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

Protocol applies to all carcinomas of the thyroid gland. This protocol does not apply to lymphoma or sarcoma.

Based on:

AJCC/UICC TNM, 8th edition
CAP Cancer Protocol version: Thyroid 4.0.0.0
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Revision History:

None

Summary of Changes:

This protocol is revised to the 8th edition of the AJCC Cancer Staging Manual and the current version of the CAP Cancer Protocol Thyroid 4.0.0.0.

Procedures Covered in this Protocol:

- Completion thyroidectomy (reoperative)
- Partial excision, right or left (anything less than a lobectomy, including substernal excision)
- Lobectomy, right or left
- Lobectomy, right or left, with isthmusectomy (hemithyroidectomy)
- Right lobe with partial left lobectomy (subtotal or near total thyroidectomy)
- Left lobe with partial right lobectomy (subtotal or near total thyroidectomy)
- Total thyroidectomy

Lymph Node Sampling

- Focused or single lymph node resection
- Central compartment dissection (level VI)
- Lateral neck dissection (level I-V)
- Superior mediastinal lymph nodes (level VII)

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The purpose of the Protocols is to support Laboratory Personnel engaged in the macroscopic examination of cancer resection specimens. The Protocols are based on specified relevant source documents, drafted by pathologists' assistant experts, and supported by information provided by the College of American Pathologists (CAP) and the American Joint Committee on Cancer (AJCC). These Protocols are intended to serve patients by ensuring that the macroscopic examination of cancer resection specimens is compliant with CAP Cancer Protocols, the AJCC Cancer Staging Manual, and provide optimization of the pre-analytic steps necessary to promote appropriate molecular studies.

The AAPA cautions that the use of the Protocols in practice may require the use of additional considerations that are beyond the scope of the Protocols. The AAPA does not offer medical advice or diagnoses, or engage in the practice of medicine. The information provided in the Protocols is not intended or implied to be a substitute for the Laboratory Personnel's own training, professional medical opinion, diagnosis, or treatment advice. All content, including text, graphics, images and information contained in the Protocols are for the above stated purposes only. Laboratory Personnel are encouraged to confirm any information provided in these Protocols with other sources. The inclusion of a product name, organization, or service in an AAPA publication, including without limitation the Protocols, should not be construed as an endorsement of such product, organization, or service, nor is failure to include the name of a product, organization or service to be construed as disapproval.

Immunohistochemical Markers:

- Papillary Carcinoma:
  - Cytokeratin 19
  - Galectin 3
  - Mesothelium-associated antibody HBME1
  - CITED-1

  Some of these markers are not specific for papillary carcinoma and cannot be relied on for the diagnosis of papillary carcinoma.

- Medullary Carcinoma:
  - Calcitonin
  - CEA

  Used to assess the amount of C-cell hyperplasia and any micromedullary carcinomas in prophylactic thyroidectomy specimens for Familial Medullary Carcinoma, MEN2A, or MEN2B.

- Lymph Nodes
  - Thyroglobulin - TTF-1 and PAX8 for papillary carcinoma
  - Calcitonin, CEA, and neuroendocrine markers (e.g., chromogranin, synaptophysin, CD56) for medullary thyroid carcinoma

Molecular Considerations:

- Papillary Carcinoma:
  - *RET/PTC* translocations
  - *BRAF* and *RAS* mutations

- Follicular Variant of Papillary/Follicular Adenoma/Follicular Carcinoma:
  - *RAS* mutations
  - *PAX8-PPAR*gamma translocations

- Medullary Carcinoma:
  - *RET* proto-oncogene mutations*

  *Germline *RET* mutations are associated with MEN2A, and MEN2B. See below for specific grossing procedure of prophylactic thyroidectomy. Familial isolated forms of Medullary Thyroid Carcinoma (FMTC) are now classified as a manifestation of MEN2A syndrome.

These tests can be performed on formalin fixed paraffin embedded tissue sections. The macroscopic description should provide the fixative used. 10% neutral buffered formalin is the preferred fixative. It is recommended that the duration of fixation be provided as well.

