

1. J Clin Endocrinol Metab. 2019 Apr 24. pii: jc.2019-00851. doi: 10.1210/jc.2019-00851. [Epub ahead of print]

Response to Letter to the Editor: [Time to Separate Persistent from Recurrent Differentiated Thyroid Cancer: Different Conditions with Different outcomes].

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2. J Clin Endocrinol Metab. 2019 Apr 24. pii: jc.2019-00634. doi: 10.1210/jc.2019-00634. [Epub ahead of print]

"Letter to the Editor: [Time to Separate Persistent from Recurrent Differentiated Thyroid Cancer: Different Conditions with Different outcomes]".

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3. J Clin Endocrinol Metab. 2019 May 22. pii: jc.2018-02809. doi: 10.1210/jc.2018-02809. [Epub ahead of print]

Stage II Differentiated Thyroid Cancer Is a High-risk Disease in Patients <45/55 Years Old.

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PURPOSE: The mortality risk of stage II differentiated thyroid cancer (DTC) on the American Joint Committee on Cancer (AJCC) staging system remains to be further investigated.

METHODS: Retrospective study of DTC in the USA Surveillance, Epidemiology, and End Results for disease-specific mortality risk in various AJCC stages, with patient age stratification of stage II disease.

RESULTS: On AJCC 6.0, compared with stage I, hazard ratios (HRs) of mortality for stages II in patients <45 yo, II in patients ≥45 yo, III, IVA, IVB, and IVC were 46.95, 4.95, 9.82, 57.37, 222.10, and 468.68, respectively, showing a robustly higher mortality risk in stage II disease in patients <45 yo than older patients (P<0.001), comparable with stage IVA (P=0.482). Similar results were obtained on

AJCC 7.0. On AJCC 8.0, compared with stage I, HRs of mortality for stages II in patients <55 yo, II in patients ≥55 yo, III, IVA, and IVB were 75.16, 11.23, 69.45, 134.94, and 235.70, respectively, showing a robustly higher risk in stage II disease in patients <55 yo than older patients (P<0.001), comparable with stage III (P=0.57). Kaplan-Meier survival curves displayed a sharp decline with stage II disease in patients <45/55 yo compared with older patients.

CONCLUSIONS: The mortality risk of stage II DTC is sharply differentiated at patient age 45/55 years, being robustly high in younger patients and comparable with stage III/IVA; this emphasizes the importance of taking age in consideration when managing stage II DTC and not treating it as a uniformly low-risk disease.

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Prognostic Impact of the Turin Criteria in Poorly Differentiated Thyroid Carcinoma.

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BACKGROUND: The Turin criteria including solid, trabecular, and/or insular architecture, lack of typical nuclear features of papillary carcinoma, and mitoses, necrosis, or convoluted nuclei were adopted in the recent 4th edition of the World Health Organization classification published in 2017.

MATERIALS AND METHODS: Between 2006 and 2017, 11,001 cases underwent initial surgery for primary malignant thyroid tumor derived from follicular cells. A total of 75 (0.7%) cases were diagnosed with PDTC according to the 2004 WHO classification. Based on the Turin criteria, 30 (40%) cases were re-classified as PDTC-Turin (+) and 45 (60%) cases were PDTC-Turin (-). Clinicopathological features and prognosis were compared between PDTC-Turin (+) and PDTC-Turin (-).

RESULTS: Seventy-five patients (48 females and 27 males) had a median age at the time of surgery of 57 years. Preoperative diagnosis was benign in 16 (21%), follicular tumor in 40 (53%), and malignant in 19 (25%). The 5-year cause-specific survival (CSS) and disease-free survival (DFS) rates were 97% and 44% for PDTC-Turin (+) and 100% and 88% for PDTC-Turin (-). On univariate analysis, CSS and DFS rates were significantly worse in the PDTC-Turin (+) than in the PDTC-Turin (-) (p = 0.0096, and p = 0.0016). Multivariate analysis showed that Turin criteria status, Ki-67 labeling index ≥ 10%, and age 55 ≥ years were the independent prognostic factors for recurrence.

