Editorial

Using nomograms to predict the presence of papillary thyroid carcinoma

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Differentiated thyroid cancer (DTC) is the most common endocrine cancer, the incidence of which has steadily increased over recent decades (1,2). The two subtypes of DTC are papillary (PTC) and follicular (FTC) thyroid cancer, of which PTC is the most common. At disease presentation, the vast majority of the patients with PTC are classified as either stage I or stage II, and the 10-year disease specific survival (DSS) approaches 100% in stage I disease (3,4). In recent years, a less aggressive therapeutic approach has been advocated frequently, although this has not yet resulted in consensus: guidelines are neither uniform in their risk estimates nor in their resulting advice with regard to extent of surgery and the need for radioiodine therapy (5-10). It is important to note that the studies and guidelines on which de-escalating treatment studies are based, are mostly, if not exclusively, from countries with a ubiquitous availability of ultrasound (US) thyroid screening, thus leading to (over) diagnosis, and subsequently overtreatment, of clinically non-palpable tumors with likely an indolent behavior. Using US screening, earlier research showed a prevalence of thyroid nodules up to 40% in Chinese adults (11). Nevertheless, only a small percentage (approximately 10–15%) of such nodules were found to be malignant (12). Unfortunately, fine needle aspiration (FNA) frequently does not yield conclusive results, either because the material is not of diagnostic quality (Bethesda 1), or because it does not allow for further stratification (Bethesda 3/4), usually requiring histological examination of the entire thyroid nodule to make a diagnosis, i.e., resulting in a diagnostic hemithyroidectomy. Therefore, it is critical to differentiate malignant from benign thyroid nodules to avoid unnecessary investigations, like FNA, and subsequently thyroid surgery.

Characteristics of malignant nodules on conventional US, include, but are not limited to, the presence of hypoechogenicity, irregular margins, taller-than-wide, disorganized margins, and micro-calcifications. US is able to identify up to 50% of nodules as highly likely to be benign, however, inter-observer variability with respect to interpreting US characteristics may influence this percentage (12). To better separate these benign and malignant nodules before performing additional FNA, several international societies have published US-based risk stratification systems using several imaging characteristics. The Thyroid Imaging Reporting and Data System (TIRADS) is based on US features and size (13), but several others exists more-or-less based on this initial concept; e.g. Kwak-TIRADS, Korean-TIRADS, EU-TIRADS, and ACR-TIRADS (14-17). Recently, several studies compared the different stratification system regarding their diagnostic accuracy, showing the best performance of the Korean-

TIRADS in German patients (18), but the ACR-TIRADS in a recent meta-analysis (19). Next to these US features, also other factors known to be related to higher risk and/or more aggressive behavior of thyroid cancer, such as age and sex, might be able to further improve the differentiation between benign and malignant nodules (12).

Nomograms are pictorial representations of a multifactorial mathematical model aimed at predicting a specific endpoint based on statistical methods (20). By including statistically significant factors, nomograms can provide an estimated probability of an event (such as cancer-related death), based on the combinations of various factors in the individual patient. In patients with PTC, numerous reports exist in literature on predicting survival and recurrence, but also regarding the presence of lymph node metastases (20). Next to this, also US-based nomograms for differentiating benign and malignant thyroid nodules have been created [e.g. (21)], but more studies are needed to further explore other non-US-based factors to optimize these nomograms.

Recently, Tang *et al.* published the results of the development and validation of a nomogram to distinguish benign thyroid nodules from PTC (22). In this study, 531 patients who received a thyroidectomy were divided in a training set (n=414 with 500 nodules) and validation set (n=117 with 152 nodules). Those with other thyroid cancer types than PTC were excluded from this study. The constructed nomogram consisted of US-based features combined with age, preoperative thyrotropin stimulating hormone (TSH) levels, and inflammatory markers (systemic immune-inflammation index and lymphocyte-to-monocyte ratio). In the validation set, 83/99 (84%) of the PTC cases, and 44/53 (83%) of the benign cases were properly predicted. Therewith, accuracy, sensitivity, and specificity were respectively 85.5%, 90.9%, and 75.5%. The authors conclude that, using their nomogram, the preoperative PTC diagnosis may be made more accurately.

The main limitations of this study include the relative small sample sizes of both the training and validation set. Further, it is a single center study China, which potentially hampers generalizability to other parts of the world with a different availability of thyroid US and different prevalence of thyroid nodules. Next to this, the constructed nomogram can only be used for PTC, and not for other subtypes like FTC. Therewith, using the nomogram, having a benign result might still result into missing a case of FTC. Additionally, the addition of TSH to the model seems questionable, as, in general, those with low TSH levels are more likely to have a (subclinical) hyperthyroidism caused by a functioning adenoma than having malignant disease. Finally, it is unclear how the thyroid lesions were initially discovered. Recent literature suggests that the risk of recurrence is significantly higher in case PTC was diagnosed after a palpable mass was discovered (23), which suggests that the underlying risk profile of the tumor is important.

The study of Tang *et al.* adds another nomogram to distinguish benign and malignant thyroid nodules from each other. The main novelty is the use of inflammatory markers, besides the usual used US-features, to further optimize the distinction between benign and malignant disease. In contrast with stratification systems like TIRADS (in all its forms), age is also included in the current study; younger age was associated with a higher PTC risk. Recently, Chen *et al.* also showed that age improved their nomogram compared to the ACR-TIRADS (21).

