

COVID-19 pandemic and thyroid cancer

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ABSTRACT

Thyroid domain amid COVID-19 era has been involved in many ways, either in terms of patients with prior thyroid conditions who become COVID-19 positives, or coronavirus-induced *de novo* thyroid anomalies. This article represents a literature update on thyroid cancer (TC). The PubMed-based research includes a publication timeline regarding the first two years of pandemic (2020-2021). The general scientific interest on TC according to online research decreased during the first half of 2020 and got to the pre-pandemic level by the end of 2020. At the beginning of the pandemic, there was a delay in approaching the thyroid conditions, while telemedicine became a most useful tool, as seen in others areas of medicine. Post - 2020 lockdown medical presentation was associated with a more aggressive behavior of TC when compare to pre-pandemic data. Ongoing debates surround the topic of higher risk of COVID-19 infection in patients with a prior diagnostic of a thyroid malignancy in terms of having a higher risk of contracting the infection or an increased risk of developing a more severe form. There is not clear answer up to this point. Recent assets concerning TC field (non-COVID-19 data) that are released for the last two years concern the understanding of thyroid cancer genetics, the approach of shift from differentiated to anaplastic carcinoma, as well as evidence regarding new players in the oncological endocrinology like tyrosine kinase inhibitors for advanced forms of radioiodine refractory TC. For what we know so far, by the end of the second pandemic year, the patients with TC do not represent a fragile population when facing COVID-19 infection itself. However, the delay of adequate therapy amid restrictions is reflected in more severe malignancy behavior, while general concerns about the virus and pandemics increase the level of psychological and social stress. Case finding strategies to detect high risk patients as those on tyrosine kinase inhibitors with potential lung complications are needed.

Keywords: thyroid, cancer, neoplasia, tumor, differentiated thyroid cancer, ultrasound, pandemic, COVID-19

INTRODUCTION

Thyroid domain amid COVID-19 era has been involved by the presence of euthyroid sick syndrome in severe infections, a new type of subacute thyroiditis which is virus-triggered, by the risk of developing central hypothyroidism due to coronavirus-associated hypophysitis, by the risk of agranulocytosis in subjects under anti-thyroid drugs while vaccination against COVID-19 might trigger autoimmune response involving anti-thyroid antibodies or even subacute thyroiditis etc (1-10) (Figure 1).

METHOD

We aim to overview a pandemic update on thyroid cancer. This article represents a literature update. This a narrative general presentation. All papers are published on PubMed indexed journals. The publication timeline regarding thyroid cancer update concerns the first two years of COVID-19 pandemic (2020-2021) but pre-pandemic data are also included to highlight a specific topic. We only included full-length, English language published articles. The key words of research are (in different

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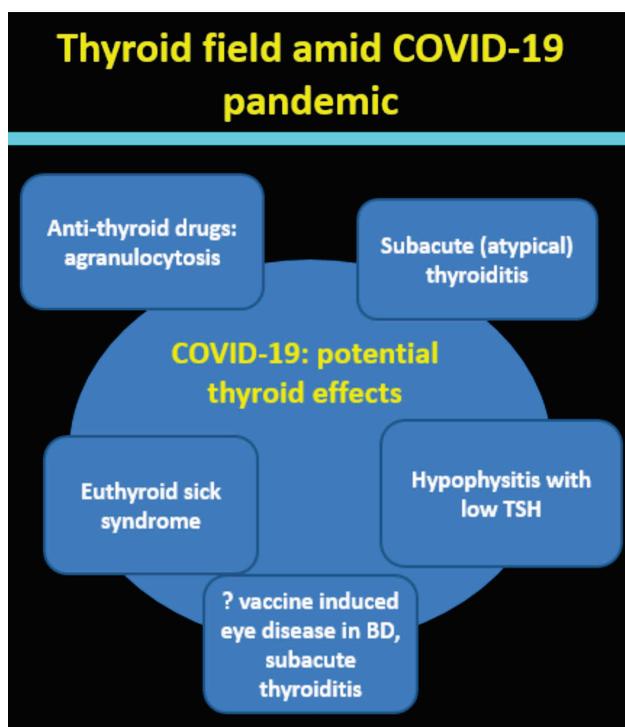


FIGURE 1. Chart of interferences between thyroid field and particular aspects surrounding the topic of COVID-19 pandemic, either in terms of patients with prior thyroid conditions going through infection or coronavirus-induced thyroid anomalies in subjects without previous diagnostic of a thyroid condition. BD = Basedow disease, TSH = thyroid stimulating hormone

combinations): “thyroid cancer” and “COVID-19” or “pandemic” or “coronavirus”. We will also introduce a brief discussion on a particular sub-section on endocrinology: thyroid cancer in acromegalic patients, referring to the most clinically revealing papers published within the last 2 years.