CONCLUSIONS: The prevalence of PDTC diagnosed with the Turin criteria was low, but it showed more aggressive behavior. The 2017 WHO classification reflects the prognosis more accurately than the 2004 WHO classification.

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5. Nat Rev Endocrinol. 2019 Jun;15(6):319-321. doi: 10.1038/s41574-019-0204-8.

Sonographic diagnosis of thyroid cancer with support of AI.

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Predicting recurrence of papillary thyroid cancer using the eighth edition of the AJCC/UICC staging system.

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BACKGROUND: The AJCC/UICC classification is widely used for predicting survival in papillary thyroid cancer (PTC), but has not been evaluated as a predictor of recurrence. The hypothesis of this study was that the eighth edition of the AJCC system can be used in this novel way.

METHODS: All patients in the study underwent surgery for PTC at a high-volume endocrine surgery centre in France between 1985 and 2015. The seventh and eighth editions of the AJCC/UICC staging system for PTC were employed to predict recurrence and disease-specific survival using the Kaplan-Meier and log rank tests.

RESULTS: Among 4124 patients (79.7 per cent female), median age was 50 (i.q.r. 38-60) years; 3906 patients (94.7 per cent) underwent total thyroidectomy, with lymph node dissection in 2495 (60.5 per cent). The eighth edition of the AJCC/UICC staging system placed 91.8, 7.1, 0.4 and 0.7 per cent of patients in stages I-IV respectively. After reclassifying patients from the seventh to the eighth AJCC/UICC edition, the disease was downstaged in 23.8 per cent. Over a median follow-up of 7 years, 260 patients (6.4 per cent) developed recurrent disease, including 5.2 per cent of patients with stage I, 19.6 per cent with stage II, 59 per cent with stage III and 50 per cent with stage IV disease, according to the eighth edition. The eighth edition was a better predictor of recurrence than the seventh edition.

CONCLUSION: The eighth edition of the AJCC/UICC staging system appears to be a novel tool for predicting PTC recurrence, which is a meaningful outcome for this

indolent disease. The eighth edition can be used to risk-stratify patients, keeping in mind that other molecular and pathological predictive factors must be integrated into the assessment of recurrence risk.

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7. J Clin Endocrinol Metab. 2019 Jun 1;104(6):2150. doi: 10.1210/jc.2019-00730.

CORRIGENDUM FOR "Hemodynamic Markers and Subclinical Atherosclerosis in Postmenopausal Women With Primary Hyperparathyroidism".

[No authors listed]

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8. Nat Rev Endocrinol. 2019 May;15(5):254-255. doi: 10.1038/s41574-019-0193-7.

Key pathways revealed in rare thyroid cancer.

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9. J Clin Endocrinol Metab. 2019 May 1;104(5):1677. doi: 10.1210/jc.2019-00546.

CORRIGENDUM FOR "Pilot Dose Comparison of Apatinib in Chinese Patients With Progressive Radioiodine-Refractory Differentiated Thyroid Cancer".

[No authors listed]

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10. World J Surg. 2019 Jun;43(6):1525-1531. doi: 10.1007/s00268-019-04944-w.

Minimally Invasive Parathyroidectomy without Intraoperative PTH Performed after Positive Ultrasonography as the only Diagnostic Method in Patients with Primary Hyperparathyroidism.

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BACKGROUND: A positive and concordant result of at least two diagnostic modalities is generally recommended prior to focused parathyroidectomy. The aim of this study was to analyze the results of surgery and the accurateness of preoperative ultrasonography (US) as single localization modality in patients who underwent parathyroidectomy without the adjunct of intraoperative Parathormone (PTH) measurement.

