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Crucial parameters in thyroid carcinoma reporting – challenges, controversies, and clinical implications

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Abstract

In the modern era, a pathology report of thyroid carcinoma requires the inclusion of numerous prognostically relevant histopathologic features, e.g. the presence and extent of vascular and capsular invasion, extrathyroidal extension, the surgical margin status, and the characteristics of nodal metastasis. These pathologic features are crucial components of the initial risk stratification to determine the need for completion thyroidectomy and/or post-operative radioactive iodine ablation therapy. The current review aims to summarize the diagnostic criteria, the controversies, the prognostic impacts, and the challenges of these pathologic characteristics, focusing specifically on the parameters that are incorporated into the American Joint Committee on Cancer (AJCC) staging system, College of American Pathologists (CAP) reporting template, American Thyroid Association (ATA), and National Comprehensive Cancer Network (NCCN) guidelines.

Keywords

Extrathyroidal extension; lymphovascular invasion; AJCC staging

Introduction

In the modern era, a pathology report requires the inclusion of numerous prognostically relevant histopathologic tumor characteristics. Thyroid carcinoma is no exception to such rules. In addition to tumor type, variant and size, other features such as the presence and extent of capsular invasion (CI), vascular invasion (VI) and extrathyroidal extension (ETE), margin status, as well as the number and size of neck lymph node(s) with metastatic carcinoma, have been shown to provide additional prognostic information, and are now required in a standardized pathology report for thyroid carcinoma¹, and in the initial risk

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stratification published by several renowned organizations, e.g. the American Thyroid Association (ATA), the National Comprehensive Cancer Network (NCCN) and the American Joint Committee for Cancer (AJCC) staging manual, to guide management and determine the need for radioactive iodine (RAI) ablation therapy²⁻⁴. Hence, it becomes increasingly important for pathologists to report these parameters, and for clinicians to understand the potential impacts of such on patients' management. The current review intends to summarize the definition, diagnostic challenges, controversies, and the clinical impacts of each pathologic parameter which is incorporated into a routine pathology report of differentiated follicular derived carcinoma.

Extrathyroidal extension

Extrathyroidal extension, defined as tumor extension beyond the thyroid capsule into the adjacent soft tissue, is a common pathologic finding detected in 23.5% of all papillary thyroid carcinomas⁵. ETE has long been considered as an adverse prognostic factor with an increased risk of recurrence and mortality⁵⁻⁸. 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 esophagus), or recurrent laryngeal nerve, and is typically established clinically by imaging or during the operation (Figure 1). These two categories of ETE bear different prognostic values: the risk of recurrence associated with minor extrathyroidal extension is approximately 3 to 9%⁹⁻¹⁵, compared with 23 to 40% risk of recurrence in patients with gross ETE^{9, 10, 12-14, 16, 17}. Furthermore, several recent studies have shown that microscopic ETE is not an independent predictor for persistent disease, recurrence free survival and disease specific survival (Figure 2)^{11, 12, 15, 18-20}. Under the 2015 ATA guidelines, microscopic ETE is considered as a feature for intermediate risk lesion which may be subjected to post-operative radioactive iodine (RAI) treatment, while tumors with gross ETE are defined as high risk lesions and thus mandating a (near-)total thyroidectomy and post-operative RAI therapy². Similarly, NCCN 2017 guidelines recommend completion thyroidectomy and post-operative RAI for lesions with gross ETE, while the administration of 30 mCi of ¹³¹I is considered optional for patients with a primary tumor of < 4 cm, clinical M0 and minor ETE³. 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 muscle²¹. Therefore, the very definition of microscopic ETE is problematic and subjective, and a universally accepted pathologic criterion for ETE is lacking. In a recent study involving eleven expert endocrine pathologists, the following histologic diagnostic criteria have been utilized and recognized as microscopic ETE: perithyroidal fat involvement by 9 of 11 pathologists; perithyroidal skeletal muscle involvement by 11 of 11 pathologists, perithyroidal nerve involvement by 9 of 11 pathologists, and perithyroidal thick-wall vessel involvement by 7 of 11 pathologists. Additionally, in tumors arising from the isthmus, three of eleven pathologists did not consider involvement of skeletal muscle as evidence of

microscopic ETE²². Not surprisingly, the interobserver agreement for minimal ETE was poor with a kappa value of 0.14 even among expert pathologists²².