PANDEMICS AND GENERAL CONCERN ADDRESSING THYROID CANCER

The general scientific interest on thyroid cancer according to online research decreased during the first half of 2020 and got to the pre-pandemic level by the end of 2020 (11). At the beginning of the pandemic, there was a delay in approaching the thyroid conditions, while telemedicine became a most useful tool, as seen in others areas of medicine (12). A retrospective study found that subjects with post-2020 lockdown delay of therapy had statistically significant more frequent multiple lesions and extra-thyroid extension as well as lymph nodes metastatic spreading of thyroid cancer when compare to pre-pandemic data (13).

Another aspect is related to the psychological stress of patients who are already known with a thyroid cancer (14). A study from China on 219 pa-

tients showed that 31.5% of them had insomnia, 39.7% had anxiety, 33.8% had depression and 20.1% had post-traumatic stress symptoms during peak incidence of infection in general population (14).

COVID-19 INFECTION IN PATIENTS WITH THYROID CANCER

Ongoing debates surround the topic of higher risk of COVID-19 infection in patients with a prior diagnostic of a thyroid malignancy in terms of having a higher risk of infection or a higher risk of developing a more severe form (15). There is not clear answer up to this point, whether a COVID-19 infection actually aggravates the clinical picture of a patient who is known with thyroid malignancy considering anomalies of inflammation, immunity, oxidative stress etc. (16).

On the other hand, specific therapy addressing thyroid cancer like surgery and/or radioiodine therapy should be performed according to local protocol during pandemic restrictions which unfortunately face a great deal of variations (17,18,19).

A specific topic is increased pro-calcitonin during COVID-19 infection (20,21,22). A case report showed a persistent post-infection high pro-calcitonin level with negative inflammatory syndrome which lead to early diagnostic of a medullary thyroid cancer (23).

Concerning the COVID-19 - related mortality in patients with *versus* without prior diagnostic of thyroid cancer, we mention a nationwide study on Turkish population, conducted between March and May 2020, on 388 adult subjects with thyroid malignancy versus 388 patients without thyroid neoplasia (all of them COVID-19 positive); the results showed similar mortality, regardless prior radioiodine therapy (24).

RECENT NON-COVID-19-RELATED ASSETS CONCERNING THYROID CANCER

The most important data that are released for the last two years concern the understanding of thyroid cancer genetics, the approach of shift from differentiated, follicle cell – derivate carcinoma to anaplastic cancer, as well as evidence regarding new players in the oncological endocrinology like tyrosine kinase inhibitors for advanced forms of thyroid malignancies which are derivate from epithelial cells, thus making 2021 “the year in basic thyroid cancer research”, as named it by Di Cristofano (25). In Figure 1) we can see the aspect of neck and thorax: voluminous space replacement process especially at the level of the right thyroid lobe, with invasive aspects at anterior and lateral level, and additional large mass effect on the structures of the

midline, with left hyoid bone, thyroid and cricoid cartilage, trachea and esophagus invasion. It develops anteriorly and posteriorly to the thyroid and cricoid cartilages, with tumor spreading to the posterior wall of the trachea; and posteriorly to the bone plane of the adjacent vertebral bodies. Trachea is displaced to the left, with 1 cm - infiltration at the level of the anterior and lateral right walls. The tumor has maximum diameters of 11.12 cm by 9.87 cm by 11.81 cm at the clavicles section level. This is a 76-year-old female admitted for compressive poly-nodular goiter with dysphagia, dysphonia (during the first year of pandemics). Fine needle aspiration cytology showed marked anisocytosis, anisokaryosis, with elongated, fusiform, squamous cells, rare multinucleated cell aggregates, highly suggestive for anaplastic/undifferentiated carcinoma (Bethesda 6).

