Description Of Neutrophil-Lymphocyte Ratio In Patients With Thyroid Nodules Study Description At Dr Soetomo Hospital Period January 2018 – December 2020

by Marjono Dwi Wibowo

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Agus Maulana[a], Marjono Dwi Wibowo[b]

[a] General Surgery Resident, Faculty of Medicine, Airlangga University / RSUD Dr. Soetomo Surabaya, Indonesia
[b] *SMF / Lab Teaching Staff. Surgery Faculty of Medicine, Airlangga University / RSUD Dr. Soetomo Surabaya, Indonesia*

Abstract

Background: Thyroid nodules are found in more than 50% of patients using ultrasonography. The incidence of thyroid nodules in the population is increasing, between 5% and 10% are malignant nodules. In today's era, to identify the exact nature of thyroid nodules is very necessary, because thyroid cancer is the most common endocrine malignancy that occurs in thyroid nodules. The inflammatory process plays a major role in many cancer events, including tumor development, growth, clinical presentation, and prognosis. The neutrophil/lymphocyte ratio (NLR) is a simple index of the systemic inflammatory response. This study aims to describe the ratio of neutrophils and lymphocytes in thyroid nodules in patients at RSUD dr. Soetomo Surabaya.

Method: In 102 cases of thyroid nodules, both benign and malignant, were retrospectively analyzed. We evaluated the neutrophil lymphocyte ratio with postoperative pathological anatomic outcomes. Complete blood count with differential count taken before surgery. The NLR was calculated by dividing the preoperative neutrophil count by the lymphocyte count. Samples were categorized into low grade (NLR < 1.91) and high grade (NLR 1.92).

Results: There was a statistically significant difference in the neutrophil-lymphocyte ratio between benign thyroid nodules and malignant thyroid nodules (p=0.001). Low NLR values <1.91 were found in 25% of patients with benign thyroid nodules and 9.82% of patients with malignant thyroid nodules. High NLR values 1.92 were found in 25% of patients with benign thyroid nodules and 40.18% of patients with malignant thyroid nodules.

Conclusion: Patients with malignant thyroid nodules tend to have a high NLR whereas patients with benign thyroid nodules tend to have a low NLR.

Keywords: thyroid nodules; neutrophil lymphocyte ratio; malignancy; cancer; health risks; humans and diseas

1. Introduce

1.1 Background

Thyroid nodules are lesions within the thyroid gland that are radiologically distinct from the surrounding thyroid parenchyma. Thyroid nodules can be caused by a variety of disorders: benign (colloidal nodules, Hashimoto's thyroiditis, simple cysts, follicular adenoma and subacute thyroiditis) and malignant (papillary cancers, follicular cancers, Hurthle cell (oncocytic) cancers), anaplastic cancers, medullary cancers, thyroid and lymphomas. metastases) (Tamhane et al., 2016). The prevalence of malignancy in a single thyroid nodule is estimated at 5%, whereas in multiple thyroid nodules it is estimated at 15% that there is a risk of malignancy in the thyroid gland (Pellegriti et al., 2013).

Globally, there are three countries with the highest incidence of thyroid cancer cases, including: China (11,016 cases in 1990 and 41,511 cases in 2017), the United States (10,833 cases in 1990 and 25,896 cases in 2017), and India (7369 cases in 1990 and 25,675 cases). in 2017). Where China has the highest number of deaths worldwide (3,636 cases in 1990 and 7,433 cases in 2017) from thyroid cancer (Daeng et al., 2020). Approximately 230,000 new cases of thyroid cancer were estimated in 2012 among women and 70,000 among men, with an age standard rate (world population) of 6.1 / 100,000 women and 1.9 / 100,000 men (La Veccia et al. , 2015).

Ultrasonography (USG) and Fine Needle Aspiration Biopsy (FNAB) are the most common diagnostic tools with high specificity for detecting thyroid nodules. Ultrasound can be used to differentiate solid and cystic nodules and can be used as a guide in biopsy. Ultrasound can detect thyroid nodules in 19%-68% of randomly selected individuals, with a higher incidence in women and the elderly. Unfortunately, the accuracy of ultrasound examination depends on the skill and experience of the examiner. So it must be understood that a single examination with ultrasound cannot diagnose a thyroid cancer (Haugen et al., 2016). The sensitivity of FNAB in thyroid cancer reaches 84%-93% and specificity up to 75%-99%. Nearly 20% of FNAB results go undiagnosed, due to sampling errors or poor preparation technique.

