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Julia Campos-Fernández*, Esperanza Aguillo-Gutiérrez, Ana Agudo-Tabuenca, Ana Lidia Medrano-Navarro, Laura Borau-Maorad

Servicio de Endocrinología y Nutrición, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain

* Corresponding author.
E-mail address: juls.campos@gmail.com
(J. Campos-Fernández).

2530-0180/

Utility of elastography in thyroid nodules with indeterminate cytology☆

Utilidad de la elastografía en los nódulos tiroideos con citología indeterminada o sospechosa de malignidad

The widespread use of neck imaging methods has increased the number of diagnoses of asymptomatic thyroid nodules. Ultrasound studies in the population have found thyroid nodules in up to 67% of cases, most of them benign (93–97%).[1–3] A major challenge is to determine whether they are malignant or benign without the need for surgery.[1,2] Fine needle aspiration (FNA) is currently the gold standard for the diagnosis of thyroid nodules. However, approximately 15–20% of the results are histologically undefined and therefore not diagnostic, which means that they have to be operated on in order to rule out malignancy.[1]

Medical advances and the development of new non-invasive, more sensitive diagnostic methods now supplement the information provided by FNA. This is especially relevant for cytological samples classified as Bethesda category III (atypia of undetermined significance or follicular lesion of undetermined significance) and IV (follicular neoplasm or suspicious for a follicular neoplasm), in which it is difficult to rule out malignancy without surgery. High-resolution ultrasound allows malignancy to be detected in a high percentage of cases, but the chances of making an accurate diagnosis are still limited.[3] Thyroid elastography is a new technique that estimates the viscoelastic properties of tissues using ultrasound, and is a promising test for ruling out thyroid malignancy and decreasing the number of surgical procedures when reasonable doubt has been cast by other tests.[4]

The objective of this study was to assess the value of elastography for distinguishing patients with Bethesda categories III or IV cytology who were candidates for surgery.

Since 2012, all patients at our center with a thyroid nodule have had thyroid elastography performed, and their data prospectively recorded in a database. From that database, patients with solitary thyroid nodules or dominant nodules within multinodular goiter were selected. Patients with prior thyroid surgery, FNA performed the month before elastography, and macrocalcifications in the nodule detected by ultrasonography were excluded. Patients with samples classified as Bethesda III and IV were selected for this study. Elastography was performed by an experienced radiologist after an ultrasound examination. The pressure applied during elastography is assessed by the quality factor (QF) on a scale of 0–100 random units. Only the images captured with QF > 50, showing fewer artifacts, were assessed. There are five elastographic patterns[5]: (I) no or small area of stiffness; (II) area of stiffness <45%: the nodule is homogeneously deformed; (III) area of stiffness >45%: the center of the nodule is deformed less than the peripheral tissue; (IV) peripheral areas of stiffness and central area of elasticity: the whole nodule is deformed less than the surrounding tissue; and (V) area of stiffness occupying the whole nodule: the nodule and surrounding tissues are less deformed than the rest of the gland.

All patients underwent surgery, and nodules were classified as benign or malignant based on the histological study. Descriptive statistics were obtained, and Student's *t* and Chi-square tests were performed. Taking elastography patterns IV and V as malignant, sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

☆ Please cite this article as: Ríos A, Rodríguez JM, Cepero A, Hernandez AM. Utilidad de la elastografía en los nódulos tiroideos con citología indeterminada o sospechosa de malignidad. Endocrinol Diabetes Nutr. 2017;64:180–182.

Table 1 Relationship between elastography and definitive histology of the thyroid nodule in nodules classified as Bethesda categories III or IV.

	Malignant histology	Benign histology
Elastographic pattern I (n = 0)	0	0
Elastographic pattern II (n = 18)	0	18
Elastographic pattern III (n = 20)	0	20
Elastographic pattern IV (n = 9)	8	1
Elastographic pattern V (n = 2)	2	0
	10	39