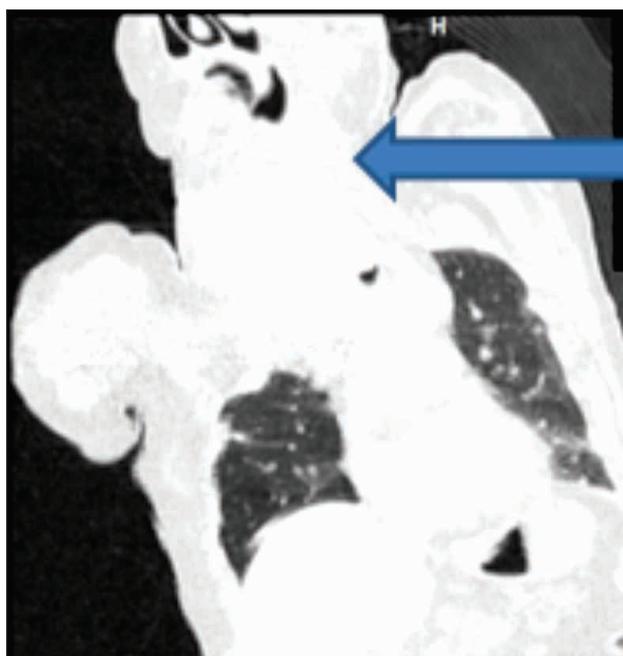


FIGURE 2. Native computed tomography (CT) aspect of neck and thorax

We already know that a patient under lenvatinib or others tyrosine kinase inhibitors for advanced thyroid cancer is at higher risk of developing pneumonia and other lung complications, including pneumothorax (26-30). A few authors reported that, under these circumstances, patients who become COVID-19 positive are at higher risk of rapidly progression to severe pulmonary complications (31,32,33). But, since tyrosine kinase inhibitors are recommended in radioiodine refractory thyroid cancers with pulmonary metastasis, if COVID-19 infection is not severe, the drugs should be continued to improve the overall survival, so a multidisciplinary, case selection is imperious (34). A case published in 2021 regarding an unexpected good re-

sponse to dabrafenib and trametinib for inoperable, anaplastic carcinoma that was treated for 4 weeks with a 90% reduction of tumor mass, showed us that pandemic circumstances should not limit us in rapidly addressing severe forms of thyroid cancers, neither limiting the use of tyrosine kinase inhibitors (35).

Moreover, more evidence that syndromic circumstances might involve some types of thyroid cancers were published for the last two years (36). Adrenal and pituitary tumors have been already reported in different associations sharing common genetic backgrounds like neurofibromatosis type 1 or Cowden syndrome etc. (37,38).

DISCUSSIONS

We choose to discuss a particular trans-disciplinary domain of endocrinology: updated of thyroid cancer on acromegalic patients during 2020 - 2021. We already know that acromegaly patients associate a higher risk of cardiovascular diseases and diabetes mellitus, but also oncologic complications (39,40,41,42). The PubMed search using the key words “thyroid cancer” and “acromegaly” showed 22 papers in humans (addressing different levels of statistical evidence). We mention the most clinically relevant data. A nationwide, Swedish study detected among 1296 acromegalic patients, 186 cancers and only 3 of thyroid carcinoma among them (no statistical significance) (43). A retrospective study from Pakistan included 89 acromegalic patients between 2000 and 2020, and a 1.12% ratio of thyroid cancer was detected (44). A first case of pituitary adenoma co-secreting GH (growth hormone) and TSH (thyroid stimulating hormone) that was diagnosed after the removal of a multifocal papillary cancer was published (45). A Turkish study on 96 adults with acromegaly found that 67.5% of them had a thyroid nodule and 4.2% of acromegalic population had thyroid cancer (46). Another study, also from Turkey, found a 7% prevalence of thyroid cancer versus 4% in non-acromegalic population, females being more prone to the condition (47). A single center study from China showed that multifocal type of thyroid malignancy represents the hallmark of a more aggressive profile in patients with papillary thyroid cancer and acromegaly (48). A prospective study showed that differentiated thyroid cancer is not more frequent in subjects with GH secretor pituitary tumors versus patients diagnosed with non-GH producing hypophyseal adenomas (49). Another retrospective, multi-centric study showed that patients confirmed with both acromegaly and differentiated thyroid cancer have an initial low rate of recurrence, with a similar prognostic versus non-acromegalic patients of the thyroid condition (50).

CONCLUSIONS

For what we know so far, by the end of the second pandemic year, the patients with thyroid cancer are not a fragile population when facing COVID-19 infection itself. However, the delay of adequate therapy amid restrictions is reflected in

more severe malignancy behavior, while general concerns about the virus and pandemics increase the level of psychological and social stress. Case finding strategies to detect high risk patients as those on tyrosine kinase inhibitors with potential lung complications are needed.