METHODS: The cases with a preoperative US as the only localization technique, who underwent parathyroidectomy between 10/1999 and 12/2017, were selected from a prospectively maintained database. Therefore, a total number of 242 patients with a mean age of 58.6 ± 13.7 years were included in the present study. US was performed by referral endocrinologist or by the surgeon during office visits.

RESULTS: The overall "cure rate" was 99.2% (240 out of 242 patients). In 228/242 patients (94.2%), a drop of perioperative PTH levels consistent with the definition of cure was observed on the day of surgery. In four of the remaining 14 patients, healing was confirmed by PTH level dropping into the normal range on the first postoperative day. Eight patients were cured after a reoperation was performed at our department. Postoperative complications included one case of permanent recurrent laryngeal nerve palsy (0.4%).

CONCLUSIONS: If performed by an experienced endocrinologist and/or endocrine surgeon, a positive US could be the only preoperative localization study in patients with pHPT. Moreover, the add-value of intraoperative PTH is limited.

Major advantages of US are a very high accuracy, the ease of performance (accessibility) and its cost-effectiveness compared with Sesta-MIBI scintigraphy.

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11. J Clin Endocrinol Metab. 2019 Jul 1;104(7):2712-2718. doi: 10.1210/jc.2018-02471.

Leukocyte Telomere Length and Risk of Papillary Thyroid Carcinoma.

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CONTEXT: Telomere length may contribute to predisposition to papillary thyroid cancer (PTC).

OBJECTIVE: To test this hypothesis, we examined the association between leukocyte telomere length and PTC risk.

DESIGN/SETTING: Case-control study in a Chinese Han population.

PARTICIPANTS/INTERVENTION: A total of 1200 PTC cases and 1201 age- and sex-matched healthy controls were included in the study. ORs and 95% CIs were calculated by logistic regression.

RESULTS: Short relative telomere length (RTL) was significantly associated with elevated risk of PTC (OR = 1.61, 95% CI = 1.35 to 1.92; $P = 1.30 \times 10^{-7}$).

Interestingly, when individuals were categorized into four groups on the basis of quartile distribution of relative telomere length (RTL) in controls, we observed a reverse U-shaped association between telomere length and PTC risk. Compared with those in the first (the longest) quartile as the reference group, ORs (95% CIs) were 5.61 (4.04 to 7.78) ($P = 6.10 \times 10^{-25}$), 9.33 (6.78 to 12.83) ($P = 6.99$

× 10⁻⁴³), and 1.23 (0.83 to 1.81) (P = 0.300) for individuals in the second, third, and fourth (the shortest) quartiles, respectively. This reverse U-shaped relationship was more apparent in younger individuals.

CONCLUSIONS: Our findings suggest that RTL is significantly associated with susceptibility to PTC. There is an obvious reverse U-shaped association between telomere length and PTC risk. Telomere length may be a potential pronouncing biomarker to identify individuals with a high risk of developing PTC.

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12. World J Surg. 2019 May;43(5):1249-1255. doi: 10.1007/s00268-019-04906-2.

Primary Squamous Cell Carcinoma in the Thyroid Gland: A Population-Based Analysis Using the SEER Database.

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OBJECTS: To evaluate prognostic factors and treatment outcomes of primary squamous cell carcinoma in thyroid (PSCCTh) over the past decades using a large national database.

METHODS: All patients diagnosed with PSCCTh between 1973 and 2015 were identified with the Surveillance, Epidemiology, and End Results Program (SEER) 18-registry database. Relevant clinical data were collected, and prognostic factors of overall survival (OS) and disease-specific survival (DSS) were analyzed.