Forty-nine thyroid nodules classified as Bethesda categories III and IV were selected. Elastography showed pattern II in 18 cases (36.7%), pattern III in 20 (40.8%), pattern IV in 9 (18.4%), and pattern V in 2 (4.1%). As is shown in Table 1, 10 of the 49 nodules were histologically malignant (20.4%). All cases with elastographic pattern V were malignant. All cases but one with pattern IV were malignant. All cases with patterns II and III were benign ($p < 0.001$). Elastography has a sensitivity of 91%, a specificity of 97%, a positive predictive value of 91%, and a negative predictive value of 100% for detecting malignancy. In 25 patients (51%), ultrasonography performed prior to elastography showed some characteristics which led to malignancy being suspected.[3] All 10 patients with malignant histology had at least one such characteristic of malignancy. According to the ultrasonographic classification Thyroid Imaging Reporting and Data System (TI-RADS),[6] 24 patients (49%) had TI-RADS 2 or 3, none of them associated with malignancy; the elastographic pattern in these patients was II or III. In the remaining 25 cases (51%), the TI-RADS was 4. Of these, 16 (33%) were TI-RADS 4a: only two of them had an elastographic pattern higher than III, and one had an associated carcinoma. Of the remaining nine patients, six had TI-RADS 4b and three TI-RADS 4c, in all cases with elastographic patterns IV–V, and one was found to have a carcinoma in the final histology. The correlation between elastography and the TI-RADS was significant ($p < 0.001$) for the association with malignancy.

In thyroid nodules classified as Bethesda category III or IV, elastography allows us to determine which patients may be followed up with a high certainty that they are benign. Thus, elastographic patterns II and III allow for patient follow-up with ultrasonography and elastography. Cantisani et al. also showed, in a prospective study with 140 nodules[7] the diagnostic value of elastography for thyroid nodules with indeterminate cytology. However, it should be noted that while quality studies such as those mentioned above suggest this predisposition, authors such as Lippolis et al.[8] did not confirm the value of elastography for the preoperative selection of nodules with indeterminate cytology. In a meta-analysis, Bojunga et al. stated that elastography may be an alternative to cytology for patient selection.[9] The systematic review and meta-analysis conducted by Remonti et al. added that the combination of different ultrasonographic characteristics seems to increase the ability of elastography to detect malignant nodules.[10] Our data support the importance of correlating elastography with ultrasound in these patients. Thus, as Trimboli et al.[11] observed in a prospective study, the grouping of ultrasound characteristics in the TI-RADS classification combined with elastography increases the sensitivity for detecting malignancy.

To conclude, based on our results, it may be stated that thyroid elastography is currently a diagnostic tool that supports ultrasonography in patients with Bethesda III or IV cytologies, so helping in the selection of candidates for surgery.

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Antonio Ríos[a,b,c,*], Jose Manuel Rodríguez[a,b,c], Angela Cepero[d], Antonio Miguel Hernandez[e]

[a] *Departamento de Cirugía, Pediatría y Obstetricia, y Ginecología, Universidad de Murcia, Murcia, Spain*
[b] *Servicio de Cirugía General y de Aparato Digestivo, Hospital Clínico Universitario Virgen de la Arrixaca, Servicio Murciano de Salud, El Palmar, Murcia, Spain*
[c] *Instituto Murciano de Investigación Bio-Sanitaria Virgen de la Arrixaca (IMIB-Arrixaca), Murcia, Spain*

[d] *Servicio de Radiología, Hospital Clínico Universitario Virgen de la Arrixaca, Servicio Murciano de Salud, El Palmar, Murcia, Spain*
[e] *Unidad de Docencia y Formación Continuada, Servicio de Endocrinología y Nutrición, Hospital Clínico Universitario Virgen de la Arrixaca, Servicio Murciano de Salud, El Palmar, Murcia, Spain*

* Corresponding author.
E-mail address: arzrios@um.es (A. Ríos).

2530-0180/

Hypothalamic obesity after craniopharyngioma surgery: Treatment with a long acting glucagon like peptide 1 derivated☆

Obesidad hipotalámica tras intervención quirúrgica de un craneofaringioma: tratamiento con un análogo del péptido similar al glucagón tipo 1

Obesity may be present in patients with primary hypothalamic lesions, particularly craniopharyngioma (CP), but it is also the most common complication after its surgical treatment.[1–4] The hypothalamic nuclei, responsible for appetite and basal metabolism, are implicated in its pathogenesis.[5,6] There is currently no effective treatment.[5] We report the case of a patient with hypothalamic obesity following surgery for CP who responded to treatment with a glucagon-like peptide-1 (GLP-1) analogue.