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REFERENCES

- Clarke SA, Abbara A, Dhillon WS. Impact of COVID-19 on the Endocrine System: A Mini-review. *Endocrinology*. 2022 Jan 1;163(1):bqab203.
- Ladani AP, Loganathan M, Kolikonda MK, Lippmann S. COVID-19 Legacy. *South Med J*. 2021 Dec;114(12):751-759.
- Clausen CL, Rasmussen ÅK, Johannsen TH, Hilsted LM, Skakkebaek NE, Szecsi PB, Pedersen L, Benfield T, Juul A. Thyroid function in COVID-19 and the association with cytokine levels and mortality. *Endocr Connect*. 2021 Sep 28;10(10):1234-1242.
- Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, Kanouta F, Kassi GN, Dimopoulos MA, Mitrakou A. Early and late endocrine complications of COVID-19. *Endocr Connect*. 2021 Sep 20;10(9):R229-R239.
- Malik J, Zaidi SMJ, Waqar AU, Khawaja H, Malik A, Ishaq U, Rana AS, Awan AH. Association of hypothyroidism with acute COVID-19: a systematic review. *Expert Rev Endocrinol Metab*. 2021 Sep;16(5):251-257.
- Dworakowska D, Morley S, Mulholland N, Grossman AB. COVID-19-related thyroiditis: A novel disease entity? *Clin Endocrinol (Oxf)*. 2021 Sep;95(3):369-377.
- Duntas LH, Jonklaas J. COVID-19 and Thyroid Diseases: A Bidirectional Impact. *J Endocr Soc*. 2021 Apr 27;5(8):bvab076.
- Șandru F, Carsote M, Petca RC, Gheorghisan-Galateanu AA, Petca A, Valea A, Dumitrașcu MC. COVID-19-related thyroid conditions (Review). *Exp Ther Med*. 2021 Jul;22(1):756.
- Ruggeri RM, Campenni A, Deandreis D, Siracusa M, Tozzoli R, Petranović Ovcariček P, Giovannella L. SARS-CoV-2-related immune-inflammatory thyroid disorders: facts and perspectives. *Expert Rev Clin Immunol*. 2021 Jul;17(7):737-759.
- Lisco G, De Tullio A, Stragapede A, Solimando AG, Albanese F, Capobianco M, Giagulli VA, Guastamacchia E, De Pergola G, Vacca A, Racanelli V, Triggiani V. COVID-19 and the Endocrine System: A Comprehensive Review on the Theme. *J Clin Med*. 2021 Jun 29;10(13):2920.
- Cohen SA, Ebrahimian S, Cohen LE, Tijerina JD. Online public interest in common malignancies and cancer screening during the COVID-19 pandemic in the United States. *J Clin Transl Res*. 2021 Nov 6;7(6):723-732.
- Nickel B, Miller JA, Cvejic E, Gild ML, Cope D, Dodd R, McCaffery K, Glover A. Thyroid cancer clinicians' views and experiences of delayed treatment during the COVID-19 pandemic: An international cross-sectional survey. *ANZ J Surg*. 2021 Dec;91(12):2562-2564.
- Liu H, Zhan L, Guo L, Yu X, Li L, Feng H, Yang D, Xu Z, Tu Y, Chen C, Sun S. More Aggressive Cancer Behaviour in Thyroid Cancer Patients in the Post-COVID-19 Pandemic Era: A Retrospective Study. *Int J Gen Med*. 2021 Oct 27;14:7197-7206.
- Yang S, Wang J, Xu X. Psychological health status among thyroid cancer patients during the COVID-19 epidemic in China. *Support Care Cancer*. 2021 Oct 20:1-9.
- Abobaker A, Darrat M. Reply: The clinical outcome of COVID-19 infection in patients with a history of thyroid cancer: A nationwide study. *Clin Endocrinol (Oxf)*. 2021 Dec 23.
- Deligiorgi MV, Siasos G, Vakkas L, Trafalis DT. Charting the Unknown Association of COVID-19 with Thyroid Cancer, Focusing on Differentiated Thyroid Cancer: A Call for Caution. *Cancers (Basel)*. 2021 Nov 18;13(22):5785.
