHODS

This is an on-going, prospective study. Hormonal parameters were evaluated in all patients at baseline and every four weeks after immunotherapy was started, until diagnosis of hypopituitarism was confirmed. In all patients we performed a Quality of Life (QoL) questionnaire (EQ-5D-3L) (39,40) at baseline and after 12 months. In patients with confirmed hypopituitarism, substitutive hormonal therapy was started and hormonal parameters were checked at 1, 2, 3, 6 months until the end of the 12 months observation period. Moreover, in all patients with pituitary deficiency we performed computerized virtual field testing and magnetic resonance imaging (MRI) to find radiological modifications at diagnosis and after 12 months.

3.2.1 Treatment regimens

All patents received treatment with Ipilimumab (10 patients) or Ipilimumab + Nivolumab (42 patients) with therapeutic schemes according to current guidelines (41). Moreover, patients with hormonal deficits began replacement therapy with glucocorticoids, thyroid hormones, testosterone, estrogen and progestogen, and desmopressin, where necessary (42).

3.2.2 Biochemical analysis

Hypopituitarism was diagnosed based on the clinical manifestations, the baseline assessment of pituitary function and stimulus test, according to the Clinical Practice Guidelines of the Endocrine Society (42). Peripheral venous blood samples were taken in the morning between 8 and 10, after an 8 hour fasting and stored

at -80 ° C until processing. Hormonal profile evaluation, Insuline-like Growth Factor 1 (IGF-1), Thyroid Stimulating Hormone (TSH), Follicle- Stimulating Hormone (FSH), Luteinizing Hormone (LH), Adrenocorticotropic Hormone (ACTH), cortisol, testosterone, estradiol, free forms of thyroid hormones and prolactin, was performed by chemiluminescence immunoassay (CLIA).

3.2.3 Morphological and visual evaluation

Computerized visual field and magnetic resonance imaging (MRI) with gadolinium contrast enhancement were performed in all patients with hypopituitarism at baseline and after 12 months in order to identify radiological signs of hypophysitis (moderate gland enlargement, symmetrical suprasellar gland extension, generally homogeneous contrast enhancement, empty sella as atrophic response after the inflammatory process, thickened and not deviated pituitary stalk, absence of posterior pituitary bright spot on T1w images, adjacent dural enhancement, sphenoid sinus mucosal thickening) (43).

3.2.4 Quality of life assessment

We evaluated the health-related QoL of all patients at baseline and after 12 months using the EQ-5D-3L standardized instrument (39, 40). Italian-translated versions of HRQL questionnaire was administered. The EQ-5D 3L is a validated, self-reported, generic measure of HRQoL composed of the EQ-5D utility index and EQ visual analog scale (VAS) (44). The EQ-5D utility index comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and

anxiety/depression), each having 3 assessment levels (1=no problem, 2=moderate problem, 3=severe problem) (45, 46) A summary index with a maximum score of 1 can be derived from these five dimensions by conversion with a table of scores. The maximum score of 1 indicates the best health state, in contrast with the scores of individual questions where higher scores indicate more severe or frequent problems. The EQ VAS evaluates the patient's self-rated health state on a 100-point vertical VAS (0, worst imaginable health state; 100, best imaginable health state) (40). According to published estimates for the EQ-5D-3L (40), a change in quality of life was considered to be clinically meaningful if the mean changes from baseline in the index score were above (better) or below (worse) the bounds of 0.08 (39, 40) for EQ-5D utility index and ≥7 for the EQ-5D VAS score (40)

3.2.5 Statistical analysis

Data were analysed using the SPSS Software (PASW Version 21.0, SPSS Inc., Chicago, IL, USA) and MedCalc® package (Version 12.3.0 1993–2012 MedCalc Software bvba-MedCalc Software, Mariakerke, Belgium). Results were described as mean ± standard deviation (SD) or percentage/number. Comparison of prevalence between baseline and 12 months was performed with Fisher's extact test. The t student test was used for intergroup comparison. P values < 0.05 were considered statistically significant.

4. RESULTS

4.1 PREVALENCE OF HYPOPITUITARISM

In our studied population the prevalence of hypopituitarism is 21.15 % (11) , in majority male patients (8) (**Table 1**). Specific prevalence of each pituitary deficit is reported in **Table 2**. No patient reported hyperprolactinemia and insipidus diabetes. The onset of presentation was variable and more frequent between 4 and 12 weeks after treatment start (**Figure 1**).

After 1 year follow up all patients with hypopituitarism were alive. Secondary adrenal insufficiency was found in 90.9 % (10) while hypothyroidism persisted only in 18.18 % (2) of patients with a significant reduction (**Table 2**).

