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# Histopathological and immunohistochemical features of thyroid carcinoma

**KEYWORDS:** Thyroid Neoplasms; Immunohistochemistry; Carcinoma, Medullary; Carcinoma, Papillary, Follicular

## ABSTRACT

*Thyroid-specific malignant tumors are derived from follicle cells (papillary and follicular carcinoma), and from parafollicular, calcitonin-producing C-cells (medullary carcinoma). The main criterion for diagnosis of papillary carcinoma is the occurrence of ground glass, hypochromic nuclei, often associated with papillae as the prominent pattern of the tumor, and psammoma bodies. The diagnosis of follicular carcinoma is based on the true infiltration of the venous vessels outside the tumor capsule and the fungus-like infiltration through the tumor capsule into the surrounding parenchyma. Anaplastic carcinoma is mostly detected by the pathologist by fine-needle aspiration biopsy, or tumor reduction specimen. Medullary thyroid carcinoma is typically composed of solid nests and infiltrating formations of polygonal or spindle-shaped cells and amyloid deposits within the stroma of the tumor. Two main discriminatory immunohistochemical markers for tumors with follicular and parafollicular origin are thyroglobulin and calcitonin, respectively. Thyroglobulin is present in more than 95% of papillary and follicular carcinomas, whereas anaplastic thyroid carcinomas are mostly immunonegative for thyroglobulin. Medullary carcinoma is characteristically positive for calcitonin, pan-neuroendocrine markers, and often numerous peptides.*

According to the World Health Organization classification malignant tumors of the thyroid are subdivided into thyroid-specific, which are unique to the thyroid (papillary, follicular and medullary carcinoma), and tumors commonly found also in other organs, but still have some particular features when they occur in the thyroid gland (e.g. lymphoma, some types of sarcoma) (1).

Thyroid-specific tumors are derived from follicle cells (papillary and follicular carcinoma), and from parafollicular, calcitonin-producing C-cells (medullary carcinoma).

Papillary carcinoma is the most frequent type of follicle-cell derived carcinoma. The main criterion for diagnosis of papillary carcinoma is the occurrence of ground-glass nuclei. These nuclei are enlarged, round to oval structures, with a pale karyoplasm condensing continuously to the nuclear membrane (this is an optical phenomenon caused by cytoplasmic pseudoinclusions). The nuclei are densely arranged and often overlap each other. Papillary carcinoma usually has papillae in its structure. Papillae are delicate stalks of epithelial cells situated on basal membranes covering stromal fibers and thin capillaries. Often the tumors contain round laminated calcifications (psammoma bodies). For technical reasons the phenomenon of ground-glass nuclei cannot be detected in frozen material, i.e., frozen sections or paraffin sections after frozen section procedures. According to the WHO classification subtypes of papillary carcinoma are: papillary microcarcinoma, encapsulated variant, follicular variant, diffuse sclerosing variant and oxyphilic cell type (1). Interestingly, papillary microcarcinoma may occur in a familial form and these tumors show more aggressive clinical behavior than sporadic cases (2). The oxyphilic-cell type of papillary carcinoma causes diagnostic problems because it obscures the pattern of ground-glass nuclei.

The diagnosis of follicular carcinoma is based on the histopathological demonstration of infiltrative growth. There are two criteria: 1) True infiltration of the venous vessels outside the tumor capsule, and 2) fungus-like infiltration through the tumor capsule into the surrounding parenchyma (capsular infiltration, or better extracapsular extension)(3). The variants of follicular carcinoma are: minimally invasive (encapsulated), widely invasive, oxyphilic cell type and clear cell variant (1). There are two main questions discussed in the literature concerning the oxyphilic (oncocyctic) cell type tumors: firstly, are large oncocyctic (follicular structured) tumors malignant even without vascular/parenchymal infiltration? Secondly, is the prognosis of oxyphilic carcinoma equal to, worse than or better when compared with their follicular counterparts with regular cytoplasm?(4).