- Martins JRM, Villagelin DGP, Carvalho GA, Vaisman F, Teixeira PFS, Scheffel RS, Sgarbi JA. Management of thyroid disorders during the COVID-19 outbreak: a position statement from the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism (SBEM). *Arch Endocrinol Metab*. 2021 Nov 3;65(3):368-375.
- Lisco G, De Tullio A, Jirillo E, Giagulli VA, De Pergola G, Guastamacchia E, Triggiani V. Thyroid and COVID-19: a review on pathophysiological, clinical and organizational aspects. *J Endocrinol Invest*. 2021 Sep;44(9):1801-1814.
- Czarnywojtek A, Ochmańska A, Zgorzalewicz-Stachowiak M, Sawicka-Gutaj N, Matyjaszek-Matuszek B, Woźniak M, Ruchała M. Influence of SARS-CoV-2 infection on thyroid gland function: The current knowledge. *Adv Clin Exp Med*. 2021 Jul;30(7):747-755.
- Houghton R, Moore N, Williams R, El-Bakri F, Peters J, Mori M, et al. C-reactive protein-guided use of procalcitonin in COVID-19. *JAC Antimicrob Resist*. 2021 Nov 28;3(4):dlab180.
- Adams B, Beaney A. Interpreting serum procalcitonin in COVID-19 patients undergoing renal replacement therapy. *J Glob Antimicrob Resist*. 2021 Dec;27:324-325.
- Richards O, Pallmann P, King C, Cheema Y, Killick C, et al. Procalcitonin Increase Is Associated with the Development of Critical Care-Acquired Infections in COVID-19 ARDS. *Antibiotics (Basel)*. 2021 Nov 22;10(11):1425.
- Sira L, Balogh Z, Vitális E, Kovács D, Győry F, Molnár C, Bodor M, Nagy EV. Case Report: Medullary Thyroid Cancer Workup Initiated by Unexpectedly High Procalcitonin Level-Endocrine Training Saves Life in the COVID-19 Unit. *Front Endocrinol (Lausanne)*. 2021 Oct 11;12:727320.
- Sahin M, Haymana C, Demirci I, Tasci I, Rifat E, Unluturk U, et al. The clinical outcomes of COVID-19 infection in patients with a history of thyroid cancer: A nationwide study. *Clin Endocrinol (Oxf)*. 2021 Oct;95(4):628-637.
- Di Cristofano A. The Year in Basic Thyroid Cancer Research. *Thyroid*. 2021 Dec 16.
- Iwasaki H, Toda S, Murayama D, Kato S, Matsui A. Relationship between adverse events associated with lenvatinib treatment for thyroid cancer and patient prognosis. *Mol Clin Oncol*. 2021 Feb;14(2):28.
- Uchida T, Yamaguchi H, Nagamine K, Yonekawa T, et al. Rapid pleural effusion after discontinuation of lenvatinib in a patient with pleural metastasis from thyroid cancer. *Endocrinol Diabetes Metab Case Rep*. 2019 Mar 18;2019:18-0158.
- Leboulleux S, Bastholt L, Krause T, de la Fouchardiere C, Tennvall J, et al. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. *Lancet Oncol*. 2012 Sep;13(9):897-905.
- Toda S, Iwasaki H, Murayama D, Nakayama H, Suganuma N, Masudo K. Invasive procedures in patients undergoing treatment with lenvatinib for thyroid cancer. *Mol Clin Oncol*. 2021 Apr;14(4):81.
- Datar S, Cabanillas M, Dadu R, Ost D, Grosu HB. Pulmonary cavitation in patients with thyroid cancer receiving antiangiogenic agents. *BMC Cancer*. 2020 Dec 2;20(1):1181.
- Toda S, Matsui A, Yasukawa M, Murayama D, Iwasaki H. Pulmonary cavitation in a patient with coronavirus disease 2019 during lenvatinib

