Lymph node status (Core)

Increasing evidence has shown that various characteristics of nodal metastases, e.g., number, size, and extranodal extension (ENE), may provide additional prognostic information. Thus, detailed features of nodal disease ought to be included in the pathology report, and be considered in risk stratification and staging systems.[1-9] A recent meta-analysis by Randolph et al (2012) has shown that small volume subclinical microscopic pathologic N1 disease, i.e., five or fewer subcentimeter metastatic lymph nodes, conveys little prognostic impact on recurrence free survival and disease specific survival in PTC, compared with clinically evident macroscopic nodal disease involving more than 5 lymph nodes, especially those with ENE.[2] The greatest dimension of the largest metastatic deposit in a lymph node should be measured. It is accepted it can be difficult to distinguish multiple small metastases in one large deposit. Many authors recommend measuring the greatest dimension end to end in a single slide including discontinuous deposits.[10] Taking this data into consideration, the National Comprehensive Cancer Network (NCCN) 2019 guidelines no longer recommend completion thyroidectomy and post-operative radioiodine (RAI) in small volume pN1a disease, i.e., <5 involved nodes with metastasis <2 mm in largest dimension.[11] Histologic features of the nodal metastasis that have been incorporated in the American Thyroid Association initial risk stratifications included number of involved lymph nodes (>5 is considered as intermediate risk) and size of the metastatic lymph nodes (≥3 cm as high risk). The presence of psammoma bodies alone in a node is subject to controversy. While some practicing pathologists do not consider these as metastasis, we are in agreement with the College of American Pathologists in considering these lymph nodes as positive for metastatic carcinoma.[12]

Extranodal extension is not an uncommon finding, being reported in up to 12% of papillary carcinoma (PTC) overall and 33% of nodal metastatic PTC.[1,6] Similar to ETE, a well-defined, consensus, histologic diagnostic criterion for ENE is currently lacking.[12,13] A recent study by Du et al (2016) has shown that involvement of perinodal adipose tissue appears to be the most consistent diagnostic criteria of ENE, being considered by eleven participating endocrine pathologists as ENE.[13] However, the overall agreement in diagnosing ENE is only fair among expert pathologists.[13] Nevertheless, studies have repeatedly demonstrated the association between ENE and persistent and/or recurrence disease.[1-8] Hence, it is important to document ENE in the pathology report of a differentiated thyroid carcinoma.

A seven compartment nomenclature is used to define anatomic lymph nodes compartments. Central neck refers to level VI (peri-thyroidal, paralaryngeal, paratracheal, and prelaryngeal (Delphian)) and VII (upper mediastinal). Lateral neck refers to level I (submental/submandibular), II (upper jugular), III (mid jugular), IV (lower jugular) and V (posterior triangle).[14]

At the current time, no additional special techniques should be used other than routine histology for the assessment of nodal metastases (i.e., sentinel lymph node-type protocols are not advocated). However, confirmation by immunohistochemical staining, including thyroglobulin for papillary carcinoma and calcitonin and neuroendocrine markers (e.g., chromogranins, synaptophysin) for medullary carcinoma, may be required.

References

1 Kim JW, Roh JL, Gong G, Cho KJ, Choi SH, Nam SY and Kim SY (2017). Extent of Extrathyroidal Extension as a Significant Predictor of Nodal Metastasis and Extranodal Extension in Patients with Papillary Thyroid Carcinoma. *Ann Surg Oncol* 24(2):460-468.

2 Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, Tufano RP and Tuttle RM (2012). The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid* 22(11):1144-1152.

3 Wu MH, Shen WT, Gosnell J and Duh QY (2015). Prognostic significance of extranodal extension of regional lymph node metastasis in papillary thyroid cancer. *Head Neck* 37(9):1336-1343.

4 Alpert EH, Wenig BM, Dewey EH, Su HK, Dos Reis L and Urken ML (2015). Size distribution of metastatic lymph nodes with extranodal extension in patients with papillary thyroid cancer: a pilot study. *Thyroid* 25(2):238-241.

5 Moritani S (2014). Impact of invasive extranodal extension on the prognosis of patients with papillary thyroid carcinoma. *Thyroid* 24(12):1779-1783.

6 Lango M, Flieder D, Arrangoiz R, Veloski C, Yu JQ, Li T, Burtness B, Mehra R, Galloway T and Ridge JA (2013). Extranodal extension of metastatic papillary thyroid carcinoma: correlation with biochemical endpoints, nodal persistence, and systemic disease progression. *Thyroid* 23(9):1099-1105.

7 Ito Y, Hirokawa M, Jikuzono T, Higashiyama T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K and Miyauchi A (2007). Extranodal tumor extension to adjacent organs predicts a worse cause-specific survival in patients with papillary thyroid carcinoma. *World J Surg* 31(6):1194-1201.

8 Asanuma K, Kusama R, Maruyama M, Fujimori M and Amano J (2001). Macroscopic extranodal invasion is a risk factor for tumor recurrence in papillary thyroid cancer. *Cancer Lett* 164(1):85-89.

9 Ricarte-Filho J, Ganly I, Rivera M, Katabi N, Fu W, Shaha A, Tuttle RM, Fagin JA and Ghossein R (2012). Papillary thyroid carcinomas with cervical lymph node metastases can be stratified into clinically relevant prognostic categories using oncogenic BRAF, the number of nodal metastases, and extra-nodal extension. *Thyroid* 22(6):575-584.

10 Bullock MJ, Beitler JJ, Carlson DL, Fonseca I, Hunt JL, Katabi N, Sloan P, Taylor SM, Williams MD and Thompson LDR (2019). Data Set for the Reporting of Nodal Excisions and Neck Dissection Specimens for Head and Neck Tumors: Explanations and Recommendations of the Guidelines From the International Collaboration on Cancer Reporting. *Arch Pathol Lab Med* 143(4):452-462.

11 National Comprehensive Cancer Network. *Thyroid Cancer* (Version 2.2019). Available from: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf (Accessed 1st November 2019).

12 College of American Pathologists (2019). *Protocol for the Examination of Specimens From Patients With Carcinomas of the Thyroid Gland*. Available from: https://www.cap.org/protocols-and-guidelines/cancer-reporting-tools/cancer-protocol-templates (Accessed 1st May 2019).

13 Du E, Wenig BM, Su HK, Rowe ME, Haser GC, Asa SL, Baloch Z, Faquin WC, Fellegara G, Giordano T, Ghossein R, LiVolsi VA, Lloyd R, Mete O, Ozbek U, Rosai J, Suster S, Thompson LD, Turk AT and Urken ML (2016). Inter-Observer Variation in the Pathologic Identification of Extranodal Extension in Nodal Metastasis from Papillary Thyroid Carcinoma. *Thyroid* 26(6):816-819.

14 Tuttle RM, Morris LF, Haugen BR, Shah JT, Sosa JA, Rohren E, Subramaniam RM, Hunt JL and Perrier ND (2017). Thyroid- differentiated and anaplastic carcinoma. In: *AJCC Cancer Staging Manual 8th edition*. Amin MB, Edge S, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds). Springer., New York