Protocol for the Examination of Specimens from Patients with Carcinomas of the Thyroid Gland

Protocol applies to all carcinomas of the thyroid gland. Lymphomas, sarcomas and metastases are not included.

Based on AJCC/UICC TNM, 7th edition

Protocol web posting date: October 2009

Authors

Ronald Ghossein, MD, FCAP*
Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY
Sylvia L. Asa, MD, PhD, FCAP
Department of Pathology, University Health Network, Toronto, ON
Leon Barnes, MD
Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA
John Chan, MD, FCAP
Department of Pathology, Queen Elizabeth Hospital, Hong Kong
Louis B. Harrison, MD
Department of Radiation Oncology, Beth Israel Medical Center, St. Luke's and Roosevelt Hospitals, New York, NY
Clara S. Heffess, MD
Department of Otorhinolaryngic and Endocrine Pathology, Armed Forces Institute of Pathology Washington, DC
Jennifer Leigh Hunt, MD, FCAP
Department of Pathology, Massachusetts General Hospital, Boston, MA
Mary S. Richardson, MD, DDS, FCAP
Department of Pathology, Medical University of South Carolina, Charleston, SC
Jatin Shah, MD, FACS
Department of Head and Neck Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY
Lester D. R. Thompson, MD, FCAP
Department of Pathology, Southern California Permanente Medical Group, Woodland Hills, CA
Bruce M. Wenig, MD, FCAP*†
Department of Pathology and Laboratory Medicine. Beth Israel Medical Center, St. Luke's and Roosevelt Hospitals, New York, NY
For the Members of the Cancer Committee, College of American Pathologists

*denotes primary author. † denotes senior author. All other contributing authors are listed alphabetically.

Previous contributors: Virginia A. LiVolsi, MD, Zubair W. Baloch, MD, Michael Cibull, MD, Susan Mandel, MD, Robert Udelsman, MD

The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the “Surgical Pathology Cancer Case Summary (Checklist)” portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

The inclusion of a product name or service in a CAP publication should not be construed as an endorsement of such product or service, nor is failure to include the name of a product of service to be construed as disapproval.

Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

THYROID GLAND: Resection

Select a single response unless otherwise indicated.

Procedure (select all that apply) (Note A)
___ Thyroid lobectomy
    ___ Right
    ___ Left
___ Partial thyroidectomy (anything less than a lobectomy)
    ___ Right
    ___ Left
___ Hemithyroidectomy (lobe and part or all of isthmus)
    ___ Right
    ___ Left
___ Total thyroidectomy
___ Total thyroidectomy with central compartment dissection
___ Total thyroidectomy with right neck dissection
___ Total thyroidectomy with left neck dissection
___ Total thyroidectomy with bilateral neck dissection
___ Other (specify): _____
___ Not specified

***Received**:
*___ Fresh
*___ In formalin
*___ Other

Specimen Integrity
___Intact
___Fragmented

Specimen Size
Right lobe: ___ x ___ x ___ cm
Left lobe: ___ x ___ x ___ cm
Isthmus ± pyramidal lobe: ___x ____x ____ cm
Central compartment: ___ x ___ x ___ cm
Right neck dissection: ___ x ___ x ___ cm
Left neck dissection: ___ x ___ x ___ cm
* Additional dimensions (specify): ___ x ___ x ___ cm

***Specimen Weight**
*Specify: ____ g

Tumor Focality (select all that apply) (Note B)
___ Unifocal
___ Multifocal (specify):
    ___ Ipsilateral
    ___ Bilateral
    ___ Midline (isthmus)

Dominant Tumor (Note B)

Tumor Laterality (select all that apply)
___ Right lobe
___ Left lobe
___ Isthmus
___ Not specified

Tumor Size **(Note C)**
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined

Histologic Type (select all that apply) (**Note D**)
___ Papillary carcinoma
    Variant, specify:
        ___ Classical (usual)
        ___ Clear cell variant
        ___ Columnar cell variant
        ___ Cribriform-morular variant
        ___ Diffuse sclerosing variant
        ___ Follicular variant
        ___ Macrofollicular variant
        ___ Microcarcinoma (occult, latent, small, papillary microtumor)
        ___ Oncocytic or oxyphilic variant
        ___ Solid variant
        ___ Tall cell variant
        ___ Warthin-like variant
        ___ Other, specify: _____
    Architecture:
        ___ Classical (papillary)
        ___ Cribriform-morular
        ___ Diffuse sclerosing
        ___ Follicular
        ___ Macrofollicular
        ___ Solid
        ___ Other, specify: _____
    Cytomorphology:
        ___ Classical
        ___ Clear cell
        ___ Columnar cell
        ___ Oncocytic or oxyphilic
        ___ Tall cell

___ Follicular carcinoma
    Variant, specify:
        ___ Clear cell
        ___ Oncocytic (Hürthle cell)
        ___ Other, specify: _____
___ Poorly differentiated thyroid carcinomas, including insular carcinoma
___ Medullary carcinoma
___ Undifferentiated (anaplastic) carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

***Histologic Grade** **(Note E)**
*___ Not applicable
*___ GX: Cannot be assessed
*___ G1: Well differentiated
*___ G2: Moderately differentiated
*___ G3: Poorly differentiated
*___ G4: Undifferentiated
*___ Other (specify): _____

Margins **(Note F)**
___ Cannot be assessed
___ Margins uninvolved by carcinoma
    *Distance of invasive carcinoma to closest margin: ___ mm
___ Margin(s) involved by carcinoma
    *Site(s) of involvement: _____

Tumor Capsule
___ Cannot be assessed
___ Totally encapsulated
___ Partially encapsulated
___ None

Tumor Capsular Invasion (select all that apply) **(Note G)**
___ Cannot be assessed
___ Not identified
___ Present:
    Extent:
    ___ Minimal
    ___ Widely invasive
___ Indeterminate

Lymph-Vascular Invasion (select all that apply**) (Note G)**
___ Cannot be assessed
___ Not identified
___ Present:
    Extent:
    ___ Focal (less than 4 vessels)
    ___ Extensive (4 or more vessels)
___ Indeterminate