- treatment for thyroid carcinoma: a case report. *Ann Palliat Med.* 2021 Dec 3;apm-21-2663.
32. Chen X, Zhang G, Hao SY, Bai L, Lu JJ. Similarities and Differences of Early Pulmonary CT Features of Pneumonia Caused by SARS-CoV-2, SARS-CoV and MERS-CoV: Comparison Based on a Systemic Review. *Chin Med Sci J.* 2020 Sep 30;35(3):254-261.
 33. Cui N, Zou X, Xu L. Preliminary CT findings of coronavirus disease 2019 (COVID-19). *Clin Imaging.* 2020 Sep;65:124-132.
 34. Locantore P, Del Gatto V, Corsello A, Pontecorvi A. Lenvatinib treatment for thyroid cancer in COVID era: safety in a patient with lung metastases and SARS-CoV-2 infection. *Anticancer Drugs.* 2021 Nov 1;32(10):1116-1117.
 35. Chevalier B, Dupuis H, Jannin A, Lemaitre M, Do Cao C, Cardot-Bauters C, Espiard S, Vantyghem MC. Phakomatoses and Endocrine Gland Tumors: Noteworthy and (Not so) Rare Associations. *Front Endocrinol (Lausanne).* 2021 May 6;12:678869.
 36. Bueno F, Abelleira E, von Stecher F, de Lima AP, Pitoia F. Dramatic clinical response to dabrafenib plus trametinib in anaplastic thyroid carcinoma and the challenges faced during the COVID-19 pandemic. *Arch Endocrinol Metab.* 2021 Nov 1;65(2):242-247.
 37. Carsote M, Paun S, Neamtu MC, Avramescu ET, Iosif C, Terzea D, Constantinoiu S, Danculescu Miulescu R, Neamtu OM, Poiana C. The immunohistochemistry aspects in two cases of neurofibromatosis-associated abdominal tumors, *Rom Journal Morphol Embryol*, 2012; 53(2):401-405.
 38. Sandru F, Carsote M, Valea A, Albu SE, Petca RC, Dumitrascu MC. Somatostatinoma: Beyond neurofibromatosis type 1 (Review). *Exp Ther Med.* 2020;20(4):3383-3388.
 39. Valea A, Carsote M, Ghervan C, Georgescu C. Glycemic profile in patients with acromegaly treated with somatostatin analogue. *J Med Life.* 2015;8(Spec issue):79-83.
 40. Valea A, Ghervan C, Carsote M, Morar A, Iacob I, Tomesc F, Pop DD, Georgescu C. Effects of combination therapy: somatostatin analogues and dopamine agonists on GH and IGF1 levels in acromegaly. *Clujul Medical.* 2015;88(3):310-313.
 41. Terzolo M, Puglisi S, Reimondo G, Dimopoulou C, Stalla GK. Thyroid and colorectal cancer screening in acromegaly patients: should it be different from that in the general population? *Eur J Endocrinol.* 2020 Oct;183(4):D1-D13.
 42. Gul N, Soyuluk O, Dogansen SC, Kurtulmus N, Yarman S. Disease Activity May Not Affect the Prognosis of Coexisting Thyroid Cancer in Acromegalic Patients. *Exp Clin Endocrinol Diabetes.* 2020 Sep;128(9):567-572.
 43. Esposito D, Ragnarsson O, Johannsson G, Olsson DS. Incidence of Benign and Malignant Tumors in Patients With Acromegaly Is Increased: A Nationwide Population-based Study. *J Clin Endocrinol Metab.* 2021 Nov 19;106(12):3487-3496.
 44. Khan SA, Ram N, Masood MQ, Islam N. Prevalence of Comorbidities among Patients with Acromegaly. *Pak J Med Sci.* 2021 Nov-Dec; 37(7):1758-1761.
 45. Yoon JH, Choi W, Park JY, Hong AR, Kim SS, Kim HK, Kang HC. A challenging TSH/GH co-secreting pituitary adenoma with concomitant thyroid cancer; a case report and literature review. *BMC Endocr Disord.* 2021 Aug 30;21(1):177.
 46. Can M, Kocabaş M, Çordan İ, Çalıřkan Burgucu H, Karaköse M, Kulaksızođlu M, Karakurt F. Prevalence of comorbidities and associated factors in acromegaly patients in the Turkish population. *Turk J Med Sci.* 2021 Jun 28;51(3):1146-1152.
 47. Cankurtaran Y, Öruk GG, Tozduan B. Evaluation of thyroid disease and thyroid malignancy in acromegalic patients. *Minerva Endocrinol (Torino).* 2021 May 14.
 48. Zhao Y, Wang Y, Zhang X, Jia N, Ma Z, Fu J, Liu S. Papillary Thyroid Carcinoma in Patients with Acromegaly from a Single Center in China. *World Neurosurg.* 2021 May;149:e22-e28.
 49. Spricido IY, Feckinghaus CM, Silva RHM, Mesa Junior CO, Boguszewski CL. Prevalence of thyroid cancer in patients with acromegaly and non-growth hormone secreting pituitary adenomas: A prospective cross-sectional study. *Growth Horm IGF Res.* 2021 Feb;56:101378.
 50. Danilowicz K, Sosa S, Gonzalez Pernas MS, Bamberger E, Diez SM, et al. Acromegaly and thyroid cancer: analysis of evolution in a series of patients. *Clin Diabetes Endocrinol.* 2020 Nov 17;6(1):24.