The patient, a 30-year-old woman referred from another hospital, had undergone surgery for CP at the age of 11 years and required another two surgical procedures and radiation therapy. She had panhypopituitarism with primary amenorrhea, daytime somnolence, and slight intellectual impairment. Patient complained of excess appetite and episodes of binge eating. Shortly after surgery, she was diagnosed with diabetes mellitus, and insulin therapy was started. She is on hormone replacement therapy with levothyroxin 200 mcg/day, hydrocortisone 25 mg/day in three divided doses (15 mg–5 mg–5 mg), antidiuretic hormone (six intranasal applications daily), transdermal patches with 600 mcg of ethinylestradiol/6 mg of norelgestromin (one weekly patch three weeks per month). Antidiabetic treatment consists of metformin/vildagliptin 1000/50 mg/12 h, insulin detemir 12 IU/12 h, and insulin glulisine as needed (5–10 IU with each meal). Her blood glucose control has always been poor, with hypoglycemic episodes and obesity. Patient is also being treated with valproic acid 1000 mg/12 h, topiramate 100 mg/12 h, perampanel 18 mg/24 h, fluoxetine 40 mg/24 h, and levetiracetam 1000 mg/12 h. Physical examination found a height of 161 cm, 88 kg of weight (body mass index 34), sexual infantilism with telarche but no adrenarche, and mild diabetic retinopathy.

Table 1 shows her relevant laboratory data. We decided to modify treatment by adjusting levothyroxin to 225 mcg/day, changing to insulin degludec 19 IU at night and metformin 1000 mg/12 h, and adding dulaglutide 1.5 mg one application each week. Start of growth hormone treatment was delayed because of poor blood glucose control at the time and presence of diabetic retinopathy.

After two months, patient reported that a decreased appetite and absence of binge eating episodes or hypoglycemia. She was less drowsy. She had lost 10.3 kg, and basal insulin dose had to be gradually tapered, while prandial insulin dose was decreased to 6–6–3 (Table 1). Levothyroxin was increased again to 250 mcg/day due to persistently low T4 levels. On the third month, rapid insulin was discontinued based on capillary glucose levels.

Research conducted over the past few decades has shown that the body's energy homeostasis depends on: (1) infundibulo-tuberal nuclei; (2) peripheral tissues (white and brown adipose tissue); (3) autonomic nervous system; (4) hormonal and metabolic signals (insulin, glucocorticoids), and gastrointestinal tract signals.[4,7]

After surgery and radiation therapy for CP, patient experienced panhypopituitarism, *infundibulo-tuberal syndrome* (diabetes insipidus, somnolence, and adiposogenital dystrophy[1,2]), and diabetes mellitus. Infundibulo-tuberal syndrome is the result of damage to the arcuate, ventromedial, tuberal, and tuber cinereum nuclei.[1,6] Additionally, despite the age of onset, diabetes mellitus was not caused in this patients by autoimmune pancreatic failure but more probably by damage to the arcuate nucleus, which has leptin receptors responsible for regulating glucose metabolism, modulating the function of the sympathetic nervous system.[6]

Obesity is common in patients with hypothalamic lesions (25%), but is rarely the first symptom. Obesity usually occurs when large lesions are present. Specifically, bilateral destruction of ventromedial nuclei causes obesity, and is due in 90% of cases to tumors, of which CP is most common (60% of cases).[8] A 70% prevalence of obesity has been reported with this tumor. After surgery, obesity appears as a complication in 50% (30–77%) of patients in whom it did not exist before, half of them with severe hyperphagia.[1,4,9,10]

Four risk factors for development of obesity after treatment of brain tumors in children have been reported[5]: (1) tumor location in hypothalamus or thalamus; (2) diencephalic tumors; (3) direct radiation to hypothalamus; (4) concurrent hormone deficiency. All these circumstances, present in our patient, reflect hypothalamic damage. It has been postulated that topographic location of CP is

☆ Please cite this article as: Castro-Dufourny I, Carrasco R, Pascual JM. Obesidad hipotalámica tras intervención quirúrgica de un craneofaringioma: tratamiento con un análogo del péptido similar al glucagón tipo 1. Endocrinol Diabetes Nutr. 2017;64:182–184.