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

*Perineural Invasion
*___ Not identified
*___ Present
*___ Indeterminate

Extrathyroidal Extension (select all that apply) **(Note H)**
___ Cannot be assessed
___ Not identified
___ Present
Extent:
___ Minimal
___ Extensive

Second Tumor (for multifocal tumors only)

Tumor Laterality (select all that apply)
___ Right lobe
___ Left lobe
___ Isthmus
___ Not specified

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined

Histologic Type (select all that apply)
___ Papillary carcinoma
Variant, specify:
___ Classical (usual)
___ Clear cell variant
___ Columnar cell variant
___ Cribriform-morular variant
___ Diffuse sclerosing variant
___ Follicular variant
___ Macrofollicular variant
___ Microcarcinoma (occult, latent, small, papillary microtumor)
___ Oncocytic or oxyphilic variant
___ Solid variant
___ Tall cell variant
___ Warthin-like variant
___ Other, specify: _____
Architecture:
___ Classical (papillary)
___ Cribriform-morular
___ Diffuse sclerosing
___ Follicular
___ Macrofollicular
___ Solid
___ Other, specify: _____

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Cytomorphology:
___ Classical
___ Clear cell
___ Columnar cell
___ Oncocytic or oxyphilic
___ Tall cell

___ Follicular carcinoma
Variant, specify:
___ Clear cell
___ Oncocytic (Hürthle cell)
___ Other, specify: _____

___ Poorly differentiated thyroid carcinomas, including insular carcinoma
___ Medullary carcinoma
___ Undifferentiated (anaplastic) carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

*Histologic Grade
*___ Not applicable
*___ GX: Cannot be assessed
*___ G1: Well differentiated
*___ G2: Moderately differentiated
*___ G3: Poorly differentiated
*___ G4: Undifferentiated
*___ Other (specify): _____

Margins
___ Cannot be assessed
___ Margins uninvolved by carcinoma
*Distance of invasive carcinoma to closest margin: ___ mm
___ Margin(s) involved by carcinoma
*Site(s) of involvement: _____

Tumor Capsule
___ Cannot be assessed
___ Totally encapsulated
___ Partially encapsulated
___ None

Tumor Capsular Invasion (select all that apply)
___ Cannot be assessed
___ Not identified
___ Present:
Extent:
___ Minimal
___ Widely invasive
___ Indeterminate

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Lymph-Vascular Invasion (select all that apply)
___ Cannot be assessed
___ Not identified
___ Present
    Extent:
    ___ Focal (less than 4 vessels)
    ___ Extensive (4 or more vessels)
___ Indeterminate

*Perineural Invasion
*___ Not identified
*___ Present
*___ Indeterminate

Extrathyroidal Extension (select all that apply)
___ Cannot be assessed
___ Not identified
___ Present
    Extent:
    ___ Minimal
    ___ Extensive

Pathologic Staging (pTNM) (Notes J through N)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (post-treatment)

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pT1: Tumor size 2 cm or less, limited to thyroid
___ pT1a: Tumor 1 cm or less in greatest dimension limited to the thyroid.
___ pT1b: Tumor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
___ pT2: Tumor more than 2 cm, but not more than 4 cm, limited to thyroid
___ pT3: Tumor more than 4 cm limited to thyroid or any tumor with minimal extrathyroid extension (eg, extension to sternothyroid muscle or perithyroid soft tissues)
___ pT4a: Moderately advanced disease. Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve
___ pT4b: Very advanced disease. Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels

Note: There is no category of carcinoma in situ (pTis) relative to carcinomas of thyroid gland.

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Anaplastic Carcinoma

___ pT4a: Intrathyroidal anaplastic carcinoma—surgically resectable
___ pT4b: Extrathyroidal anaplastic carcinoma—surgically unresectable

Regional Lymph Nodes (pN)[#] (**Note L**)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1a: Nodal metastases to Level VI (pretracheal, paratracheal and prelaryngeal/Delphian) lymph nodes
___ pN1b: Metastases to unilateral, bilateral or contralateral cervical (Levels I, II, III, IV, V) or retropharyngeal or superior mediastinal lymph nodes (Level VII).
Specify: Number examined: ___
Number involved: ___

[#] *Superior mediastinal lymph nodes are considered regional lymph nodes (level VII). Midline nodes are considered ipsilateral nodes.*

* Lymph Node, Extranodal Extension (**Note L**)
* ___ Not identified
* ___ Present
* ___ Indeterminate

Distant Metastasis (pM)
___ Not applicable
___ pM1: Distant metastasis
*Specify site(s), if known: _____
* Source of pathologic metastatic specimen (specify): _____

***Additional Pathologic Findings (select all that apply)**
*___ Adenoma
*___ Adenomatoid nodule(s) or Nodular follicular disease (eg, nodular hyperplasia, goitrous thyroid)
*___ Diffuse hyperplasia (Graves' disease)
*___ Thyroiditis:
  *___ Advanced
  *___ Focal (nonspecific)
  *___ Palpation
  *___ Other (specify): _____
*___ Parathyroid gland(s):
  *___ Within normal limits
  *___ Hypercellular
  *___ Other (specify): _____
*___ C-cell hyperplasia
*___ None identified
*___ Other (specify): _____

***Ancillary Studies (Note O)**
*Specify type (eg, histochemistry, immunohistochemistry, DNA analysis: _____
*Specify results: _____

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

***Clinical History (select all that apply)**

*___ Radiation exposure:
    *___ Yes (specify type): _____
    *___ No
    *___ Indeterminate
*___ Family history
*___ Other (specify): _____

***Comment(s)**

Explanatory Notes

Scope of Guidelines

The reporting of thyroid cancer is facilitated by the provision of a checklist illustrating the features required for comprehensive patient care. However, there are many cases in which the individual practicalities of applying such a checklist may not be straightforward. Common examples include finding the prescribed number of lymph nodes, trying to determine the compartments of the radical neck dissection, and determining if isolated tumor cells in a lymph node represent metastatic disease. Checklists have evolved to include clinical, radiographic, morphologic, immunohistochemical, and molecular results in an effort to guide clinical management. This checklist tries to remain simple while still incorporating important pathologic features as proposed by the American Joint Committee on Cancer (AJCC) Cancer Staging Manual,[1] the World Health Organization Classification of Tumours,[2] the TNM classification, the American College of Surgeons Commission on Cancer, and the International Union Against Cancer (UICC).[3] This checklist is to be used as a guide and resource, an adjunct to diagnosing and managing cancers of the thyroid gland in a standardized manner. It should not be used as a substitute for dissection or grossing techniques and does not give histologic parameters to reach the diagnosis. Subjectivity is always a factor, and elements listed are not meant to be arbitrary but are meant to provide uniformity of reporting across all the disciplines that use the information. It is a foundation of practical information that will help to meet the requirements of daily practice to benefit both clinicians and patients alike.