The developing systemic inflammatory response plays a role in the physiopathogenesis of malignant transformation. Recently, a number of studies investigated Neutrophil-lymphocyte ratio (NLR) as an indicator of inflammatory response, which is an easy and cost-effective method. There are two markers of inflammatory status that are most often used in cancer patients, namely C-Reactive Protein (CRP) and NLR. The ratio of neutrophils to lymphocytes has emerged as a simple and valid marker of the systemic inflammatory response. Compared to serum CRP, which is not routinely measured as part of cancer evaluation, NLR is inexpensive and easy to calculate (Liu et al., 2013).

Neutrophil-lymphocyte ratio(NLR) thyroid nodules are expected to be helpful in predicting malignancy in thyroid nodules, which can aid in the choice of surgical or conservative decision. In addition, the NLR can also confirm the results of benign FNAB in the thyroid, considering that FNAB has a false negative value from 2% to 10%.

2. Literature Review

2.1 Anatomy of the thyroid gland

The thyroid is a hormone gland; has no ductus and consists of 2 lobes (right and left) connected by the isthmus which is located in front of the trachea just below the cricoid cartilage.

Embryologically, the thyroid gland is initially a protrusion of the anterior middle wall of the pharynx. The protrusion is called the pharyngeal pouch, which is between the brachial arches 1 & 2 at ± 4 weeks of fetal age. This bulge will then disappear. However, in some patients, a remnant is found, called Ductus Thyroglossus which extends from the foramen caecum at the base of the tongue that protrudes downwards when the thyroid gland reaches maturity in its growth, then this thyroid gland can be found in front of the 5, 6, & 7 cervical vertebrae. These remnants of the thyroid gland are also often found at the base of the tongue (duct. thyroglossus/ lingua thyroid) and other parts of the neck. Under normal circumstances it weighs 25-40 grams (adults). Size and weight vary depending on age and sex as well as endemic factors.

In adults, the thyroid measures about 4 cm superior to inferior, is about 15-20 mm wide and about 20-39 mm thick. The right and left lobes are connected by the thyroid isthmus which is located anterior to the trachea. In certain cases, a pyramidal lobe can be seen, a small lobe located near the midline. The size of this thyroid gland can change drastically according to the accompanying disease.

The thyroid is covered by a capsule consisting of fibrous tissue without a marked lobulated appearance. The lateral lobe of the thyroid is located medial to the trachea and larynx, and lateral to the sternocleidomastoid muscle. Anteriorly, the thyroid is covered by superficial fascia and platysma, posteriorly it is covered by a mixed structure originating from the deep cervical fascia which forms the suspensory ligament of Berry which will fix the thyroid to the trachea and larynx. Anatomical description of the thyroid gland can be seen in Figures 1 and 2.

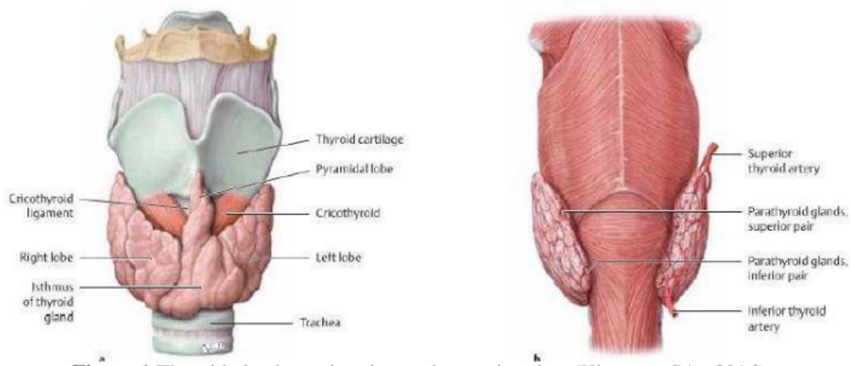

Figure 1. Thyroid gland anterior view and posterior view (Khonsary SA., 2016)