4.2 RADIOLOGICAL AND VISUAL ALTERATIONS

We found radiological alteration in 9 (81.81%) patients with hypopituitarism. The most frequent alteration was gland enlargement **(Table 3**) (**Figure 2**). After 12 months MRI alterations decreased significantly and were found only in 2 (18.18%) patients ($p < 0.05$) (**Table 3**). Regarding visual field alterations, only one patient reported bitemporal hemianopia which reverted after 12 months (**Table 3**).

4.3 QUALITY OF LIFE

All hypopituitary (11) patients completed HRQoL questionnaire at baseline and at the end of the study. In the non-hypopituitary group 11 patients died during the study, therefore HRQoL questionnaire was performed in 41 patients at baseline and in 30 patients at 12 months (**Table 4**). The mean EQ-5D utility index baseline

scores were 0.582 (SD 0.300) for hypopituitary patients and 0.754 (SD 0.296) for all other patients. At 12 months the mean scores were 0.8003 (SD 0.310) and 0.775 (SD 0.313) for hypopituitary patient and other patients respectively (**Table 4**). From baseline to late 12 months observation changes in the index EQ-5D utility index score were out of the 0.08 boundary in patients with hypopituitarism and within the 0.08 boundary in patients without hypopituitarism (**Table 4**). For the EQ-5D VAS, the mean baseline scores were 64.7 (SD 12.9) for hypopituitary patients and 70.5 (SD 8.64) for other patients. At 12 months the mean scores were 72.7 (SD 9.71) and 73.1 (SD 8.80) for hypopituitary patient and other patients respectively (**Table 4**). The change for EQ-5D VAS was > 7 from baseline to 12 months in hypopituitary patients and < 7 in non-hypopituitary patients (Table 4). There was a statistically significant difference between hypopituitary e non hypopituitary group at baseline for EQ-5D utility index and VAS (**Table 4**).

5. DISCUSSION

This is a single centre prospective study analysing the prevalence of hypopituitarism in patients with advanced melanoma undergoing CTLA-4 and PD-1 inhibitors treatments. At first the study design regarded only patients undergoing ipilimumab treatment, but subsequently we enrolled patients under ipilimumab+nivolumab treatment too, according to the current guidelines (41). Infact, the characteristics of the combination therapy (ipilimumab+nivoloumab) patients are similar to ipilimumab monotherapy hypophysitis patients (15) and considering that hypophysitis is much more common following treatment with ipilimumab, this medication is likely the more dominant contributing factor in the presentation of combination therapy induced hypophysitis (15, 25);therefore we excluded patients with other treatment regimens (for example pembrolizumab). This distinction between anti-PD-1 and ipilimumab is linked to the different mechanism proposed for ipilimumab-mediated hypophysitis, in which there is a direct targeting of anterior pituitary cells by the monoclonal antibody (16, 18, 47), and anti- PD1 hypophysits pathogenetic effect, which is IgG4-based and does not effectively activate the classical complement pathway or antibody-dependent cell mediated cytotoxicity (16, 18, 47). Precise mechanistic details for anti-PD-1-associated hypophysitis are currently unknown.

Our analysis confirms the specific endocrinological adverse events that can occur in these patients and adds informations about quality of life alterations and modifications during treatment with or without hypopituitarism onset.

Meta-analysis by Barroso-Sousa et al. (4) and by Faje et al. (15) were derived from prospective and retrospective oncologic studies respectively, about the use of

immunotherapy in all type of cancers. They reported a low rate of hypophysitis compared to our study, but they analize the rate for anti-PD-1 monotherapy patients, that is known to be lower than ipilimumab monotherapy. Infact, the group of Faje et al. (15) reported a rate of hypophysitis in ipilimumab monotherapy patients quite similar to our study in which the analysis was conducted in ipilimumab monotherapy and ipilimumab+nivolumab combined therapy and this fact can explain differences. Moreover, we studied in particular the incidence of hypopituitarism and not only of hypophysitis, reporting the rate of MRI alterations. The group of Barroso-Sousa et al. (4) reported a lower rate of hypophysitis in ipilimumab monotherapy compared to our study. This discordance can be explained by the fact that the presence or absence of other medication-related effects (such as exogenous glucocorticoids) is not well specified and a difference between primary versus central deficit is lacking.

Some prospective studies reported, in the same way, the rate of all endocrine adverse events. In particular, the study for ipilimumab monotherapy in melanoma by Hodi et al., reported events for hypophysitis, hypopituitarism and adrenal insufficiency separately (2). Postow et al. listed separate categories for the following: thyroid disorder, blood TSH decreased, hypophysitis, adrenal insufficiency, hypothyroidism and hyperthyroidism (48). Calculating accurate estimates of risk from such studies is challenging.

