

Extrathyroidal extension (Core)

Extrathyroidal extension (ETE), defined as tumour extension beyond the thyroid capsule into the adjacent soft tissue, is a common pathologic finding detected in 23.5% of all papillary thyroid carcinomas.¹ ETE has long been considered as an adverse prognostic factor with an increased risk of recurrence and mortality.¹⁻⁴ It can be further subdivided into two categories: 1) minimal (or microscopic) ETE, which is invasion into the immediate perithyroidal soft tissue, detected solely at microscopic level and not appreciated clinically or grossly at the time of surgery; and 2) extensive (or gross) ETE that is defined as gross direct extension of the carcinoma into strap muscles (e.g., sternohyoid, sternothyroid, thyrohyoid, and omohyoid muscles), subcutaneous tissue, adjacent viscera (e.g., larynx, trachea, and oesophagus), or recurrent laryngeal nerve, and is typically established clinically by imaging or during the operation. These two categories of ETE bear different prognostic values: the risk of recurrence associated with minor extrathyroidal extension is approximately 3 to 9%,⁵⁻¹¹ compared with 23 to 40% risk of recurrence in patients with gross ETE.^{5,6,8-10,12,13} Furthermore, several recent studies have shown that microscopic ETE is not an independent predictor for persistent disease, recurrence free survival and disease specific survival.^{7,8,11,13-15} National Comprehensive Cancer Network (NCCN) 2019 guidelines recommend completion thyroidectomy and post-operative radioactive iodine (RAI) for lesions with gross ETE, while the administration of 30 mCi of iodine 131 is considered optional for patients with a primary tumour of <4 cm, clinical M0 and minor ETE.¹⁶ Histologically, the thyroid gland is devoid of a well-defined capsule in many areas along its periphery, and the follicles are often intermingled with adipose tissue or even skeletal muscle.¹⁷ Therefore, the very definition of microscopic ETE is problematic and subjective, and a universally accepted pathologic criterion for ETE is lacking. The fact that microscopic ETE is associated with poor interobserver agreement¹⁷ and does not affect recurrence and survival raise concerns of whether microscopic ETE alone is sufficient to upstage a patient. Because of all the above, in the most recent American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) 8th editions, microscopic ETE has been removed entirely from the staging system of differentiated thyroid carcinoma.^{18,19} Gross ETE invading strap muscles only, by a tumour of any size, will be staged as pT3b, while gross ETE with invasion into subcutaneous soft tissue, larynx, trachea, oesophagus, or recurrent laryngeal nerve will be staged as pT4a. In view of the above, the pathologists' role is 1) to mention in their report the ETE seen histologically (whether microscopic or gross) and 2) communicate with the surgeon in regard to staging since the determination of gross ETE is done intra-operatively.

References

- 1 Ortiz S, Rodriguez JM, Soria T, Perez-Flores D, Pinero A, Moreno J and Parrilla P (2001). Extrathyroid spread in papillary carcinoma of the thyroid: clinicopathological and prognostic study. *Otolaryngol Head Neck Surg* 124(3):261-265.
- 2 Andersen PE, Kinsella J, Loree TR, Shaha AR and Shah JP (1995). Differentiated carcinoma of the thyroid with extrathyroidal extension. *Am J Surg* 170(5):467-470.
- 3 Carcangiu ML, Zampi G, Pupi A, Castagnoli A and Rosai J (1985). Papillary carcinoma of the thyroid. A clinicopathologic study of 241 cases treated at the University of Florence, Italy. *Cancer* 55(4):805-828.
- 4 McConahey WM, Hay ID, Woolner LB, van Heerden JA and Taylor WF (1986). Papillary thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. *Mayo Clin Proc* 61(12):978-996.

- 5 Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K and Miyauchi A (2006). Prognostic significance of extrathyroid extension of papillary thyroid carcinoma: massive but not minimal extension affects the relapse-free survival. *World J Surg* 30(5):780-786.
- 6 Jukkola A, Bloigu R, Ebeling T, Salmela P and Blanco G (2004). Prognostic factors in differentiated thyroid carcinomas and their implications for current staging classifications. *Endocr Relat Cancer* 11(3):571-579.
- 7 Nixon IJ, Ganly I, Patel S, Palmer FL, Whitcher MM, Tuttle RM, Shaha AR and Shah JP (2011). The impact of microscopic extrathyroid extension on outcome in patients with clinical T1 and T2 well-differentiated thyroid cancer. *Surgery* 150(6):1242-1249.
- 8 Radowsky JS, Howard RS, Burch HB and Stojadinovic A (2014). Impact of degree of extrathyroidal extension of disease on papillary thyroid cancer outcome. *Thyroid* 24(2):241-244.
- 9 Riemann B, Kramer JA, Schmid KW, Dralle H, Dietlein M, Schicha H, Sauerland C, Frankewitsch T and Schober O (2010). Risk stratification of patients with locally aggressive differentiated thyroid cancer. Results of the MSDS trial. *Nuklearmedizin* 49(3):79-84.
- 10 Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K and Miyauchi A (2006). Minimal extrathyroid extension does not affect the relapse-free survival of patients with papillary thyroid carcinoma measuring 4 cm or less over the age of 45 years. *Surg Today* 36(1):12-18.
- 11 Shin JH, Ha TK, Park HK, Ahn MS, Kim KH, Bae KB, Kim TH, Choi CS, Kim TK, Bae SK and Kim SH (2013). Implication of minimal extrathyroidal extension as a prognostic factor in papillary thyroid carcinoma. *Int J Surg* 11(9):944-947.
- 12 Fukushima M, Ito Y, Hirokawa M, Miya A, Shimizu K and Miyauchi A (2010). Prognostic impact of extrathyroid extension and clinical lymph node metastasis in papillary thyroid carcinoma depend on carcinoma size. *World J Surg* 34(12):3007-3014.
- 13 Xu B, Ibrahimasic T, Wang L, Sabra MM, Migliacci JC, Tuttle RM, Ganly I and Ghossein R (2016). Clinicopathologic Features of Fatal Non-Anaplastic Follicular Cell-Derived Thyroid Carcinomas. *Thyroid* 26(11):1588-1597.
- 14 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.
- 15 Rivera M, Ricarte-Filho J, Tuttle RM, Ganly I, Shaha A, Knauf J, Fagin J and Ghossein R (2010). Molecular, morphologic, and outcome analysis of thyroid carcinomas according to degree of extrathyroid extension. *Thyroid* 20(10):1085-1093.
- 16 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).
- 17 Su HK, Wenig BM, Haser GC, Rowe ME, Asa SL, Baloch Z, Du E, 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 Minimal Extrathyroidal Extension in Papillary Thyroid Carcinoma. *Thyroid* 26(4):512-517.

- 18 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, Meyer LR and (eds). (2017). *AJCC Cancer Staging Manual. 8th ed.* Springer., New York.
- 19 International Union against Cancer (2017). *TNM Classification of Malignant Tumours (8th Edition)*. Brierley JD, Gospodarowicz MK and Wittekind C (eds). Wiley-Blackwell., New York.