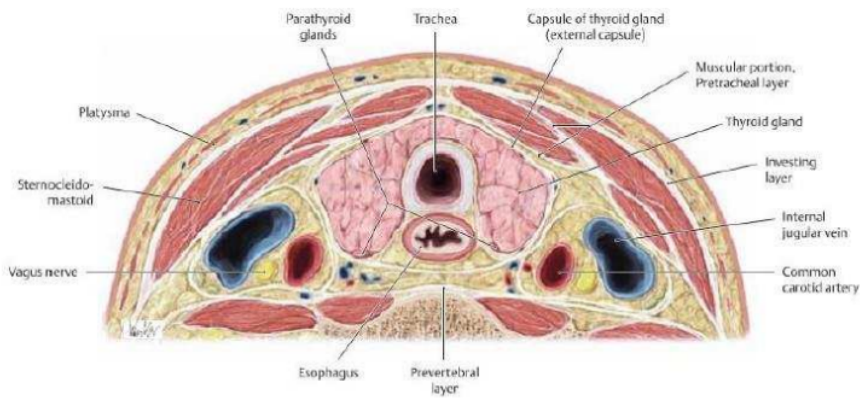

Figure 2. Axial section at thyroid level (Khonsary SA., 2016)

The thyroid gland is vascularized by two main arteries, namely the superior thyroid artery and the inferior thyroid artery. Sometimes there is also the thyroidea ima artery, a direct branch of the aorta or the brachiocephalic artery. These arteries branch off and communicate with each other. The superior and inferior thyroid arteries often anastomose posteriorly and these anastomoses lead to the location of the parathyroid glands. The thyroid gland is vascularized by three main pairs of veins, namely the superior thyroid vein, medial thyroid vein, and inferior thyroid vein, which drain into the left brachiocephalic vein. Generally these veins pass through the thyroid gland anteriorly and also across the isthmus and trachea.

Thyroid gland lymph flow consists of two streams, namely intraglandular lymph nodes and extraglandular lymph nodes. Both of these lymph flows will lead to the pretracheal lymph nodes and then to the deep lymph nodes around the jugular vein. From around the jugular vein it is passed to the superior mediastinal lymph nodes.

The innervation of the thyroid gland consists of the middle and inferior cervical (from the trunk sympathic) sympathetic nerves. While the parasympathetic nerves are regulated by the superior laryngeal nerve and recurrent laryngeal nerve (branch of the vagus nerve). The superior and inferior laryngeal nerves are often injured during surgery, resulting in disturbed vocal cords (stridor/hoarse).

2.2 Physiology

The thyroid gland is an endocrine organ that secretes thyroid hormones. This hormone regulates the basal metabolic rate. There are 2 types of thyroid hormones, namely thyroxine (T4) and triiodothyronine (T3). The most quantitative is T4 as the main hormone and a little T3. T3 is an active hormone (3x metabolic potential than T4) and T4 is considered a precursor or prohormone which when needed is cleaved in tissues to form T3.

Iodine is an important element in thyroid hormones, making up 65% of the weight of T4 and 58% of the weight of T3. In peripheral tissues such as the liver, T4 deiodination occurs which produces T3 and reverse T3 (rT3) which has no biological activity. The resulting T3 and T4 are stored in colloid form in the thyroid parenchyma. Most of the T4 will be released into the blood circulation and a small portion is stored in colloids and will undergo recycling.

The half-life of T4 is 4-6 days, whereas that of T3 is only 1 day. In the blood circulation, most (85%) of this T4 will bind to Thyroid Binding Globulin (TBG) and 10-15% bind to Thyroid Binding PreAlbumin (TBPA) and 5% bind to albumin. A small portion, less than 1% in the free form is not bound, free T3 (FT3) and free T4 (FT4). The regulation of secretion in the thyroid gland is influenced by a hormone called Thyroid Stimulating Hormone (TSH) which is produced by the anterior lobe of the pituitary. In contrast, TSH secretion is regulated by RTH from the hypothalamus. In general, blood thyroid hormone levels above normal levels will inhibit the release of TRH and TSH. Elevated TSH levels are associated with increased thyroid cell proliferation and stimulation of T3 and T4 production. The main function of T3 is to regulate carbohydrate and protein metabolism in all cells. Based on this mechanism, the secretion of the thyroid gland can be adjusted to conditions or changes inside and outside the body. Schematic of thyroid hormone regulation can be seen in Figure 3.