In the seventh edition of AJCC staging system, a tumor with minimal ETE is staged as pT3 regardless of tumor size, while gross ETE beyond strap muscles is staged as T4 disease²³. The facts that microscopic ETE is associated with poor interobserver agreement and does not affect recurrence and survival raise concerns of whether microscopic ETE alone is sufficient to upstage a patient as pT3. Therefore, in the upcoming AJCC eighth edition that will be implemented on January 1st, 2018, microscopic ETE has been removed entirely from the staging system of differentiated thyroid carcinoma⁴. Gross ETE invading strap muscles only by a tumor of any size will be staged as pT3b, while gross ETE with invasion into subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve as pT4a.

In summary, recent evidence has shown that microscopic or minimal ETE bears limited prognostic significance (i.e. does not impart worse outcome than absence of ETE), and may not be a reproducible histologic feature. In comparison, carcinomas with gross ETE are associated with high risk of recurrence, and are considered as high stage (at least pT3) and high risk lesions, which should trigger additional therapy, e.g. completion thyroidectomy and post-operative RAI. Therefore, it is crucial for the pathologists and clinicians to realize the difference between microscopic and gross ETE. A knee jerk response from the clinicians to consider completion thyroidectomy and post-operative RAI to a pathologic report mentioning microscopic ETE only may subject the patient to unnecessary treatment especially in PTC cases²⁰.

Margin assessment

The margin status of a surgical resection for differentiated thyroid carcinoma is a mandatory reporting element in the current College of American Pathologists (CAP) guidelines¹, and can be divided into three categories: a R0 resection (microscopically negative margin), a R1 resection (grossly complete resection with microscopically positive margin), and a R2 resection (grossly positive margin or incomplete resection)⁴. Histologically, a positive margin is defined by the presence of tumor cells at the inked tissue border and/or the outer aspect of the thyroid gland (Figure 3)^{24–27}. The reported frequency of microscopically positive margin is between 6.1% and 14.1%^{24–27}. Several recent studies have shown that microscopically positive margin is not an independent predictor for recurrence and disease free survival, especially after adjusting for tumor stage and ETE^{25–27}. Taken these into consideration, the current ATA guideline has only included incomplete R2 resection into the risk stratification as a feature of high risk lesions². In contrast, NCCN 2017 guideline has included any positive resection margin as one of the criteria along with large tumor (> 4 cm), gross ETE, macroscopic nodal metastasis, macroscopic multifocal disease, and vascular invasion to recommend completion thyroidectomy³.

Interestingly, Lang et al. has shown that a microscopic positive posterior margin was an independent predictor for recurrence free survival with a 23-fold risk of recurrence, while a positive anterior margin did not pose a significant risk for recurrence²⁵. Hence, it may be prudent to ink the anterior and posterior margins differently when processing thyroid

specimens in pathology laboratories and to document the status of anterior and posterior margins separately in the pathology report.

Characteristics of regional nodal metastases

Regional lymph node metastasis is a common finding in papillary thyroid carcinoma, being detected in up to 80% of patients as a result of extensive neck dissection and meticulous histological examination²⁸. Most studies have shown that regional nodal metastasis, especially lateral neck nodal disease, carries prognostic significance^{4, 28–32}. The impact of nodal metastases on disease specific survival and recurrence free survival are relatively small, and are most evident in older patients^{30–32}. Nodal metastases are incorporated into AJCC tumor, nodal disease, and distant metastasis (TNM) staging and prognostic stage group, and can be further divided into central (pN1a) and lateral compartment involvement (pN1b)^{4, 29}.

Recently, 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 system^{18, 28, 33–39}. A recent meta-analysis by Randolph et al. 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 ENE²⁸. Taken this data into consideration, the NCCN 2017 guidelines no longer recommend completion thyroidectomy and post-operative RAI in small volume pN1a disease, i.e. < 5 involved nodes with metastasis < 2 mm in largest dimension³. Histologic features of the nodal metastasis that has been incorporated in the ATA 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).