Undifferentiated (anaplastic) carcinoma is mostly detected by the pathologist by fine-needle aspiration biopsy (FNAB), or tumor reduction specimen. The diagnosis of malignancy is evident by cytological polymorphism and histological dedifferentiation. Histopathologically, this tumor reveals solid sheets of highly anaplastic cells or spindle cells with morphologically sarcoma-like areas and frequent appearance of giant cells. Most tumors show large areas of necrosis and hemorrhage. Some cases of anaplastic carcinoma have remnants of preexisting differentiated (papillary or follicular) carcinoma, indicating a dedifferentiation pathway from differentiated to anaplastic carcinoma (5,6). Medullary (C-cell) thyroid carcinoma is characteristically composed of solid nests and infiltrating formations of polygonal or spindle-shaped cells. Amyloid deposits within the stroma are found in about the half of the tumors. There are eleven subtypes of medullary carcinoma, among them: classical, carcinoid-like, papillary, giant-cell type, or with squamous differentiation. Even mucus production and melanin pigmentation have been observed (7). According to general agreement no preexisting adenoma exists; all the tumors exceeding 50 cells are considered malignant and separate from C-cell hyperplasia. Immunohistochemistry is strongly indicated for all cases of solid tumors without typical features of papillary or follicular carcinoma to prevent underdiagnosis of medullary carcinoma. Thyroid paraganglioma, hyalinizing trabecular adenoma and metastatic neuroendocrine tumor are typical differential diagnoses (8).

Two main discriminatory immunohistochemical markers for tumors with follicular and parafollicular origin are thyroglobulin and calcitonin, respectively.

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Thyroglobulin is present in more than 95% of papillary and follicular carcinomas. Poorly differentiated carcinomas contain less thyroglobulin than do better differentiated tumors (9). Anaplastic thyroid carcinomas are mostly immunonegative for thyroglobulin.

The vast majority of papillary carcinomas are cytokeratin type 19 immunopositive (however, cytokeratin 19 is also present in other thyroid tumor types) (10). Low molecular weight and broad-spectrum keratins are present in up to 75% of anaplastic carcinomas. Vimentin is coexpressed regularly in thyroid carcinomas (11).

CEA (carcinoembryonic antigen) is absent in follicular and papillary carcinoma but positive in medullary carcinoma and certain metastatic carcinomas to thyroid (12).

Thyroid transcription factor-1 (TTF-1) is positive in 96% of papillary, 100% of follicular, 20% of oxyphilic, and 90% of medullary carcinomas, whereas anaplastic carcinomas are essentially immunonegative for TTF-1 (13).

Ninety-five percent of medullary carcinomas are positive for calcitonin. Other numerous peptides may also be present: somatostatin, gastrin-releasing peptide, ACTH and other pro-opiomelanocortin peptides, neurotensin, substance P, vasoactive intestinal peptide (VIP), catecholamines and serotonin (14,15). Generic neuroendocrine markers are typically positive in medullary carcinoma and include NSE (neuron-specific enolase), synaptophysin, chromogranins A and B, and secretogranin II.

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# Principles of surgery for thyroid carcinoma

**KEYWORDS:** Thyroid Neoplasms; Carcinoma; Surgery; Lymph Node Excision; Thyroidectomy; Surgical Procedures, Operative

## ABSTRACT

*Surgery is the initial therapy in thyroid carcinoma. The basic principles of surgical oncology in malignant epithelial tumors have their full improvement in thyroid carcinoma (TC). The surgery is performed on organ of tumor origin and regional lymphatic basins. The aim of surgery in thyroid carcinoma is to eradicate all tumor foci, cure the most number of patients, reduce recurrence and mortality rate, and provide good quality of life. There is no doubt between oncologists that the surgery for thyroid carcinoma has no alternative. The extent of surgery is matter of actual controversies. Surgery is the initial treatment for all differentiated, papillary and follicular, as well as medullary and even anaplastic thyroid carcinoma. It should be performed by well-trained surgeons. The surgery of thyroid gland is the surgery of laryngeal recurrent nerve and parathyroid glands. The extent of primary surgery should be dictated by stage of disease and prognostic factors. The quality of surgery and incidence of complications depends on surgeon's skill and experience. That is why the surgeon is factor of prognosis in treatment of patients with TC.*