A. Anatomical Sites of the Thyroid Gland (Figure 1)

The thyroid gland ordinarily is composed of a right and a left lobe lying adjacent and lateral to the upper trachea and esophagus. An isthmus connects the two lobes, and in some cases a pyramidal lobe is present extending cephalad anterior to the thyroid cartilage.

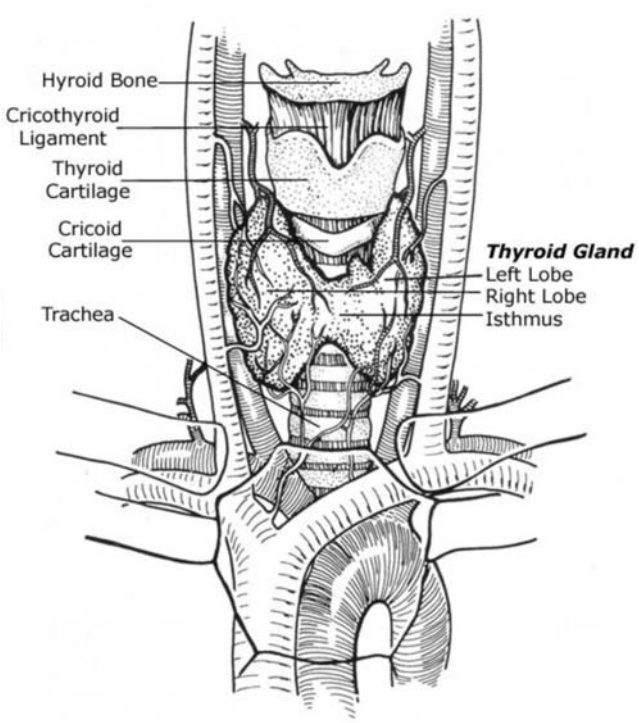

Figure 1. Anatomy of the thyroid gland and adjacent structures. From Kini SR. *Thyroid Cytopathology: An Atlas and Text*. Phildelphia, PA: Lippincott Williams & Wilkins; 2008. Modified with permission.

B. Tumor Site

The thyroid may give rise to multiple foci of carcinoma in the same gland. This protocol primarily is applicable to the dominant excised tumor, but in the case of multiple lesions, the second tumor should also be detailed. To this end, the protocol includes complete sections for the "Dominant Tumor" as well as for "Second Tumor." If more than two foci of carcinoma are identified, other foci should be noted in the section on Additional Pathological Findings.

C. Tumor Size

Tumor size has a significant impact on prognosis. Papillary carcinomas measuring less than 1 cm are associated with an excellent prognosis, while tumors measuring over 4 cm are associated with a worse prognosis.[3-5] For follicular carcinomas, tumor size over 3.5 cm is associated with a worse prognosis. [5] For medullary carcinomas, small tumors discovered through screening are associated with an excellent prognosis, whereas tumors measuring over 1 cm are associated with a worse prognosis. [5]

D. Histologic Type

The histologic classification recommended below is modified from the World Health Organization (WHO) published recommendations.[2] This protocol applies only to carcinomas and does not apply to lymphomas, sarcomas or metastatic tumors to the thyroid gland. Given the fact that the classification of papillary carcinoma is predicated on the combination of architectural and cytomorphologic findings, in addition to the WHO classification, this protocol recommends detailing the architectural and cytomorphologic findings of each carcinoma.

Papillary microcarcinomas (also referred to as papillary microtumor, occult, latent or small papillary carcinoma) refer to papillary carcinomas that are found incidentally measuring 1 cm or less.[2] In spite of their rather common identification in thyroid gland resections and apparent indolent biologic behavior, it is the recommendation to issue a protocol for all cases in which papillary thyroid carcinoma is found, including subcentimeter carcinomas whether incidentally found in a thyroid gland removed for other reasons (eg, multinodular goiter), discovered clinically (palpable, visible nodule), and/or discovered by imaging. Given the more sophisticated diagnostic (eg, imaging) modalities currently available, small (ie, less than 1 cm) lesions are being identified and resected. In an effort to have these papillary microcarcinomas reported and documented in tumor registries, thereby providing for long-term follow-up and better determination of their biologic nature, it is recommended that they should also be reported following the CAP thyroid protocol.

WHO Classification of Carcinoma of the Thyroid

Papillary carcinoma
- Variants (in alphabetical order):
  - Classical (usual)
  - Clear cell variant
  - Columnar cell variant
  - Cribriform-morular variant
  - Diffuse sclerosing variant
  - Follicular variant
  - Macrofollicular variant
  - Microcarcinoma (occult, latent, small, papillary microtumor)
  - Oncocytic or oxyphilic variant (follicular variant, non-follicular variant)
  - Solid variant
  - Tall cell variant
  - Warthin-like variant

Follicular carcinoma
- Variants:
  - Clear cell variant
  - Oncocytic (Hürthle cell) variant

Poorly differentiated thyroid carcinomas including insular carcinoma
Medullary carcinoma
Undifferentiated (anaplastic) carcinoma
Carcinoma, type cannot be determined

E. Histologic Grade

The majority of thyroid cancers are well-differentiated (ie, G1) carcinomas including papillary carcinoma and follicular carcinoma as well as their histologic variants. The histologic (microscopic) grading of the majority of thyroid gland carcinomas does not represent an independent predictor of behavior and does not specifically play a role in therapy. There is a subset of papillary carcinomas categorized as “aggressive” types, including tall cell, columnar, and diffuse sclerosing, but their behavior may be more predicated on tumor size and extent of invasion (ie, extrathyroidal extension) rather than simply based on their histology. Similarly, oncocytic (Hürthle cell) type of follicular carcinoma is a histologically differentiated carcinoma whose biologic behavior is better based on the size of the tumor and extent of invasiveness rather than on its histology.