Extranodal extension is not an uncommon finding, being reported in up to 12% of PTC overall and 33% of nodal metastatic PTC^{18, 36}. Similar to ETE, a well-defined consensus histologic diagnostic criterion for ENE is currently lacking^{1, 40}. A recent study by Du et al. 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 ENE⁴⁰. However, the overall agreement in diagnosing ENE is only fair with a kappa value of 0.35 among expert pathologists⁴⁰. Nevertheless, studies have repeatedly demonstrated the association between ENE and persistent and/or recurrence disease^{18, 28, 33–38}. Hence, it is important to document ENE in the pathology report of a differentiated thyroid carcinoma.

Taken these recent data into consideration, the upcoming AJCC 8th edition has recommended recording detailed histologic features of nodal metastasis in the pathologic report, including number of involved lymph nodes, number of lymph nodes sampled, location of the involved lymph nodes, size of the largest involved lymph node, size of metastatic foci within involved lymph node, and the presence of extranodal extension⁴.

Vascular invasion

Vascular invasion was first described in thyroid malignancy by Graham ⁴¹ in 1924. Although three groups have shown that the mere existence of VI, regardless of the extent, entails a substantial risk of distant metastasis, a larger body of literature have shown that the extent (rather than the existence) of vascular invasion is a prognostic factor in low grade thyroid carcinomas^{42–47}. Based on these evidences, the current ATA and NCCN guideline, as well as the upcoming 4th edition of WHO classification, have advocated to encapsulated follicular and Hurthle cell carcinoma with extensive vascular invasion from those with capsular invasion only and/or focal (a few foci) of vascular invasion ^{3, 48, 49}. Tumors with minimal VI (defined as a few microscopic foci by NCCN, or less than 5 foci by ATA guidelines) are associated with a low risk of recurrence (0 – 5%) with an overall similar outcome to those without VI in low grade thyroid carcinoma^{42–46}. Fortunately, extensive VI appears to be a relatively rare event in differentiated thyroid carcinoma, being present in 8.7% of well-differentiated encapsulated thyroid carcinomas in one study⁴⁶. When it occurs, extensive vascular invasion is an independent predictor of recurrence, is associated with 42% risk of distant metastasis, and is frequently observed in patients who died of thyroid carcinoma^{19, 43, 46, 50}. Based on these emerging evidences, the most recent ATA guidelines have classified an intrathyroidal follicular thyroid carcinoma with minimal VI as low risk lesion, which does not command a completion thyroidectomy and RAI ablation therapy². Similarly, the NCCN 2017 guidelines have defined minimal vascular invasion as a few (one to four foci) of VI, and does not mandate RAI administration in an intrathyroidal well defined follicular or Hurthle cell carcinoma with minimal VI³. On the other hand, the presence of extensive vascular invasion (>4 foci) in a differentiated thyroid carcinoma will place the patient into the high risk group, which mandates total thyroidectomy and post-operative RAI therapy^{2, 3}. In Hurthle cell carcinoma, tumors with extensive VI (≥ 4 foci) or extrathyroidal VI were associated with a different RNA expression profile compared with minimally invasive Hurthle cell carcinoma including those with focal VI (< 4 foci), suggesting that the molecular signatures might be different according to the extent of VI⁵¹. Hence, it is crucial for pathologists to reliably evaluate and report the presence and extent of vascular invasion in low grade thyroid carcinoma in order to direct risk stratification and subsequent clinical treatment decisions.

However, the very definition of vascular invasion has been surrounded by controversies. The initial definition of VI delineated in the authoritative 1992 and 2015 AFIP fascicles ^{52, 53} and adopted in the majority of the published literature mandated the following two conditions to be qualified for VI: (1) the involved blood vessels has to be located within or outside of the tumor capsule; and (2) the intravascular polypoid tumor growth must be attached to the vessel wall, admixed with fibrin or covered by endothelium (Figure 4). Areas of VI that are closely adjacent to one another are typically counted as separate foci ⁴⁶. On the other hand, a recent study published by Mete and Asa did not consider tumor protrusion into vascular space lined by endothelial cells alone as a diagnostic criterion for VI, but rather required fibrin thrombus adherent to intravascular tumor⁵⁴. This is based on the idea that intravascular endothelial lined tumor is separated from the bloodstream by endothelial cells, while thrombus formation is indicative of host response and coagulation pathway

activation⁵⁴. When this more stringent criterion of VI is applied, the incidence of VI in differentiated thyroid carcinoma decreased drastically from 7–62%^{46, 47, 55–57} to 3%⁵⁴, while the risk of distant metastasis in association with the mere existence of VI becomes 35%. This latter approach may fail to identify a significant proportion of thyroid tumors with VI, focal or extensive, that should be classified as carcinoma based on the presence of invasion, and that may benefit from appropriate risk stratification and/or additional therapies.