## SURGERY FOR DIFFERENTIATED THYROID CARCINOMA

Surgery is the initial therapy in thyroid carcinoma. The basic principles of surgical oncology in malignant epithelial tumors have their full improvement in thyroid carcinoma (TC). The surgery is performed on organ of tumor origin and regional lymphatic basins. The aim of surgery in thyroid carcinoma is to eradicate all tumor foci, cure the most number of patients, reduce recurrence and mortality rate, and provide good quality of life. There is no doubt between oncologists that the surgery for thyroid carcinoma has no alternative. The extent of surgery is matter of actual controversies (1-15).

Postoperative radioiodine ablation is proposed for patients with high risk for recurrence. External radiotherapy is indicated in older patients (over 45 years at diagnosis) with residual tumor without radioiodine uptake.

The extent of primary surgery should be dictated by stage of disease and prognostic factors. The quality of surgery and incidence of complications depends on surgeon's skill and experience. That is why the surgeon is factor of prognosis in treatment of patients with TC (16).

Surgery is the initial treatment for all differentiated, papillary and follicular, thyroid carcinoma. It should be performed by well-trained surgeons.

### Pre-operative diagnosis and evaluation

Clinical examination is the keystone in diagnosis of TC. Ultrasound of the neck is the next step and it is very informative. Fine needle aspiration biopsy of thyroid nodule or neck lymph node for cytology examination is inevitable part of pre-operative diagnostic.

Indirect laryngoscopy and ORL examination gives the information of vocal cord status in cases of laryngeal nerve infiltration with local tumor growth.

Chest X ray, bone scan, ultrasound of abdominal organs, blood tests, hormonal thyroid status, serum thyroglobulin and calcitonin levels, as well as scintigraphy, computed tomography (CT) or magnetic resonance imaging (MRI) of mediastinum if indicated enables detection of initial distant metastases.

Before the operation the patient should be informed about surgical procedure and eventual complications (laryngeal recurrent nerve injury, hypocalcaemia) and examined by anesthesiologist.

### Surgery of thyroid gland

Surgery for TC, as in all malignant epithelial tumors, includes surgery of organ of tumor origin and surgery of regional lymph nodes, i.e. thyroid gland and neck lymph nodes as well as mediastinal lymph nodes if indicated.

The extent of operation is planned according to tumor stage and other prognostic factors including experienced thyroid surgeon. Tumor stage is obtained by frozen-section histopathology examination of thyroid gland, neck lymph nodes, surrounding soft tissue and eventually parathyroid glands in cases of infiltration.

The complete operation should be performed in the same act in goal to avoid reoperation and to reduce percent of complications, i.e. laryngeal nerves and parathyroid glands injury (16).

The extent of primary operation is debated. The best results are achieved with total or "near" total thyroidectomy and appropriate dissections of neck and mediastinal lymph nodes.

### Choice of operation

Nodectomy or partial lobectomy is not suggested because of high percent of recurrences (3, 7, 12). Total lobectomy is the minimal surgical procedure for thyroid nodule. It is followed with minimal complications, but unfortunately laryngeal nerve injuries are registered. "Near" total thyroidectomy includes removal of affected lobe, isthmus and almost the entire opposite lobe except small amount of thyroid tissue (1 g) in Berry's ligament. With total thyroidectomy the whole thyroid gland, including pyramidal lobe, is removed. The surgery of thyroid gland is the surgery of laryngeal recurrent nerve and parathyroid

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