There are ambiguities in the grading of thyroid carcinomas, including but not limited to what cytomorphologic features constitute a moderately-differentiated (G2) carcinoma and the histologic grading of medullary carcinomas. Histologic grading is included in the protocol for completeness but at this time is not a requirement in reporting thyroid carcinomas.

F. Margins

By convention, margin status is a required data element in association with thyroid cancers. The "margin" is defined as the surface of the thyroid specimen usually the outer aspect of the thyroid gland capsule and/or inked edge of the specimen. The evaluation of the relationship of tumor to the inked edge of the tissue represents determination of margin status. It should be noted that the thyroid "capsule" is not an anatomically defined structure. Evidence has shown that microscopically the capsule is focally incomplete or absent in a majority of autopsy thyroid glands evaluated.[6] Further, unlike hollow organs such as the gastrointestinal tract where there is continuity of the entire viscera such that a real surgical and pathologic margin exists, the same does not hold true for the thyroid gland such that tumor at the margin (ie, capsule and/or ink) does not correlate to incomplete excision. Few published studies have addressed the influence of margin status and patient outcome. Most surgeons, endocrinologists, and nuclear medicine specialists request information on margin status. While this makes intuitive sense and it is recommended that a positive margin be mentioned in the final pathology report, meticulous studies on the effect of positive margins and outcome in large series of patients with long-term follow-up are lacking. Indeed, there are no data to date on the prognostic value of close margins as an independent or co-variable.

G. Invasiveness

The diagnosis of papillary carcinoma is primarily but not exclusively based on the nuclear alterations but also includes the presence of invasive growth. The diagnosis of follicular carcinoma and its differentiation from follicular adenoma primarily depends on the identification of capsular and/or invasion of vascular spaces. Given the preferential spread of papillary carcinoma via lymphatics and follicular carcinoma via hematogenous routes, the vessels invaded by papillary carcinoma are believed to be lymphatic spaces and those in follicular carcinoma are believed to be blood vessels. However, in practice, the distinction between blood vessel invasion and lymphatic space invasion is not possible as both structures share similar histologic features without any specific identifiers (by light microscopy, histochemistry or immunohistochemistry) that assist in discriminating between these spaces. As such, the protocol groups vascular and lymphatic invasion as a single designation of lymph-vascular invasion.

Relative to vascular space invasion, the blood vessels should be of venous caliber and be located outside the tumor, within, or outside the capsule.[4] The criteria defining "minimally invasive" follicular carcinoma are controversial and still evolving. In some schemes, this designation refers to encapsulated lesions with capsular and/or small caliber sized angioinvasion even if angioinvasion is extensive.[4] However, in other schemes this designation is limited to tumors with capsular invasion but no vascular invasion. It should be noted that some authorities believe that even a single focus of lymph-vascular invasion is significant potentially conferring aggressive behavior. Accordingly, the presence of any lymph-vascular invasion, even in a single vessel, obviates against the designation of "minimally invasive" and removes the requirement for reporting on the extent (ie, focal, extensive) of invasion. Instead, the designation "grossly encapsulated angioinvasive follicular carcinoma" has been suggested. Other authors

base their definition of invasiveness on the number of foci of invasion, especially vascular invasion.[7-9] In some studies, encapsulated follicular carcinoma, oncocytic variant with 4 or more foci of vascular invasion have a significant recurrence rate (47%) even if the foci of angioinvasion are microscopic.[7] On the other hand, another study showed that follicular oncocytic (Hürthle cell) carcinomas with a total of 2 foci of capsular/vascular invasion did not recur after a long follow up.[8]

It is challenging to try and accommodate the differing philosophies into this protocol. Although the extent of invasion (ie, number of vessels invaded by carcinoma) may not be a an absolute predictor of potential for aggressive behavior such that unfavorable outcome may occur in the presence of invasion of a single vascular space, the requirement is for pathologists to report on the presence of capsular and lymph-vascular invasion as well as on the extent of invasion (ie, focal, extensive). This approach has the advantage of collating the various terminologies suggested for these carcinomas, as well as and perhaps more importantly, providing a report that better assists the clinician in assessing recurrence risk and, therefore, in deciding on the extent of surgical intervention (eg, completion thyroidectomy) and the use of postoperative radioactive iodine therapy.

"Widely invasive" follicular carcinomas are those tumors with grossly apparent invasion of thyroid and/or soft tissue (ie, extrathyroidal invasion).[2]

Criteria for Invasion

Capsular Invasion

While conceptually simple, there is no consensus as to the definition of capsular invasion. Some authorities require complete transgression of the capsule while other authorities do not require complete transgression of the capsule. In **Figure 2**, Chan[5] depicts the various histologic appearances for the presence or absence of capsular invasion. While a number of the illustrated representations of capsular invasion would be accepted by all pathologists (eg, C, D, E, H), other depictions listed as "Not yet" (eg, F, G, I) may be acceptable to some pathologists as representing capsular invasion. The impact of previous biopsy may confound the interpretation of capsular invasion and must be considered.