PROCEDURES AND GENERAL ANATOMIC CONSIDERATIONS:

- **Procedures Covered by this Protocol:**

  - Completion thyroidectomy (reoperative)
  - Right partial excision (anything less than a lobectomy, including substernal excision)
  - Left partial excision (anything less than a lobectomy, including substernal excision)
  - Partial excision (specify type)
  - Right lobectomy
  - Left lobectomy
  - Right lobectomy with isthmusectomy (hemithyroidectomy)
  - Left lobectomy with isthmusectomy (hemithyroidectomy)
  - Right lobe with partial left lobectomy (subtotal or near total thyroidectomy)
  - Left lobe with partial right lobectomy (subtotal of near total thyroidectomy)
  - Total thyroidectomy

- **Lymph Node Sampling:**

  - Focused or single lymph node resection
  - Level I-V, right, left (lateral neck dissection)
  - Level VI - pretracheal, paratracheal and prelaryngeal/Delphian, perithyroidal (central compartment dissection)
  - Level VII (superior mediastinal lymph nodes)

- **Specimen Size and Extent of Resection:**

  - Specify specimen type received (see above procedure types).
  - Provide specimen weight.
  - Specify overall or aggregate weight; or, specify individual specimen or fragment weights.

  Provide three dimensions of the following structures, as applicable to the specimen received:
  - Right lobe
  - Left lobe
  - Isthmus ± pyramidal lobe
  - Single lymph node resection
  - Central compartment
  - Right neck dissection
  - Left neck dissection
  - Any additional structures

- **Specimen Integrity and Adequacy:**

  Provide an assessment of the specimen integrity:
  - Intact
  - Divided (thyroidectomy performed as lobectomy and completion thyroidectomy)
  - Fragmented - if fragmented, describe any disruptions or defects of the thyroid surface and specify location.

Note: The thyroid gland does not have a well-defined anatomic capsule as it is covered by an incomplete fibro-adipose connective tissue pseudocapsule. However, it is important to note whether the surface of the specimen removed appears relatively intact. If any defects or disruptions are noted macroscopically, state the anatomic location of the defect. Differential application of ink to the surface of the defect may also be useful. Extrathyroidal spread is typically assessed in strap muscles (see pT3b) and other adjacent anatomic structures (see pT4a and pT4b).

- **Prophylactic Total Thyroidectomy for Medullary Carcinoma:**

  - Submit the entire specimen to document the extent of C-cell hyperplasia and micromedullary carcinoma.
  - Horizontally section each lobe and submit from superior to inferior.
  - Submit the isthmus separately.

  This serially sectioning of the thyroid is performed because C-cells are restricted to a zone deep within the middle to upper third of the lateral lobes.

TUMOR ("T" of TNM)

- **Tumor Size:**

  Give three dimensions of each tumor from dominant (largest) to smallest. *

  **Tumor size has a significant impact on prognosis:*
  - Papillary carcinomas:
    <1 cm are often associated with an excellent prognosis.
    >4 cm are often associated with a worse prognosis.
  - Follicular carcinomas:
    >3.5 cm are often associated with a worse prognosis.
  - Medullary carcinomas:
    Medullary microcarcinomas measure <1cm; they have a 20% rate of regional spread and a 5% distant metastatic rate.

- **Tumor Focality:**

  - State whether the tumor is unifocal or multifocal.

- **Tumor Site(s):**

  - Right lobe
  - Left lobe
  - Isthmus
  - Pyramidal lobe
  - Other (specify)

  - State specific location, including laterality, for each tumor, from dominant (largest) to smallest.
  - If the tumor is multifocal, specify the number of tumors identified, along with their relation to the dominant (largest) tumor:
    - Ipsilateral
    - Contralateral
    - Isthmus
  - The dominant (largest) tumor can be defined as the most aggressive tumor, specifically the tumor that imparts the highest stage and dictates patient management.

- **Tumor Depth of Invasion and Relationship to Attached Organs/Structures:**

  Tumor Capsular Invasion:
  - A statement should be made with regards to invasion of the tumor capsule:
    - Not identified.
    - Present (minimal, widely invasive).
      - This is very important to distinguish follicular adenoma from follicular carcinoma and non-invasive follicular variant papillary carcinoma (currently known as non-invasive follicular thyroid neoplasm with papillary nuclei) from invasive follicular variant papillary carcinoma.

- Invasion has occurred when carcinoma is present at the outer surface of the capsule.

Criteria for Capsular Invasion (CI)

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 line drawn through the outer contour of the capsule qualifying as CI.

E. Satellite tumor nodule with similar features 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.

Extrathyroidal Extension:

- One of the most significant prognostic factors of thyroid carcinoma is the extent of invasion into surrounding tissues and metastatic spread. Extrathyroidal extension refers to the involvement of strap muscles (pT3b) and other adjacent structures (pT4a and pT4b) by a primary thyroid cancer.