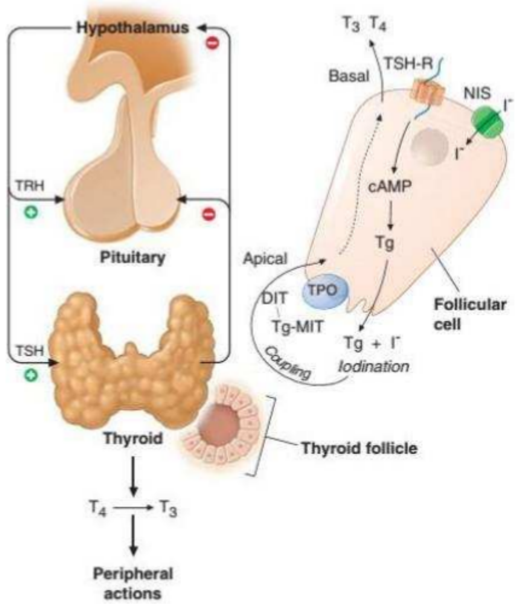

Figure 3. Thyroid gland physiology scheme(Khonsary SA., 2016)

2.3 Histology

The thyroid gland is a unique endocrine gland with a follicle and an extracellular component that stores large amounts of hormones in an inactive form. The gland is surrounded by a fibrous capsule, and a fine collagenous septum that divides the thyroid gland into lobules consisting of many thyroid follicles resembling a ring-shaped structure with an average diameter of about 200 m. The thyroid follicle is the main functional and structural component of the thyroid gland that synthesizes and releases T3 and T4. Each follicle is filled with colloid, which contains a gelatinous substance that stores T3 and T4. In an active thyroid gland, colloids are predominantly basophilic, whereas in an inactive gland, colloids are acidophilic.

There are two types of cells in the thyroid gland, namely follicular cells and parafollicular cells (Figure 4). Follicular cells are responsible for producing thyroid hormones. These cells are cuboidal cells but can turn into squamous (inactive) or columnar (active) cells depending on their state of secretion. Hematoxylin eusin staining of the thyroid gland shows that the follicular cells have basophilic cytoplasm and a round nucleus with one or more nucleoli. The Golgi apparatus is located in a supranuclear position. Ultrastructurally, the cell contains organelles that exhibit secretory and absorptive characteristics as well as short microvilli at the apical surface of the cell. At the basal location, the cells contain a large amount of rough endoplasmic reticulum. At the apical location,

Parafollicular cells or clear cells (C cells) are the second type of thyroid cells, located within the follicular epithelium or as small clumps adjacent to the follicle. These cells are relatively large oval or ellipsoid cells with round nuclei and pale cytoplasm and are found lying on the basement membrane of the follicle. These cells have cytoplasm that is not stained by hemooxylin eosin staining and are therefore called "C" cells. These cells produce the hormone calcitonin which is produced in response to high blood calcium and inhibits osteoclast activity (Omer Engin., 2019).

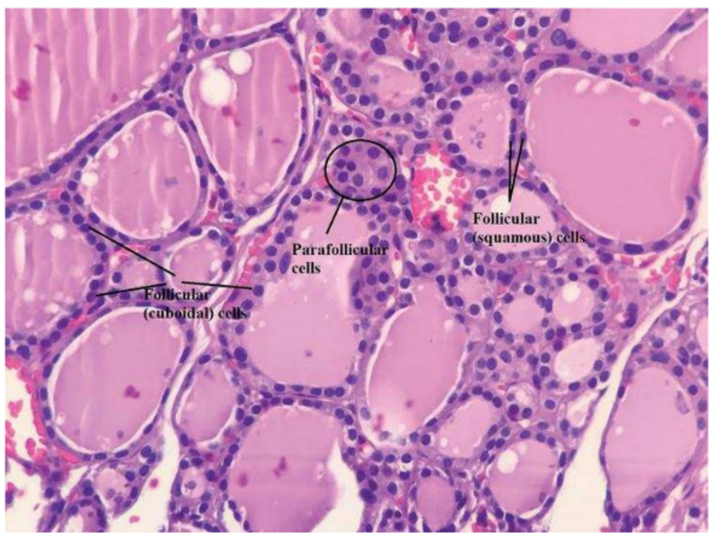

Figure 4. Thyroid gland cell types(Omer Engin., 2019).