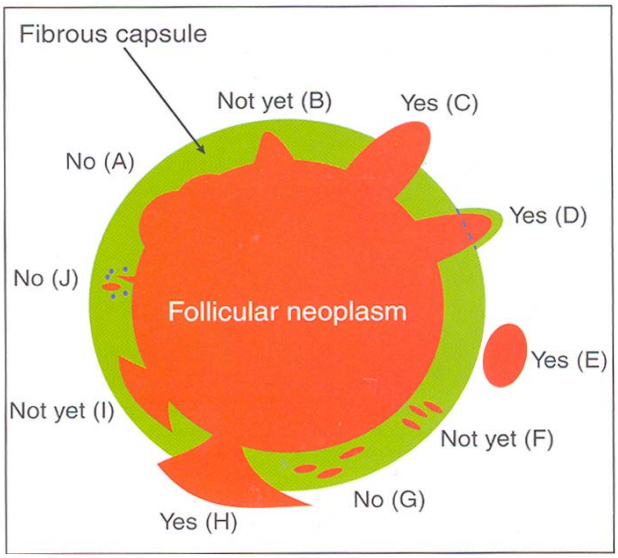

Figure 2: **Capsular invasion (CI):** Schematic drawing for the interpretation of the presence or absence of CI. The diagram depicts a follicular neoplasm (orange) surrounded by a fibrous capsule (green). A: Bosselation on the inner aspect of the capsule does not represent CI; B: Sharp tumor bud invades into but not through the capsule suggesting invasion requiring deeper sections to exclude; C: tumor totally transgresses the capsule invading beyond the outer contour of the capsule qualifying as CI; D: tumor clothed by thin (probably new) fibrous capsule but already extending beyond an imaginary (dotted) line drawn through the outer contour of the capsule qualifying as CI; E: satellite tumor nodule with similar features (architecture, cytomorphology) to the main tumor lying outside the capsule qualifying as CI; F: Follicles aligned perpendicular to the capsule suggesting invasion requiring deeper sections to exclude G: Follicles aligned parallel to the capsule do not represent CI; H: mushroom-shaped tumor with total transgression of the capsule qualifies as CI; I: mushroom-shaped tumor within but not through the capsule suggests invasion requiring deeper sections to exclude invasion; J: neoplastic follicles in the fibrous capsule with a degenerated appearance accompanied by lymphocytes and siderophages does not represent CI but rather capsular rupture related to prior fine needle aspiration. From Fletcher CDM, ed. *Diagnostic Histopathology of Tumours*. 3rd ed. Edinburgh: Churchill Livingstone Elsevier; 2007. Modified with permission © Elsevier.

Lymph-Vascular Invasion

For lymph-vascular invasion, the involved spaces should include capsular or extra-capsular vessels. The criteria for lymph-vascular invasion are also controversial and not uniformly accepted. Figure 3 depicts the various histologic appearances of lymph-vascular invasion.[5] In this illustration, the presence of endothelialized tumor alone is identified as representing lymph-vascular space invasion, a finding supported in the literature.[4] However, other authorities do not accept endothelialized tumor alone as representing lymph-vascular invasion unless accompanied by thrombus formation .

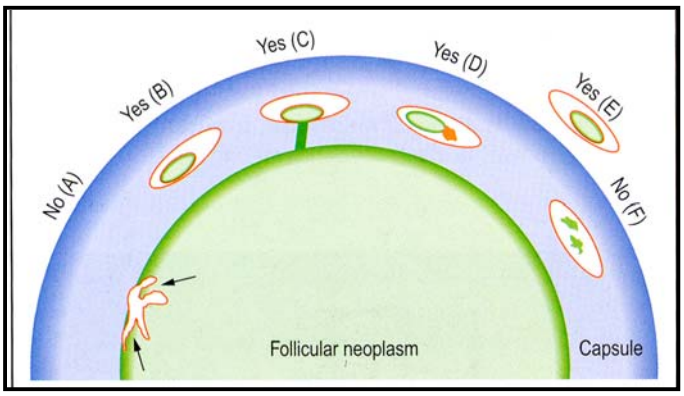

Figure 3. Vascular invasion (VI): Schematic drawing for the interpretation of the presence or absence of VI. The diagram depicts a follicular neoplasm (green) surrounded by a fibrous capsule (blue). A: Bulging of tumor into vessels within the tumor proper does not constitute VI. B: Tumor thrombus covered by endothelial cells in intracapsular vessel qualifies as VI. C: Tumor thrombus in intracapsular vessel considered as VI since it is attached to the vessel wall. D: Although not endothelialized, this tumor thrombus qualifies for VI because it is accompanied by a fibrin thrombus. E: Endothelialized tumor thrombus in vessel outside the tumor capsule represents VI. F: Artefactual dislodgement of tumor manifesting as irregular tumor fragments into vascular lumen unaccompanied by endothelial covering or fibrin thrombus. From Fletcher CDM, ed. *Diagnostic Histopathology of Tumours*. 3rd ed. Edinburgh; Churchill Livingstone Elsevier; 2007. Modified with permission © Elsevier.

H. Extra-Thyroidal Extension

Extrathyroidal extension refers to involvement of the perithyroidal tissues by a primary thyroid cancer. Since the thyroid gland does not have a well defined capsule,[6] the definition of extrathyroidal extension is problematic and subjective. On gross examination, the capsule may appear complete but evidence has shown that microscopically the capsule is focally incomplete or absent in a majority of autopsy thyroid glands evaluated.[6] The perithyroidal tissues include sizable blood vessels as well as small peripheral nerves and is continuous with the pretracheal fascia.[10] Diagnostic findings for minimal extrathyroidal extension includes the presence of carcinoma extending into perithyroidal tissues, including infiltration of adipose tissue and skeletal muscle, as well as around (and into) sizable vascular structures and nerves. Extension into adipose tissue can be problematic given the fact that adipose tissue can be found within the thyroid gland proper under normal conditions and also may be a component of a variety of thyroid lesions including carcinomas. [11,12] As such, the presence of adipose tissue in association with a thyroid carcinoma should not be mistaken for extrathyroidal extension. Some authorities only accept invasion of skeletal muscle as the identifier for minimal extrathyroidal extension. Of note, similar to adipose tissue in the thyroid, skeletal muscle may be seen in the thyroid gland under normal conditions, especially in relation to the isthmus portion of the thyroid gland, as well as in a variety of pathologic conditions. [11,13] If present, a desmoplastic response may be a helpful finding in the determination of extrathyroidal extension. The identification of thick-walled vessels and/or small peripheral nerves in association with adipose tissue may be of greater assistance as these structures are not located in the thyroid gland proper and their presence would be helpful in determining whether the carcinoma is extrathyroidal in extent.

In contrast to minimal extrathyroidal extension, the histologic diagnosis of extensive extrathyroidal extension is rather straightforward, and is usually established clinically by documentation of carcinoma well beyond the thyroid gland with direct invasion (ie, not metastasis) into one or more of the following structures:

- subcutaneous soft tissues;
- adjacent viscera, including the larynx, trachea and/or esophagus;
- the recurrent laryngeal nerve, carotid artery or mediastinal blood vessels.