About the time of diagnosis after treatment start our findings are in line with data reported in literature (15) in which the more frequent time of presentation was between 4 and 12 weeks after treatment start. In the meta-analysis of Faje et al. (15) a difference with treatment with PD-1 monotherapy not considered in our

study was reported. In patients treated with anti-PD-1 monotherapy, hypophysitis was diagnosed at more variable and later time points than those receiving ipilimumab monotherapy or combination therapy. Authors explain this difference with a frequent lack of localizing symptoms or pituitary enlargement on MRI in the majority of anti-PD-1 monotherapy hypophysitis patients which can be explained also with the delay in clinical and biochemical diagnosis. Most of our hypopituitary patients had an alteration in MRI findings (especially pituitary enlargement) which often resolves rapidly in patients with hypophysitis secondary to ipilimumab (30). This fact can explain the absence of MRI alteration in some of our patients with hypopituitarism in which the diagnosis was obtained later than the occurrence of morphological modifications and also explains the absence of radiological signs in the majority of hypopituitary patients at 12 months follow up. The low percentage of visual defect findings is probably due to this condition, too.

Regarding data on QoL of these patients, our study found a clinically meaningful change from baseline to 12 months in hypopituitary group with a significant lower score in hypopituitary patients than no-hypopituitary patients at baseline. The unchanged score in no hypopituitary patients is in line with data reported in literature (37, 38, 49) for patients in treatment with ipilimumab+nivolumab and nivolumab alone. Some authors reported a worsening of QoL in patients in treatment with ipilimumab alone (37), but in our work we did not study these differences, considering all patients together.

However, these studies did not consider separately the onset of endocrine side effects. In fact, it is known that hypopituitarism is associated to higher mortality and lower QoL (50-52) and this evidence is probably the reason why in our study

patients with hypopituitarism had a lower HRQoL than patients without hypopituitarism. The replacement hormonal therapy ,started in our hypopituitary patients, improved clinical and hormonal status and this explains the improvement in QoL at 12 months in our hypopituitary cohort. This data are also confirmed by the QoL studies carried out in patients with pituitary diseases (53,54). Moreover, in our study the HRQoL did not differ between the two groups of patients at 12 months of observation, suggesting that hypopituitarism associated to hypophysitis, when well treated, did not lead to a continuous QoL worsening.

A limitation of our study is the relatively small cohort, due to the rare endocrinological adverse event and to a difficulty in enrollment phase especially during 2020 due to covid pandemic period. Another limitation is the lack of considerations about differences in various treatment regimens.

Strong points are the prospective design of the study and considerations about quality of life in this particular category of patients.

6. CONCLUSION

Immunotherapy with Ipilimumab alone and Ipilimumab+ nivolumab for advanced melanoma is associated with high risk of acquired hypopituitarism. The pituitary defect is often multiple with secondary thyroid and adrenal disfunction being the most frequent ones. In some cases, the functional impairment seems to occur in the absence of a well-defined morphological damage suggesting the need to establish a well-defined endocrinological adverse event program monitoring for these patients. From a practical point of view, a neuroendocrine follow-up over time is always mandatory in these patients. The QoL of life of these patients seems to be affected by the presence of hypopituitarism at diagnosis but during follow up this difference disappeared, especially when endocrinopathy is well monitored and treated. Further studies therefore appear necessary in this regard. It may be useful, in the future, for larger-scale and longer-follow-up studies to analyse the changes in QoL in patients with hypopituitarism and hypophysitis secondary to immunotherapy for advanced melanoma.

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8.TABLES AND FIGURES

Table 1. Patients characteristics (n 52)

Parameters	**Baseline**
Age (years) mean±SD	58.09±9.30
Gender (M/F) n	34/18
Treatment regimen (Ipi/Ipi+Niv) n	10/42
Hypopituitarism Diagnosis n (%) (M/F)	11 (21.15) (8/3)

SD: standard deviation; Ipi: Ipilimumab; Ipi+Niv: Ipilimumab+Nivolumab.

Table 2. Immune checkpoint inhibitor-associated hypopituitarism

Pituitary deficiency n (%)	**Baseline**	**12 Months**	**P value**
Hypoadrenalism	7 (63.63)	10 (90.90)	NS
Hypothyroidism	8 (72.72)	2 (18.18)	p <0.05
Hypogonadism	5 (45.45)	1 (9.09)	0.05
Hyperprolactinemia	0	0	NS
GHD (Low IGF-I)	1 (9.09)	0	NS
Diabetes Insipidus	0	0	NS

GHD: growth hormone deficiency; IGF-I: insuline like growth factor-I. NS: not significant