- Microscopic extrathyroidal extension that is not macroscopically evident is no longer a criterion for upstaging. pT3b, pT4a, and pT4b are now defined by extrathyroidal extension into at least skeletal muscle, which requires review of macroscopic, intraoperative, and radiologic findings.

- A thorough macroscopic examination and review of the operative and radiologic findings are required to document the “gross” extrathyroidal extension required to upstage a tumor.

- Specify if tumor invades:
    - Not identified
    - Strap muscles (pT3b)
    - Subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve (pT4a)
    - Prevertebral fascia or encases the carotid artery or mediastinal vessels (pT4b)
    - Cannot be determined

TNM Stage Groupings

For Papillary, Follicular, Poorly Differentiated, Hurthle Cell, and Anaplastic Thyroid Carcinoma

Definition of Primary Tumor (pT)

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pT1	Tumor size ≤2 cm in greatest dimension, limited to the thyroid
pT1a	Tumor ≤1 cm in greatest dimension, limited to the thyroid
pT1b	Tumor >1 cm but ≤2 cm in greatest dimension, limited to thyroid
pT2	Tumor >2 cm but ≤4 cm in greatest dimension, limited to thyroid
pT3	Tumor >4 cm limited to thyroid, or gross extrathyroidal extension invading only strap muscles
pT3a	Tumor >4 cm limited to the thyroid
pT3b	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size
pT4	Includes gross extrathyroidal extension beyond the strap muscles
pT4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size.
pT4b	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size

Note: All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest tumor determines the classification).

For Medullary Thyroid Carcinoma

Definition of Primary Tumor (pT)

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pT1	Tumor size ≤2 cm in greatest dimension, limited to the thyroid
pT1a	Tumor ≤1 cm in greatest dimension, limited to the thyroid
pT1b	Tumor >1 cm but ≤2 cm in greatest dimension, limited to thyroid
pT2	Tumor >2 cm but ≤4 cm in greatest dimension, limited to thyroid
pT3	Tumor >4 cm in greatest dimension or with extrathyroidal extension
pT3a	Tumor >4 cm in greatest dimension, limited to the thyroid
pT3b	Tumor of any size with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles)
pT4	Advanced disease
pT4a	Moderately advanced disease; tumor of any size with gross extrathyroidal extension into the nearby tissues of the neck, including subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve
pT4b	Very advanced disease; tumor of any size with extension toward the spine or into nearby large blood vessels, gross extrathyroidal extension invading the prevertebral fascia, or encasing the carotid artery or mediastinal vessels

TNM Descriptors:

pT(m)NM: For multiple primary tumors in single site, the T score is modified with the suffix "(m)" recorded in parentheses following the pT indicator (pT indicating primary tumor).

ypTNM: If the classification is performed during or following initial multi-modality therapy (e.g., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy), the prefix "y" is used. The ypTNM categorizes the extent of tumor actually present at the time of examination, not an estimate of tumor prior to initiation of multimodality therapy.

rTNM: The "r" prefix indicates a recurrent tumor when staged after a documented disease-free interval.

aTNM: The "a" prefix designates the stage determined at autopsy

Residual Tumor (R) Category

The absence or presence of residual tumor at the primary tumor site after treatment is denoted by the symbol R. The R categories for the primary tumor site are as follows:

R	R Definition
RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor at the primary cancer site or regional nodal sites (This designation is not used to indicate metastatic disease identified, but not resected, at surgical resection.)

For the surgeon, the R categories may be useful to indicate the status of the completeness of a surgical excision. For the pathologist, the R category is relevant to the status of the margins of a surgical resection specimen. 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).

For the thyroid gland, residual tumor is mainly applicable to anaplastic carcinoma.

- **Margins:**

  - Provide the distance of the tumor to the closest inked margin with location in mm.
    - 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.
  - State if any margin is macroscopically involved by tumor.
    - Tumor at the margin or capsule does *not* correlate to an incomplete excision.

  Note: A key requirement for noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP) is that the entire lesional border be submitted for microscopic evaluation.