I. TNM and Stage Groupings

According to the American Joint Committee on Cancer (AJCC) [1] the TNM stage groupings for papillary and follicular carcinomas, and variants thereof are stratified by age including patients under 45 years of age and patients 45 years and older. Similar stratification is not used in the staging of medullary carcinomas and undifferentiated carcinoma. However, undifferentiated (anaplastic) carcinoma is always assigned Stage IV. Tumor size and lymph node status are also considered in the TNM classification.

All categories may be subdivided: (a) solitary tumor, (b) multifocal tumor. With multifocal tumors, the largest one is used for classification. The lymph nodes must be specifically identified to classify regional node involvement.

Primary Tumor (pT)

pTX: Cannot be assessed
pT0: No evidence of primary tumor
pT1: Tumor size 2 cm or less, limited to thyroid
pT1a: Tumor 1 cm or less in greatest dimension limited to the thyroid
pT1b: Tumor more than 1 cm but not more than 2 cm in greatest, dimension, limited to the thyroid
pT2: Tumor more than 2 cm, but not more than 4 cm, limited to thyroid
pT3: Tumor more than 4 cm limited to thyroid or any tumor with minimal extrathyroid extension (eg, extension to sternothyroid muscle or perithyroid soft tissues)
pT4a: Moderately advanced disease. Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve
pT4b: Very advanced disease. Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels

Note: There is no category of carcinoma in situ (pTis) relative to carcinomas of thyroid gland.

All anaplastic carcinomas are considered T4 tumors.

T4a Intrathyroidal anaplastic carcinoma—surgically resectable
T4b Extrathyroidal anaplastic carcinoma—surgically unresectable

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

Regional Lymph Nodes (N)

pNX:	Cannot be assessed
pN0:	No regional lymph node metastasis
pN1a:	Nodal metastases to Level VI (pretracheal, paratracheal and prelaryngeal/Delphian) lymph nodes
pN1b:	Metastases to unilateral, bilateral or contralateral cervical (Levels I, II, III, IV, V) or retropharyngeal or superior mediastinal lymph nodes (Level VII).

Distant Metastasis (pM)

pM0:	No distant metastasis
pM1:	Distant metastasis

Stage Groupings

Papillary or Follicular Carcinoma

	Under 45 Years of Age		
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
	45 Years or Older		
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Medullary Carcinoma (All Age Groups)

Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage III	T1	N1a	M0
	T2	N1a	M0

	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Undifferentiated (Anaplastic) Carcinoma

All anaplastic carcinomas are considered Stage IV

Stage IVA	T4a	Any N	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.
The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

The “a” prefix designates the stage determined at autopsy: aTNM.

Additional Descriptors

Residual Tumor (R)

In the thyroid gland, residual tumor may only be applicable to anaplastic carcinoma. Residual tumor is tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor

involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

J. Classification of Neck Dissection

1. Radical neck dissection
2. Modified radical neck dissection, internal jugular vein and/or sternocleidomastoid muscle spared
3. Selective neck dissection (SND), as specified by the surgeon
   a. Supraomohyoid neck dissection
   b. Posterolateral neck dissection
   c. Lateral neck dissection
   d. Central compartment neck dissection
4. Selective neck dissection (SND), as specified by the surgeon -"SND" with levels and sublevels designated (see Figure 3).[14-16]
5. Extended radical neck dissection, as specified by the surgeon

K. Lymph Nodes

Regional lymph node spread from thyroid cancer is common but of less prognostic significance in patients with well-differentiated tumors (papillary) than in medullary cancers. The adverse prognostic influence of lymph node metastasis in patients with differentiated carcinomas is observed, only in the older age group.[1] The first echelon of nodal metastasis consists of the paralaryngeal, paratracheal, and prelaryngeal (Delphian) nodes adjacent to the thyroid gland in the central compartment of the neck generally described as Level VI.[1] Metastases secondarily involve the mid- and lower jugular, the supraclavicular, and (much less commonly) the upper deep jugular and spinal accessory lymph nodes.[1] Lymph node metastasis to submandibular and submental lymph nodes is very rare. Upper mediastinal (Level VII) nodal spread occurs frequently both anteriorly and posteriorly. Retropharyngeal nodal metastasis may be seen, usually in the presence of extensive lateral cervical metastasis.[1] Bilateral nodal spread is common. The components of the N category are described as follows: first echelon (central compartment/Level VI), or N1a, and lateral cervical and/or superior mediastinal or N1b. The lymph node metastasis should also be described according to the level of the neck that is involved. In comparison to metastatic head and neck squamous cell carcinoma, the risk for increased locoregional disease and distant metastasis in the presence of extranodal extension of thyroid cancer has not been validated although one study has shown an increase risk for distant metastases and death in the presence of extranodal extension.[17] Nevertheless, as a recommendation the pathologist should comment on the presence or absence of extranodal extension. Nodal metastases from medullary thyroid cancer carry a much more ominous prognosis, although they follow a similar pattern of spread.

For purposes of pathologic evaluation, lymph nodes are organized by levels as shown in **Figure 4**.[18]

Figure 4. The six sublevels of the neck for describing the location of lymph nodes within levels I, II, and V. Level IA, submental group; level IB, submandibular group; level IIA, upper jugular nodes along the carotid sheath, including the subdigastric group; level IIB, upper jugular nodes in the submuscular recess; level VA, spinal accessory nodes; and level VB, the supraclavicular and transverse cervical nodes. From: Flint PW, et al, eds. *Cummings Otolaryngology: Head and Neck Surgery.* 5th ed. Philadelphia, PA; Saunders: 2010. Reproduced with permission © Elsevier.

In order for pathologists to properly identify these nodes, they must be familiar with the terminology of the regional lymph node groups and with the relationships of those groups to the regional anatomy. Which lymph node groups surgeons submit for histopathologic evaluation depends on the type of neck dissection they perform. Therefore, surgeons must supply information on the types of neck dissections that they perform and on the details of the local anatomy in the specimens they submit for examination, or in other manners, orient those specimens for pathologists.[15,16]
If it is not possible to assess the levels of lymph nodes (for instance, when the anatomic landmarks in the excised specimens are not specified), then the lymph node levels may be estimated as follows: level II, upper third of internal jugular (IJ) vein or neck specimen; level III, middle third of IJ vein or neck specimen; level IV, lower third of IJ vein or neck specimen, all anterior to the sternocleidomastoid muscle.