Capsular invasion

The CAP guidelines and AFIP fascicle define capsular invasion as a tumor that completely transgressed the tumor capsule beyond the outer contour with or without neocapsule formation or satellite nodule lying outside of the tumor capsule (Figure 5)^{1, 53}. Some authorities have advised to use the term minimally invasive to describe those carcinomas with microscopic capsular invasion only (regardless of number of CI foci), since their metastatic rate is close to 0^{45, 46, 58–61}. In contrast, widely invasive follicular carcinoma was used for carcinoma with grossly apparent invasion into the thyroid and peri-thyroidal soft tissue (i.e. ETE)¹ and is associated with a high risk of distant metastasis⁶². The existence of invasion, including CI, is the histologic characteristics which distinguish and differentiate certain types of malignant thyroid tumors from their non-malignant counterparts, e.g. follicular carcinoma from follicular adenoma, Hurthle cell carcinoma from Hurthle cell adenoma, as well as encapsulated follicular variant of papillary thyroid carcinoma with invasion from noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)⁶³. However, as multiple studies have shown that carcinomas with only CI, regardless of extent, is associated with an overall excellent prognosis^{44, 46, 58, 64–66}, CI was not a factor being considered in risk stratification in ATA and NCCN guidelines^{2, 3}.

Conclusions

The field of thyroid pathology has evolved dramatically over the past several decades. Several major changes occurred, including incorporation of numerous detailed pathologic characteristics (e.g. the presence and extent of VI and ETE) into the pathology report. These shifts in the characterization of thyroid carcinoma have led to the refining of risk stratification and de-escalation of therapy in differentiated thyroid carcinoma. The prognosis and therapy of thyroid carcinomas can be better delineated if a meticulous microscopic analysis is performed. An accurate assessment of the extent of VI for example is crucial. Hence, it is important for pathologists to meticulously report on histopathologic features other than tumor type such as extent of invasion in order to better predict tumor spread and survival and assist clinical decision making.

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Figure 1. Extrathyroidal extension (ETE). (A/B) Gross ETE: A patient with papillary thyroid carcinoma (PTC) with pre-operative radiological evidence of invasion into trachea. Macroscopically (A), an infiltrative firm beige mass was present involving thyroid gland proper and infiltrating between tracheal rings (T). Microscopically, the carcinoma infiltrated in between tracheal cartilage and was present at the tracheal mucosal surface. This tumor should be staged as pT4a based on gross ETE into trachea. (C/D) Microscopic (minimal)

ETE: tumor nests were present in between perithyroidal adipose tissue (FAT, panel C) or skeletal muscle (M, panel D).

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Figure 2. Adverse outcome (defined as the presence of disease at last follow-up) according to degree of extra-thyroid extension (ETE) in papillary thyroid carcinoma cases with adequate follow-up. Only patients with gross ETE (15 cases) had an adverse outcome. There was no survival difference between patients without ETE (11 cases) and those with microscopic (micro) ETE (31 cases). Reprinted with permission from reference ²⁰.

Figure 3. Microscopic positive resection margin (i.e. R1 resection). Arrows: tumor cells with thermal artifact are present at the inked tissue edge. The lesion is an encapsulated follicular variant of papillary thyroid carcinoma.

Figure 4. Vascular invasion. Tumor emboli covered by endothelial cells are present within capsular vasculature (A), which may be associated with fibrin thrombus (B, arrow heads).

Figure 5.

Common forms of capsular invasion. A: Hurthle cell carcinoma showing the typical mushroom like shape invasion (ci) into the full thickness of the capsule (c). Note the presence of a new fibrous capsule at the leading edge of the invasive tumor bud (arrow). B: Hurthle cell carcinoma in a different patient displaying capsular invasion in the form of a tumor nodule (ci) lying immediately outside an intact capsule (c). The point of entry into the capsule is not apparent at this particular level. This is not an uncommon finding.