RESULTS: This cohort study included 242 patients, accounting for 0.12% of all primary thyroid carcinomas from 1973 to 2015 nationwide. Of the patients with PSCCTh, 75% were older than 60 years at diagnosis. Patient age older than 60 years (HR 2.242, 95% CI 1.367-3.676, P = 0.001) and a tumor size larger than or equal to 50 mm (HR 1.479, 95% CI 1.011-2.165, P = 0.044) were independent negative prognostic factors. The univariate analysis suggested that the morphological subtype (OS, P = 0.033; DSS, P = 0.048), clinical treatment modality (OS, P < 0.0001; DSS, P < 0.0001), and T stage (OS, P = 0.004; DSS, P = 0.001) were important predictive factors for OS and DSS. In contrast, gender, race, year of diagnosis, geographic location, N stage, and M stage were not prognostic factors.

CONCLUSIONS: PSCCTh is a rare malignancy with an aggressive nature and poor

prognosis. Survival is predicted by the treatment modality, patient age, T stage, tumor size, and morphological subtypes. This study showed that early diagnosis and complete surgical resection plus adjuvant radiation therapy were associated with a better outcome.

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13. World J Surg. 2019 May;43(5):1256-1263. doi: 10.1007/s00268-019-04924-0.

High-Dose RAI Therapy Justified by Pathological N1a Disease Revealed by Prophylactic Central Neck Dissection for cN0 Papillary Thyroid Cancer Patients: Is it Superior to Low-Dose RAI Therapy?

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OBJECTIVE: One of the presumed advantages of prophylactic central neck dissection (pCND) is offering staging basis for more aggressive radioactive iodine (RAI) therapy, which postulates the necessity of high dose for treatment efficacy. The present study aims to compare the effectiveness between low-dose and high-dose RAI in a select cohort of cN0 papillary thyroid cancer (PTC) patients with pathological N1a (pN1a) disease revealed by pCND in terms of ablation rate and response to therapy. The frequency of short-term adverse effects between the two groups was also compared.

PATIENTS AND METHODS: From January 2014 to April 2016, cN0 PTC patients with pN1a disease revealed by pCND in our hospital were retrospectively reviewed. Patients with other indications for high-dose RAI, such as the presence of extrathyroidal extension, vascular invasion or suspicions of distant metastasis, were excluded.

For the included patients, high dose (3700 MBq) was administered between January 2014 and August 2015 and low dose (1110 MBq) between August 2015 and April 2016. Ablation assessment was performed 6 months after RAI therapy. Response evaluation after RAI therapy was performed after 46.3 ± 9.5 months for high-dose group and 29.1 ± 2.6 months for low-dose group. All patients were also evaluated for short-term adverse effects 24 and 72 hours after RAI administration.

RESULTS: A total of 84 patients were enrolled. Among them, 42 were in the high-dose group and the other 42 in the low-dose group. There was no significant difference in ablation rate ($P = 0.7707$) and response to RAI therapy ($P = 0.6454$) between the two groups. Twenty-four hours after RAI administration, neck pain and swelling (33.3% VS. 11.9%; $P = 0.0372$) and gastrointestinal discomfort (45.2% vs. 21.4%; $P = 0.0373$) were significantly more frequent in the high-dose group.

CONCLUSION: High-dose RAI therapy, with higher frequency of short-term adverse effects, appears to be not superior to low-dose RAI therapy for cN0 PTC patients

with pN1a disease revealed by pCND to achieve better response to therapy. Further randomized studies with larger series of patients and longer follow-up duration, especially with the low-dose group, are needed to validate our results.

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14. World J Surg. 2019 May;43(5):1243-1248. doi: 10.1007/s00268-019-04920-4.

Does Primary Hyperparathyroidism Have an Association with Thyroid Papillary Cancer? A Retrospective Cohort Study.

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BACKGROUND: To investigate the relationship between primary hyperparathyroidism (pHPT) and papillary thyroid cancer (PTC).

METHODS: The perioperative findings of 275 patients with pHPT who underwent surgery between January 2014 and December 2017 were retrospectively reviewed. Thirty-one patients were diagnosed with pHPT and PTC concurrently. Pathology results and demographic findings of these patients were compared with 186 patients who underwent thyroidectomy and diagnosed with PTC at the same time interval.