Any stratification/prediction system is most useful when easily applicable. Increasing the number of factors involved in stratification/prediction will complicate the process of risk estimation in clinical practice: the more complicated the equation of which the model consists, the more it's application and acceptance in clinical practice will be complicated. Nevertheless, the study of Tang *et al.* adds to the knowledge how current TIRADS system could be potentially improved in further editions to avoid unnecessary FNA, and subsequently thyroid surgery. Furthermore, this study shows that a clinically useful nomogram for estimating PTC risk using factors which can be determined relatively easily and at low cost [this in contrast with e.g., diagnostic molecular tests or fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) (12,24)] is within reach for clinical practice. Perhaps some refinement and certainly prospective external clinical validation of this nomogram, or others, will enhance the clinical usability and at some points help us in reducing the number of unnecessary thyroid surgeries.

In conclusion, adding other factors, such as age and inflammatory markers, to the present US-based stratification/prediction systems might result into further improvement of the differentiation between benign and malignant nodules.

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References

1. La Vecchia C, Malvezzi M, Bosetti C, et al. Thyroid cancer mortality and incidence: a global overview. Int J Cancer 2015;136:2187-95.
2. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006;295:2164-7.
3. van Velsen EFS, Visser WE, Stegenga MT, et al. Finding the Optimal Age Cutoff for the UICC/AJCC TNM Staging System in Patients with Papillary or Follicular Thyroid Cancer. Thyroid 2021;31:1041-9.
4. van Velsen EFS, Peeters RP, Stegenga MT, et al. Evaluating the use of a two-step age-based cutoff for the UICC/AJCC TNM staging system in patients with papillary or follicular thyroid cancer. Eur J Endocrinol 2022;186:389-97.
5. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1-133.
6. Pacini F, Fuhrer D, Elisei R, et al. 2022 ETA Consensus Statement: What are the indications for post-surgical radioiodine therapy in differentiated thyroid cancer? Eur Thyroid J 2022;11:e210046.
7. Pacini F, Schlumberger M, Dralle H, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154:787-803.
8. Dutch Thyroid Cancer Guidelines 2015. Available online: https://richtlijnendatabase.nl/richtlijn/schildkliercarcinoom
9. Perros P, Boelaert K, Colley S, et al. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf) 2014;81 Suppl 1:1-122.
10. Zerdoud S, Giraudet AL, Leboulleux S, et al. Radioactive iodine therapy, molecular imaging and serum biomarkers for differentiated thyroid cancer: 2017 guidelines of the French Societies of Nuclear Medicine, Endocrinology, Pathology, Biology, Endocrine Surgery and Head and Neck Surgery. Ann Endocrinol (Paris) 2017;78:162-75.
11. Li Y, Jin C, Li J, et al. Prevalence of Thyroid Nodules in China: A Health Examination Cohort-Based Study. Front Endocrinol (Lausanne) 2021;12:676144.
12. Alexander EK, Cibas ES. Diagnosis of thyroid nodules. Lancet Diabetes Endocrinol 2022;10:533-9.
13. Horvath E, Majlis S, Rossi R, et al. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. J Clin Endocrinol Metab 2009;94:1748-51.
14. Kwak JY, Han KH, Yoon JH, et al. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. Radiology 2011;260:892-9.
15. Shin JH, Baek JH, Chung J, et al. Ultrasonography Diagnosis and Imaging-Based Management of Thyroid Nodules: Revised Korean Society of Thyroid Radiology Consensus Statement and Recommendations. Korean J Radiol 2016;17:370-95.
16. Russ G, Bonnema SJ, Erdogan MF, et al. European Thyroid Association Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults: The EU-TIRADS. Eur Thyroid J 2017;6:225-37.
17. Tessler FN, Middleton WD, Grant EG, et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS):

White Paper of the ACR TI-RADS Committee. J Am Coll Radiol 2017;14:587-95.
18. Seifert P, Schenke S, Zimny M, et al. Diagnostic Performance of Kwak, EU, ACR, and Korean TIRADS as Well as ATA Guidelines for the Ultrasound Risk Stratification of Non-Autonomously Functioning Thyroid Nodules in a Region with Long History of Iodine Deficiency: A German Multicenter Trial. Cancers (Basel) 2021;13:4467.
19. Kim DH, Kim SW, Basurrah MA, et al. Diagnostic Performance of Six Ultrasound Risk Stratification Systems for Thyroid Nodules: A Systematic Review and Network Meta-Analysis. AJR Am J Roentgenol 2023;220:791-803.
20. Luisa Garo M, Deandreis D, Campennì A, et al. Accuracy of papillary thyroid cancer prognostic nomograms: a systematic review. Endocr Connect 2023;12:e220457.
21. Chen L, Zhang J, Meng L, et al. A new ultrasound nomogram for differentiating benign and malignant thyroid nodules. Clin Endocrinol (Oxf) 2019;90:351-9.
22. Tang ZW, Li XX, Luo J. Development and validation of the nomogram based on ultrasound, thyroid stimulating hormone, and inflammatory marker in papillary thyroid carcinoma: a case-control study. Transl Cancer Res 2023;12:490-501.
23. Lee IA, Moon G, Kang S, et al. Predictive Factors Indicative of Hemithyroidectomy and Close Follow-Up versus Bilateral Total Thyroidectomy for Aggressive Variants of Papillary Thyroid Cancer. Cancers (Basel) 2022;14:2757.
24. de Koster EJ, de Geus-Oei LF, Dekkers OM, et al. Diagnostic Utility of Molecular and Imaging Biomarkers in Cytological Indeterminate Thyroid Nodules. Endocr Rev 2018;39:154-91.

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