2.4 Etiopathology

Iodine deficiency, intake of goitrogenic or autoimmune processes can cause increased proliferation of thyroid cells as a result of thyroid hyperplasia. Furthermore, this increased proliferation of thyroid cells together with DNA damage due to the action of H2O2 causes an increase in the mutational load containing a number of mutated thyroid cells. Some of these mutated cells result in activation of the cAMP constitutional cascade that stimulates growth and function. Finally, in the proliferating thyroid cells, there is an increase in thyroid growth factor (TGF). As a result of TGF, all cells become divided and form small clones. Furthermore, clones with the activation of these mutations will proliferate if they have their own stimulation and form small foci which will develop into thyroid nodules. This is what causes the formation of benign thyroid nodules (Kumar V et al., 2018)

In other conditions, malignant thyroid nodule formation is initiated by DNA damage resulting from interactions with radiation and iodine deficiency. In conditions of DNA damage followed by failure to repair DNA, it will result in mutations in the somatic cell genome. Then there is oncogenic activation, inactivation of tumor suppressor genes and changes in apoptotic regulatory cells that result in clonal expansion. The clonal expansion together with the process of angiogenesis and additional mutations resulted in the growth of tumor cells which subsequently became malignant thyroid nodules. Furthermore, with this malignant nature, the nodule undergoes rapid growth, crosses the capsular boundary, invades the surrounding tissue and is hypervascular and neovascular. In the papillary type, it has psammoma bodies with concentric fine calcifications. (Kumar V et al.

Most thyroid nodules are not true neoplasms but are benign growths caused by a cycle of hyperplasia and involution of the underlying thyroid tissue. The result of this process is the fusion of the region of the colloid-containing follicles and parenchyma, forming an adenomatoid image or colloid nodule.

Colloidal nodules have the following properties:

a. Benign, the most common type of thyroid nodule. Generally adenomas (70%), some are solitary, multinodular goiter and inflammatory nodules.

b. Malignant, about 4-7% histopathologically thyroid nodules are cancer. Of the malignant thyroid nodules about 80% are papillary, follicular (well differentiated) and mixed papillary-follicular carcinoma. While the rest are medullary carcinomas (10%). Undiffferentiated or anaplastic carcinomas (3%) and Hurthle cell (2%) were the fewest types. In a very small number there are also types of malignancies in the thyroid that are not primary thyroid nodules, namely metastases and lymphomas (Kumar V et al., 2018).

2.5 Thyroid nodules

Enlargement of the thyroid gland (nodule) can be an inflammatory disorder, hyperplasia or neoplasm, which is clinically difficult to distinguish. Malignancies in the thyroid gland are relatively rare and only 1.5% of all malignancies that exist throughout the body, but constitute 90% of malignancies that arise in endocrine organs.

Thyroid nodules are a common occurrence in humans. Findings of nodules in adults are about 4-8% by palpation method, about 10-41% by finding on ultrasound examination and about 50% by pathological examination or at autopsy. (Haugen BR et al., 2016)

Inflammation or thyroiditis or inflammation of the thyroid gland includes a number of disorders of the thyroid from acute suppurative inflammation to chronic processes. Acute thyroiditis is rare, with lesions that are red, painful, and feverish. Included in these criteria are granulomatous thyroiditis (subacute or deQuervain), lymphocytic thyroiditis (Hashimoto's disease), and Riedel's goiter.