RESULTS: The co-occurrence of pHPT and PTC was 11.3% (31/275). The median ages of the pHPT, pHPT + PTC, and PTC groups were 55, 57, and 50 years old, respectively ($p < 0.001$). The diameter of tumor was smaller in the pHPT + PTC group [median 7 mm (range 0.5-25 mm) vs. 15 mm (range 1-100 mm)], with higher rates of microcarcinomas ($p < 0.001$), than the patients in the PTC group. Examination of tumor morphology showed higher rates of tumor capsule invasion and multicentricity in the pHPT + PTC group than those in the isolated PTC group ($p = 0.02$, $p = 0.04$, respectively).

CONCLUSION: The pHPT + PTC group had significantly smaller tumor diameter than the PTC group. This result may support the idea that pHPT leads to overdiagnosis of PTC. However, observation of high rates of tumor capsule invasion and multicentricity in the pHPT + PTC group may suggest an associative etiology with more aggressive PTC.

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15. World J Surg. 2019 May;43(5):1232-1242. doi: 10.1007/s00268-019-04910-6.

18F-Fluorocholine PET/CT and Parathyroid 4D Computed Tomography for Primary Hyperparathyroidism: The Challenge of Reoperative Patients.

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BACKGROUND: To evaluate FCH-PET/CT and parathyroid 4D-CT so as to guide surgery in patients with primary hyperparathyroidism (pHPT) and prior neck surgery.

METHODS: Medical records of all patients referred for a FCH-PET/CT in our institution were systematically reviewed. Only patients with pHPT, a history of neck surgery (for pHPT or another reason) and an indication of reoperation were included. All patients had parathyroid ultrasound (US) and Tc-99m-sestaMIBI scintigraphy, and furthermore, some patients had 4D-CT. Gold standard was defined by pathological findings and/or US-guided fine-needle aspiration with PTH level measurement in the washing liquid.

RESULTS: Twenty-nine patients were included in this retrospective study. FCH-PET/CT identified 34 abnormal foci including 19 ectopic localizations. 4D-CT, performed in 20 patients, detected 11 abnormal glands at first reading and 6 more under FCH-PET/CT guidance. US and Tc-99m-sestaMIBI found concordant foci in 8/29 patients. Gold standard was obtained for 32 abnormal FCH-PET/CT foci in 27 patients. On a per-lesion analysis, sensitivity, specificity, positive and negative predictive values were, respectively, 96%, 13%, 77% and 50% for FCH-PET/CT, 75%, 40%, 80% and 33% for 4D-CT. On a per-patient analysis, sensitivity was 85% for FCH-PET/CT and 63% for 4D-CT. FCH-PET/CT results made it possible to successfully remove an abnormal gland in 21 patients, including 12 with a negative or discordant US/Tc-99m-sestaMIBI scintigraphy result, with a global cure rate of 73%.

CONCLUSION: FCH-PET/CT is a promising tool in the challenging population of reoperative patients with pHPT. Parathyroid 4D-CT appears as a confirmatory imaging modality.

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16. J Clin Endocrinol Metab. 2019 May 1;104(5):1655-1657. doi: 10.1210/jc.2018-02437.

Still Perfecting Radioiodine in Thyroid Cancer, After All These Years.

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17. J Clin Endocrinol Metab. 2019 May 1;104(5):1417-1428. doi: 10.1210/jc.2018-01478.

Vemurafenib Redifferentiation of BRAF Mutant, RAI-Refractory Thyroid Cancers.

Dunn LA(1)(2), Sherman EJ(1)(2), Baxi SS(1)(2), Tchekmedyian V(1), Grewal RK(3), Larson SM(3), Pentlow KS(4), Haque S(3), Tuttle RM(1), Sabra MM(1), Fish S(1), Boucai L(1), Walters J(1), Ghossein RA(5), Seshan VE(6), Ni A(6), Li D(3), Knauf JA(7), Pfister DG(1)(2), Fagin JA(1)(2)(7), Ho AL(1)(2).