Level I. Submental Group (Sublevel IA)
Lymph nodes within the triangular boundary of the anterior belly of the digastric muscles and the hyoid bone.

Submandibular Group (Sublevel IB)
Lymph nodes within the boundaries of the anterior and posterior bellies of the digastric muscle and the body of the mandible. The submandibular gland is included in the specimen when the lymph nodes within this triangle are removed.

Level II. Upper Jugular Group (Sublevels IIA and IIB)
Lymph nodes located around the upper third of the internal jugular vein and adjacent spinal accessory nerve extending from the level of the carotid bifurcation (surgical landmark) or hyoid bone (clinical landmark) to the skull base. The posterior boundary is the posterior border of the sternocleidomastoid muscle, and the anterior boundary is the lateral border of the sternohyoid muscle.

Level III. Middle Jugular Group
Lymph nodes located around the middle third of the internal jugular vein extending from the carotid bifurcation superiorly to the omohyoid muscle (surgical landmark), or cricothyroid notch (clinical landmark) inferiorly. The posterior boundary is the posterior border of the sternocleidomastoid muscle, and the anterior boundary is the lateral border of the sternohyoid muscle.

Level IV. Lower Jugular Group
Lymph nodes located around the lower third of the internal jugular vein extending from the omohyoid muscle superiorly to the clavicle inferiorly. The posterior boundary is the posterior border of the sternocleidomastoid muscle, and the anterior boundary is the lateral border of the sternohyoid muscle.

Level V. Posterior Triangle Group (Sublevels VA and VB)
This group comprises predominantly the lymph nodes located along the lower half of the spinal accessory nerve and the transverse cervical artery. The supraclavicular nodes are also included in this group. The posterior boundary of the posterior triangle is the anterior border of the trapezius muscle, the anterior boundary of the posterior triangle is the posterior border of the sternocleidomastoid muscle, and the inferior boundary of the posterior triangle is the clavicle.

Level VI. Anterior (Central) Compartment
Lymph nodes in this compartment include the pre- and paratracheal nodes, precricoid (Delphian) node, and the perithyroidal nodes, including the lymph nodes along the recurrent laryngeal nerve. The superior boundary is the hyoid bone, the inferior boundary is the suprasternal notch, the lateral boundaries are the common carotid arteries, and the posterior boundary by the prevertebral fascia.

Level VII. Superior Mediastinal Lymph Nodes
Metastases at Level VII are considered regional lymph node metastases; all other mediastinal lymph node metastases are considered distant metastases.

Lymph node groups removed from areas not included in the above levels, eg, scalene, suboccipital, and retropharyngeal, should be identified and reported from all levels separately. Midline nodes are considered ipsilateral nodes.

L. Lymph Node Number
Histological examination of a selective neck dissection specimen will ordinarily include 6 or more lymph nodes. Histological examination of a radical or modified radical neck dissection specimen will ordinarily include 10 or more lymph nodes in the untreated neck.[1]

M. Special Procedures for Lymph Nodes
At the current time, no additional special techniques should be used other than routine histology for the assessment of nodal metastases although confirmation by immunohistochemical staining, including thyroglobulin for papillary carcinoma and calcitonin and neuroendocrine markers (eg, chromogranin, synaptophysin, CD56) for medullary carcinoma may be required.

N. Ancillary Testing

A number of immunohistochemical markers have been proposed to confirm the diagnosis of papillary carcinoma allowing for distinction from other lesions/tumors in the differential diagnosis. These markers include (but are not limited to) cytokeratin 19, galectin 3 and mesothelium-associated antibody HBME1. However, these markers are not totally specific for papillary carcinoma and cannot relied on for the diagnosis of papillary carcinoma. At present, morphologic criteria remain the “gold standard” in the diagnosis of papillary carcinoma.

Distinct molecular mutations have been identified in papillary carcinoma. Potential molecular markers of papillary carcinoma include activation of proto-oncogene receptor tyrosine (RET) kinase as a result of chromosomal translocation collectively referred to as RET/PTC translocations. RET/PTC translocation may be seen in up to 60% of papillary carcinomas.[19] RET/PTC1 fusion is correlated to papillary carcinoma with predominant papillary architecture and papillary microcarcinoma; RET/PTC3 fusion is correlated to tall cell and solid variants, as well as to radiation-induced tumors. RET/PTC expression is not found in follicular carcinoma, poorly-differentiated carcinoma and undifferentiated carcinoma,[5] but there are no data on the DNA status of these lesions to exclude progression in tumors with these rearrangements.[19] Mutation of the gene for B-raf (BRAF) can be seen from 29% to 69% of papillary carcinomas and is more prevalent in the classic type of papillary carcinoma, tall cell variant, Warthin tumor-like papillary carcinoma and the oncocytic type of papillary carcinoma.[5] The follicular variant of papillary carcinoma harbors *ras* gene mutations and may have PAX8/PPARγ translocation but rarely have RET/PTC translocation and have a very low frequency of BRAF mutation. This molecular profile of the follicular variant of papillary carcinoma is similar to that of follicular adenoma and follicular carcinoma. In spite of advances in the molecular categorization of thyroid follicular epithelial cell tumors, in general, and papillary carcinoma specifically, the use of molecular testing in the diagnosis and differential diagnosis of papillary carcinomas and follicular carcinomas is still evolving. Recent studies have shown that molecular testing of fine needle aspirates of thyroid nodules may enhance the diagnostic accuracy of thyroid nodules that are indeterminate or suspicious on cytology.[20-24]

The molecular genetics of medullary carcinoma is well established showing mutations in the RET proto-oncogene. Germline RET mutations are associated with hereditary medullary carcinomas, including with familial medullary carcinoma (familial MTC) and the multiple endocrine neoplasia syndromes (MEN2a and 2b). In this setting, prophylactic total thyroidectomy is performed for family members based on positive mutational analysis.[25] Many of the thyroidectomy specimens appear grossly normal. In such cases, comprehensive examination of the entire thyroid gland is required to document the extent of C-cell hyperplasia and to assess for micromedullary carcinoma.[26] Horizontal sections of each lobe should be taken serially in a superior to inferior direction for each lobe, and the isthmus should be submitted separately. This serial sectioning of the thyroid is performed because C-cells are restricted to a zone deep within the middle to upper thirds of the lateral lobes. The extreme upper and lower poles of each lobe and the isthmic regions are generally devoid of C-cells. Immunostains for calcitonin and CEA are usually required to assess the extent of C-cell disease.