Goiter or goiter is characterized by nodular or diffuse enlargement of the thyroid gland. Some literature refers to it as adenomatous goiter, endemic goiter, or multinodular goiter. This condition is usually caused by hyperplasia of the thyroid gland due to iodine deficiency. This condition can affect the entire gland or appear focally and form a solitary nodule. This lesion is the most common lesion found on aspiration biopsy. (Brunicardi FC et al., 2019)

Thyroid neoplasms include benign neoplasms (follicular adenomas) and malignant neoplasms (carcinomas). The differential diagnostic classifications of thyroid nodules are summarized in Table 1. Thyroid nodules are clinically palpable in about 5–10% of the adult population in the United States. Thyroid cancer in Indonesia is the fourth most common malignancy after cervical, breast and skin cancer.

Table 2.1 Differentiated classification of thyroid nodules (Pemayun et al., 2016)

- Non-neoplastic nodules
  - Hyperplastic
    - Spontaneous
    - Compensatory after partial thyroidectomy
  - Inflammatory
    - Acute bacterial thyroiditis
    - Subacute thyroiditis
    - Lymphocytic (Hashimoto's) thyroiditis
- Benign neoplasms
  - Non-functioning (cold nodules)
    - Solid (or mixed): adenoma
    - Cystic
  - Functioning (hot nodules)
    - Adenoma
- Malignant neoplasms
  - Primary carcinoma
    - Papillary carcinoma
    - Follicular carcinoma
    - Anaplastic carcinoma
    - Medullary carcinoma
  - Thyroid lymphoma
  - Thyroid metastasis from other primaries

2.5.1 Benign nodules

A solitary follicular or adenomatous adenoma or adenomatoid nodule is defined as a benign encapsulated mass of the follicle, often showing a uniform pattern along the nodule margin. Follicular adenomas with papillary hyperplasia (some of which are functional) should not be classified as papillary adenomas, but as papillary hyperplastic nodules. A solitary adenoma, indeed, if there are multiple nodules in one lobe or thyroid gland, may be more accurately diagnosed as a multinodular goiter with adenomatous change (adenomatous hyperplasia). Histological features that differentiate between adenomas and adenomatous nodules include encapsulation, uniformity of pattern within the adenoma, and compression of the surrounding gland by the adenoma and its capsule. (Baloch ZW et al., 2018)

Follicular adenomas (15-40%) arise from the follicular epithelium and are usually solitary, with a firm capsule. On scintigraphy examination, there is a picture of a toxic adenomas functioning (hot on scintigraphy) or a hyperfunctioning adenoma in a multinodular goiter. The appearance of a non-functioning adenoma on scintigraphy is a cold nodule. (Haugen BR et al., 2016)

2.5.2 Malignant nodules

The most common malignant nodules of thyroid origin are well-differentiated follicular epithelial carcinomas, up to 80% of which are papillary carcinomas. Most non-neoplastic thyroid diseases do not appear to be precursors of malignancy, with the exception that autoimmune thyroiditis may predispose to malignant lymphoma. Anaplastic carcinomas frequently arise in the thyroid and are associated with a goiter, and careful examination of resected tissue often reveals benign tumors or well-differentiated carcinomas that are closely associated with anaplastic neoplasms. These findings have led to the opinion that benign tumors or lowgrade carcinomas can "transform" into anaplastic carcinomas.

a. Papillary carcinoma

It is the most common malignant glandular tumor in iodine-sufficient or dietary iodine-excess countries, accounting for 80% of thyroid malignancies in the United States. Papillary thyroid carcinoma (PTC) is clinically slow and carries an excellent prognosis (>90% survival at 20 years). These carcinomas invade the lymphatics causing multifocal lesions and regional lymph node metastases. Venous invasion is rare and metastases outside the neck are not uncommon (5-7% of cases). Papillary thyroid carcinoma can occur at any age and is rarely diagnosed as a congenital tumor. Most tumors are diagnosed in patients in the third and fifth decades. Women are affected more than men with a 2:1 to 4:1 ratio. (Baloch ZW et al., 2018)