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CONTEXT: BRAFV600E mutant thyroid cancers are often refractory to radioiodine (RAI).

OBJECTIVES: To investigate the utility and molecular underpinnings of enhancing lesional iodide uptake with the BRAF inhibitor vemurafenib in patients with RAI-refractory (RAIR).

DESIGN: This was a pilot trial that enrolled from June 2014 to January 2016.

SETTING: Academic cancer center.

PATIENTS: Patients with RAIR, BRAF mutant thyroid cancer.

INTERVENTION: Patients underwent thyrotropin-stimulated iodine-124 (124I) positron emission tomography scans before and after ~4 weeks of vemurafenib. Those with increased RAI concentration exceeding a predefined lesional dosimetry threshold (124I responders) were treated with iodine-131 (131I). Response was evaluated with imaging and serum thyroglobulin. Three patients underwent research biopsies to evaluate the impact of vemurafenib on mitogen-activated protein kinase (MAPK) signaling and thyroid differentiation.

MAIN OUTCOME MEASURE: The proportion of patients in whom vemurafenib increased RAI incorporation to warrant 131I.

RESULTS: Twelve BRAF mutant patients were enrolled; 10 were evaluable. Four patients were 124I responders on vemurafenib and treated with 131I, resulting in tumor regressions at 6 months. Analysis of research tumor biopsies demonstrated that vemurafenib inhibition of the MAPK pathway was associated with increased thyroid gene expression and RAI uptake. The mean pretreatment serum thyroglobulin value was higher among 124I responders than among nonresponders (30.6 vs 1.0 ng/mL; P = 0.0048).

CONCLUSIONS: Vemurafenib restores RAI uptake and efficacy in a subset of BRAF mutant RAIr patients, probably by upregulating thyroid-specific gene expression via MAPK pathway inhibition. Higher baseline thyroglobulin values among responders suggest that tumor differentiation status may be a predictor of vemurafenib benefit.

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Risk Factors for Recurrence After Treatment of N1b Papillary Thyroid Carcinoma.

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OBJECTIVES: To examine risk factors for posttreatment recurrence in papillary thyroid carcinoma (PTC) patients with initial presentation of lateral neck metastasis (N1b).

SUMMARY OF BACKGROUND DATA: N1b PTC recurs after definitive treatment.

METHODS: Study subjects were 437 consecutive PTC patients who underwent total thyroidectomy and therapeutic neck dissection of central and lateral compartments and postoperative radioactive iodine ablation therapy. The patients' demographics and pathological factors, including factors related to tumors and lymph nodes (LNs), and postoperative thyroglobulin levels were reviewed. Univariate and multivariate Cox proportional hazards regression analyses were used to identify factors associated with recurrence-free survival (RFS).

RESULTS: During a median follow-up of 83 months (range, 32-135 months), recurrence occurred in 81 (18.1%) patients. Univariate analyses showed that male sex, tumor size, macroscopic extrathyroidal extension, perineural invasion, extranodal extension, LN involvement, LN ratio, MACIS score, and postoperative serum levels of thyroglobulin were significantly associated with RFS (P < 0.05). Multivariate analyses revealed that LN ratio (> 0.25) in the lateral compartment (adjusted hazard ratio = 2.099, 95% confidence interval = 1.278-3.448; P = 0.003), and postoperative serum levels of stimulated (>5.0 ng/mL; 3.172, 1.661-6.056, P < 0.001) and unstimulated (>0.1 ng/mL; 3.200, 1.569-6.526, P = 0.001) thyroglobulin were independent predictors of any-site RFS. Clinical and tumor factors were not independent predictors of RFS outcomes (P > 0.1).

CONCLUSIONS: Posttreatment recurrence is predicted by the LN ratio in the lateral compartment and postoperative serum levels of thyroglobulin in patients with

metastatic PTC in the lateral neck.
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