References

1. Patel S, Shah JP. Part II: Head and neck sites. In: Edge SB, Byrd DR, Carducci MA, Compton CA, eds. *AJCC Cancer Staging Manual.* 7th ed. New York, NY: Springer; 2009.
2. DeLellis RA, Lloyd RV, Heitz PU, Eng C, eds. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Endocrine Organs*. Lyon: IARC Press; 2004.
3. Sobin LH, Wittekind C. *UICC TNM Classification of Malignant Tumours*. 6th ed. New York: Wiley-Liss; 2002.
4. Rosai J, Carcangiu ML, DeLellis RA. *Atlas of Tumor Pathology. Tumors of the Thyroid Gland.* 3rd series. Fascicle 5. Washington, DC: Armed Forces Institute of Pathology; 1992.
5. Chan JKC. The thyroid gland. In: Fletcher CDM, ed. *Diagnostic Histopathology of Tumours.* 3rd ed. Edinburgh; Churchill Livingstone Elsevier; 2007:1018.
6 Komorowski RA, Hanson GA. Occult thyroid pathology in the young adult: an autopsy study of 138 patients without clinical thyroid disease. *Hum Pathol.* 1988;19:689-696.
7. Ghossein RA, Hiltzik RA, Carlson DL, et al. Prognostic factors of recurrence in encapsulated Hürthle cell carcinoma of the thyroid gland: a clinicopathologic study of 50 cases. *Cancer.* 2006;106:1669-76.
8. Stojadinovic A, Ghossein RA, Hoos A, et al. Hürthle cell carcinoma: a critical histopathologic appraisal. *J Clin Oncol*. 2001;19:2616-25.
9. Collini P, Sampietro G, Pilotti S. Extensive vascular invasion is a marker of risk of relapse in encapsulated non-Hürthle cell follicular carcinoma of the thyroid gland: a clinicopathological study of 18 consecutive cases from a single institution with a 11-year median follow-up. *Histopathology.* 2004;44:35-9.
10. Standring S. Thyroid gland. In: Standring S, ed. *Gray's Anatomy: The Anatomical Basis of Clinical Practice.* 39th ed. Edinburgh: Elsevier Churchill Livingstone; 2005:560-564.
11. Rosai J, Carcangiu ML, DeLellis RA. The normal thyroid gland. In: Rosai J, ed. *Tumors of the Thyroid. Atlas of Tumor Pathology.* Facicle 5. Third series. Washington, DC: Armed Forces Institute of Pathology; 1992: 1-17.
12. Gnepp DR, Ogorzalek JM, Heffess CS. Fat-containing lesions of the thyroid gland. *Am J Surg Pathol.* 1989;13;605-612.
13. Carcangiu ML. Thyroid. In: Mills SE, ed. *Histology for Pathologists*. Third ed. Philadelphia; Lippincott Williams & Wilkins; 2007: 1129-1148.
14. Robbins KT et al. Neck dissection classification update. *Arch Otolaryngol Head Neck Surg.* 2002;128:751-758.
15. Robbins TK et al. Consensus statement on the classification and terminology of neck dissection. *Arch Otolaryngol Head Neck Surg.* 2008;134:536-538.
16. Robbins T, Medina JE, Wolfe GT, Levine PA, Sessions RB, Pruet CW. Standardizing neck dissection terminology: official report of the academy's committee for head and neck surgery and oncology. *Arch Otolaryngol Head Neck Surg.* 1991;117:601-605.
17. Yamashita H, Noguchi S, Murakami N et al. Extracapsular invasion of lymph node metastasis is an indicator of distant metastasis and poor prognosis in patients with thyroid papillary carcinoma. *Cancer.* 1997;80:2268-72.
18. From: Cummings, CW. *Cummings: Otolaryngology: Head and Neck Surgery.* 4th ed. Philadelphia; Mosby, Inc: 2005. (Electronic Textbook)
19. Kondo T, Ezzat S, Asa SL. Pathogenetic mechanisms in thyroid follicular-cell neoplasia. *Nat Rev Cancer.* 2006;6:292-306.

20. Cheung CC, Carydis B, Ezzat S, Bedard YC, Asa SL. Molecular genetic analysis refines the fine needle aspiration diagnosis of thyroid cancer. *J Clin Endocrinol Metab.* 2001;86:2187-2190.
21. Sapio MR, Posca D, Raggioli A, et al. Detection of RET/PTC, TRK and BRAF mutations in preoperative diagnosis of thyroid nodules with indeterminate cytological findings. *Clin Endocrinol.* 2007;66:678-683.
22. Kim SK, Kim DL, Han HS, et al. Pyrosequencing analysis for detection of BRAFV600E mutation in an FNAB specimen of thyroid nodules. *Diagn Mol Pathol.* 2008;17:118-125.
23. Marchetti I, Lessi F, Mazzanti CM, et al. A morpho-molecular diagnosis of papillary thyroid carcinoma: BRAF V600E detection as an important tool in preoperative evaluation of fine-needle aspirates. *Thyroid.* 2009;19:837-842.
24. Nikiforov YE, Steward DL, Robinson-Smith TM, et al. Molecular testing for mutations in improving fine-needle aspiration diagnosis of thyroid nodules. *J Clin Endocrinol Metab.* 2009;94:2092-2098.
25. Altanerova V. Cancers connected with mutations in RET proto-oncogene. *Neoplasma*. 2001;48:325-31.
26. Stoler MH. Prophylactic surgical pathology. *Am J Surg Pathol*. 2002;26:257-259.