b. Follicular carcinoma

Follicular carcinoma comprises about 5% of thyroid cancers; However, in areas of iodine deficiency, these tumors are more common, up to 25-40% of thyroid cancer. The true incidence of follicular carcinoma is difficult to determine because the follicular variant of papillary carcinoma may still fall into this category. Risk factors include iodine deficiency, older age, female gender, and radiation exposure (although the association of radiation for follicular carcinoma is much higher compared to papillary cancer). Clinically, follicular carcinoma usually presents as a solitary mass in the thyroid. Follicular carcinoma has a marked propensity for vascular invasion and evasion of lymphatics; hence, it is true that lymph node embolic metastases are extremely rare. Follicular carcinoma extends haematogenously and metastasizes to bone, lung, brain, and liver. (Baloch ZW et al, 2018)

c. Anaplastic thyroid tumors

Anaplastic thyroid carcinoma is an aggressive carcinoma and accounts for 8-16% of thyroid carcinomas. The prevalence of this carcinoma is found in endemic areas of goiter. Especially at the age of 60-80 years, the ratio of women to men on average is 3:1. Most patients are symptomatic and have a rapidly expanding neck mass. The initial complaint is usually pain in the neck, dysphonia, dysphagia and dyspnoea (Khan et al., 2020)

d. Medullary carcinoma

Medullary carcinoma, there are 3-10% of thyroid malignancies, this carcinoma is derived from parafollicular cells (C cells), with elevated calcitonin levels, these levels are reported to have a correlation with tumors.

Although more common in women than men, medullary carcinoma is less sex-specific than other thyroid malignancies. Family relationships are found in 10-20% of patients, with an autosomal dominant hereditary pattern. Medullary carcinoma is a component of the multiple endocrine neoplasia (MEN) syndrome types IIA and IIB and is associated with pheochromocytoma and parathyroid adenoma or parathyroid hyperplasia. (Khan et al., 2020)

2.6 Diagnosis

2.6.1 History

Most patients with thyroid nodules are asymptomatic and most nodules are found on clinical examination or self-palpation. Sudden pain and localized swelling may be precipitated by spontaneous bleeding within the lesion. Large lesions may interfere with swallowing and the airway due to compression of the esophagus and trachea. In addition, systemic symptoms also depend on the level of thyroid hormones (T3 and T4) circulating in the blood in the form of hyperthyroidism or hypothyroidism (Khan et al., 2020).

2.6.2 Physical examination

Physical examination in cases of thyroid nodules can be done in the form of inspection of the neck from the front and side. In cases with large thyroid nodules, an enlarged neck may be seen. The thyroid can be palpated from the front when facing or from behind the patient.

Thyroid palpation from the back is more sensitive, especially when combined with swallowing instructions for the patient in determining the presence of a thyroid nodule. Unfortunately, in cases of small thyroid nodules, there is often no abnormality or thyroid nodule. (Zamora EA et al., 2020)

2.6.3 Supporting investigation

a) Laboratory examination

Laboratory tests are important in thyroid disease to differentiate the type of thyroid disease, but thyroid function tests are not performed to determine whether a thyroid nodule is benign or malignant. Several types of laboratory tests on thyroid nodules include: (Zamora EA et al., 2020)

- Measurement of thyroid-stimulating hormone (TSH) levels is often used by clinicians as a screening test. Significantly elevated levels of inadequate TSH in hormone production when levels are suppressed indicate excessive hormone production is unregulated.
- If TSH is abnormal, there may be decreased levels of the thyroid hormones T4 and T3 .

- Examination of thyroid hormones triiodothyronine (T3) and thyroxine (T4).
- Autoantibodies were detected in various variations (anti-TG, anti-TPO, TSH receptor stimulating antibodies).
- There are two carcinoma markers for thyroid-derived carcinoma. Thyroglobulin (TG) for well-differentiated papillary type or adenocarcinoma, follicular and although rarely calcitonin as a carcinoma marker in cases of medullary thyroid carcinoma.

b) Radiological examination

- **Neck-thorax plain photo**

Plain radiographs may be used to demonstrate retrosternal extension of the thyroid, calcified thyroid, bone or mediastinal lymph nodes and bone metastases. Plain radiographs have very limited ability to evaluate the thyroid. Plain radiographs show a soft tissue mass and tracheal deviation. Retrosternal extension and pulmonary metastases can also be detected on plain radiographs. (Khan et al., 2020)

Thyroid carcinoma calcifications can be seen on plain films. Micro-calcifications of the thyroid support the appearance of carcinoma, whereas peripheral rim calcifications favor benign lesions. Medullary and metastatic carcinomas also give the appearance of calcification. (Khan et al., 2020)

Plain radiographs can also show the appearance of bone metastases, suggesting the presence of lytic or blastic lesions in the bone. (Khan et al., 2020)

- **Ultrasound (USG)**

In a meta-analysis study evaluating the use of ultrasonography (USG) to predict malignancy of thyroid nodules with sensitivity between 26% - 87% and specificity between 40% - 93% (Remonti LR, et al., 2015).