LYMPH NODES ("N" of TNM)

- **Lymph Nodes:**

For all Carcinomas of the Thyroid
Definition of Regional Lymph Node (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed
pN0	No evidence of locoregional lymph node metastasis
pN0a	One or more cytologically or histologically confirmed benign lymph nodes
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis
pN1	Metastasis to regional nodes
pN1a	Metastasis to Level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease.
pN1b	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (Levels I, II, III, IV, or V) or retropharyngeal lymph nodes

Lymph Node Evaluation:

- Specify the number of lymph nodes examined and the number of macroscopically positive lymph nodes identified. Measure the size of tumor deposits if they are macroscopically identified.
    - Specify the size of the largest metastatic deposit in cm.
- Comment on the presence or absence of extranodal extension if macroscopically identified. Extranodal extension has been linked to increased risk for metastasis and mortality.
- Histologic examination of a selective neck dissection specimen will include 6 or more lymph nodes. A radical or modified radical neck dissection will include 10 or more lymph nodes in the untreated neck.
    - Specify the nodal levels
        - Level I-V
        - Level VI
        - Level VII
- Submit all lymph nodes for microscopic examination.
- Small lymph nodes can be submitted in toto.
- Submit representative sections of macroscopically positive larger lymph nodes, ensuring that areas concerning for extranodal extension are submitted for microscopic evaluation.

- Macroscopically negative larger nodes should be sectioned and entirely submitted.
- If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.
- Take steps to ensure that an accurate lymph node count can be established.

Classification of neck dissections: *(Figure 1)*

- Radical neck dissection
- Modified radical neck dissection, sparing internal jugular vein and/or sternocleidomastoid muscle
- Selective neck dissection, as specified by the surgeon:
  - Supraomohyoid neck dissection
  - Posterolateral neck dissection
  - Lateral neck dissection
  - Central compartment neck dissection
- Superselective neck dissection as specified by the surgeon, with levels and sublevels designated
- Extensive radical neck dissection, as specified by the surgeon

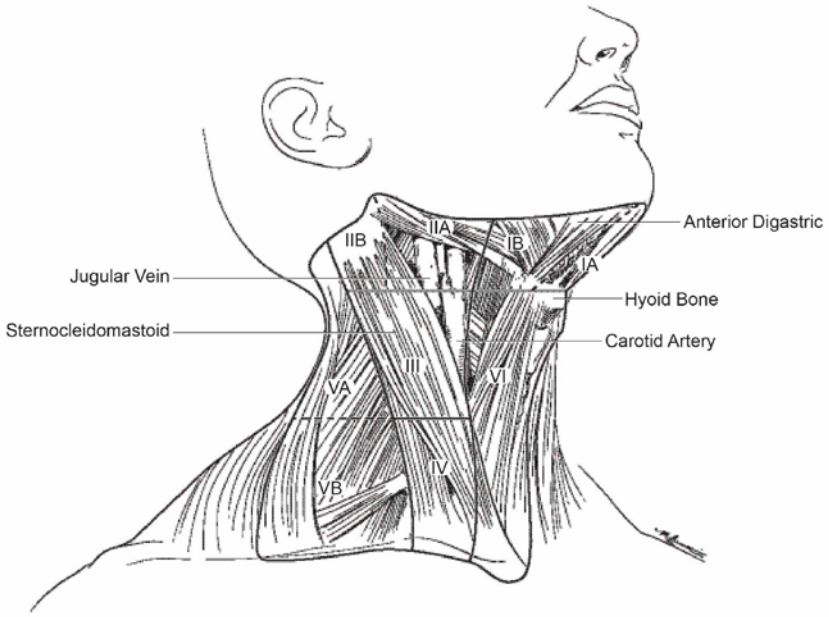

Figure 1: The Six Levels of the Neck with Sublevels

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 III: Middle jugular group
Level IV: Lower jugular group
Level VA: Spinal accessory nodes
Level VB: Supraclavicular and transverse cervical nodes
Level VI: Anterior (central) compartment

- The lymph nodes must be specifically identified according to location/level to classify regional node involvement.
- Midline nodes are considered ipsilateral nodes.

METASTASIS ("M" of TNM)

- **Metastasis:**

Definition of Distant Metastasis (pM) (required only if confirmed pathologically)

pM Category	pM Criteria
M0	No distant metastasis
pM1	Distant metastasis

Distant spread occurs by hematogenous routes – for example to lungs and bones – but many other sites may be involved.

Lymph node groups removed from beyond Levels I through VII (scalene, suboccipital, and retropharyngeal) should be identified and reported separately from all levels, to aid in assessment of distant metastases.

The identification of psammomatous microcalcifications in a cervical lymph node is considered metastatic disease and is classified as N1 disease.

The adverse prognostic influence of lymph node metastasis in patients with differentiated carcinomas is observed only in the older age group (45 years and older).

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