Table 3. Radiological and visual field modification in hypopituitary patients

	Baseline	**12 months**	**p value**
MRI findings abnormalities n (%)	9 (81.81)	2 (18.18)	p <0.05
Moderate gland enlargement	8 (72.72)	0	p <0.05
Symmetrical suprasellar gland extension	2 (18.18)	0	NS
Homogeneous contrast enhancement	11 (100)	11 (100)	NS
Empty sella	0	2 (18.18)	NS
Thickened and not deviated pituitary stalk	3 (27.27)	0	NS
Adjacent dural enhancement	0	0	NS
Absence of posterior pituitary bright spot on T1w images	0	0	NS
Sphenoid sinus mucosal thickening	0	0	NS
Visual Field modification n (%)	1 (9.09)	0	NS
Bitemporal hemianopia	1 (9.09)	0	NS
Right temporal hemianopia	0	0	NS
Left temporal Hemianopia	0	0	NS
Other visual defects	0	0	NS

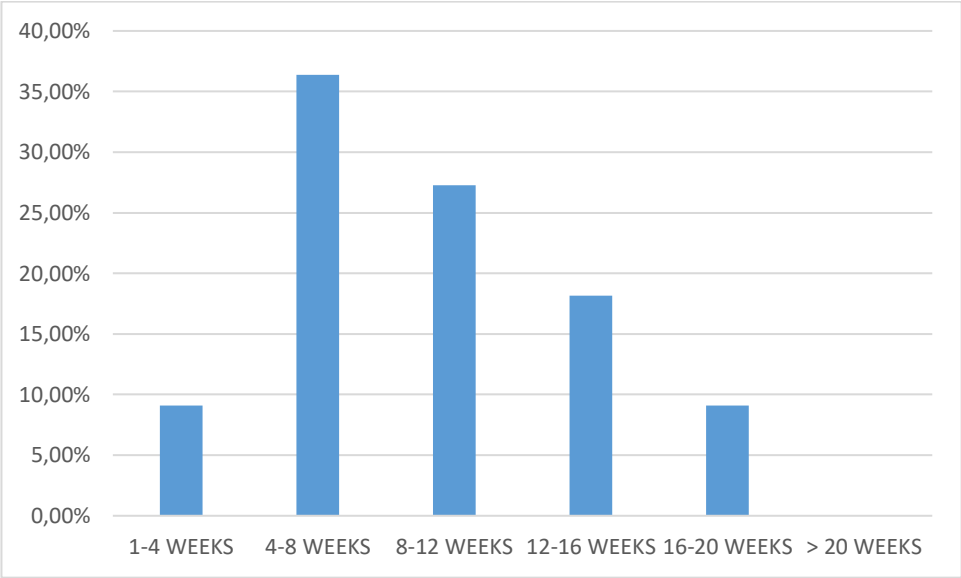
NS: not significant.

Table 4. EQ-5D utility index and EQ-5D VAS scores at baseline and after 12 months in hypopituitary and no-hypopituitary patients.

EQ-5D utility index		Hypo patients (11)	No-hypo patients (41)	p value
	Baseline (SD)	0.582 (0.300)	0.754 (0.296)	P <0.05
	12 Months (SD)	0.800 (0.310)	0.775 (0.313)	NS
EQ-5D VAS		**Hypo patients (11)**	**No-hypo patients (30)**	
	Baseline (SD)	64.7 (12.9)	70.5 (8.64)	P<0.05
	12 Months (SD)	72.7 (9.71)	73.1 (8.80)	NS

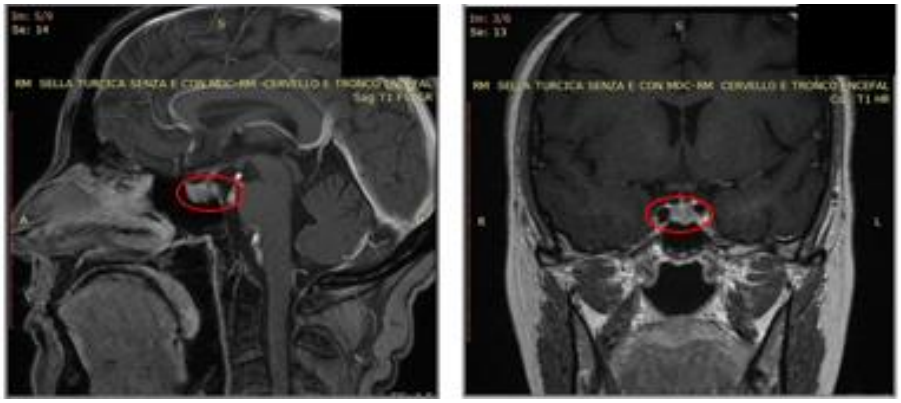
Hypo patients: hypopituitary patients; No-hypo patients: no-hypopituitary patients

Figure 1. Time to diagnosis of Hypopituitarism after treatment initiation (weeks)



1-4 weeks: 9.09% (1); 4-8 weeks: 36.36%; 8-12 weeks: 27.27% (3); 12-16 weeks: 18.18 % (2); 16-20 weeks: 9.09% (1); > 20 weeks: 0.

Figure 2. Morphological modification



Pituitary enlargement at MRI