Ultrasound can be used and can detect tumors with a size of more than 1 cm, then can be followed by a needle biopsy (FNAB), with the aim of knowing whether the tumor is benign or malignant, thyroid function is usually normal in cases of thyroid cancer. Ultrasound is also required to detect small nodules or posterior nodules that are not clinically palpable. In addition, ultrasound can be used to distinguish solid and cystic nodules and can be used as a guide in biopsy. However, the accuracy of this examination depends on the skill and experience of the examiner so it must be understood that a single examination with ultrasound cannot diagnose a thyroid cancer. (Xie C, 2016)

- **Computed tomography scan**

CT scanning is not a sensitive technique for demonstrating intrathyroid lesions. However, CT is used in the evaluation of lymphadenopathy, local spread of the tumor and spread into the mediastinum or retrotracheal region. In addition to ultrasound which is used to detect primary intrathyroid lesions, CT is used for staging. Attempts to differentiate benign and malignant nodules by measurement of the iodine content and enhancement characteristics of the nodules by CT scan were unsuccessful. (Khan et al., 2020)

- **Thyroid scintigraphy**

Currently, the indications for thyroid scintigraphy have been reduced relative to thyroid examination. Thyroid scintigraphy examination used oral iodine radiopharmaceutical (131 I and 123 I) or 99m Tc-pertechnetate which was injected intravenously. (Khan et al., 2020).

The scan results show an area of catch activity (uptake) for radiopharmaceuticals which can be divided into 3 forms, namely in the form of increased catch (hot), reduced or absent catch activity (cold), and can also catch activity that is relatively the same as healthy thyroid tissue. surroundings (warm). (Khan et al., 2020)

From the results of the thyroid scintigraphy examination, it is not certain whether the nodule is benign or malignant. Statistically about 95% of goitre nodosa presents as a cold nodule on thyroid scintigraphy. The frequency of malignancy in cold nodules is about 10-15% compared to hot nodules which is only 4%. This provides information that hot nodules are usually malignant nodules, but that malignant nodules are only slightly more common in cold nodules than hot nodules. (Fred A et al., 2012)

c) Anatomical pathology examination

Fine needle aspiration cytology (FNAB) is a widely used tool for the diagnosis of thyroid lesions with high diagnostic sensitivity, specificity and accuracy. (Renuka et al., 2012)

Cytological examination is useful to determine the type of cells in the thyroid nodule, which was previously carried out by taking tissue by means of fine needle aspiration biopsy (FNAB). FNAB by skilled operators is currently considered an effective method to differentiate benign or malignant in solitary nodules or dominant nodules in multinodular (Renuka et al., 2012)

In one study, it was reported that the use of FNAB had a sensitivity of 87.1% and a specificity of 64.6% and an accuracy of 76.1% in predicting malignancy in thyroid nodules (Murati, A., et al., 2014).

The FNAB followed by cytology of the thyroid nodule is the first diagnostic test to evaluate a goiter and the only most effective test for the preoperative diagnosis of a solitary thyroid nodule. The main indications of this FNAB are: (Kocjan 2009)

- Diagnosis by diffuse nontoxic goiter
- Diagnosis with solitary or dominant thyroid nodule
- Clear confirmation with clinical thyroid malignancy
- Obtain material for specific laboratory examinations that lead to an overview of prognostic parameters

gold standardIn determining the nature and type of thyroid nodule is histopathological examination of postoperative tissue preparations. (Kumar V et al., 2018)

Fine needle aspiration biopsy (FNAB) has an important role in the evaluation of euthyroid patients with thyroid nodules. This reduces unnecessary thyroid surgery for patients with benign nodules and correct diagnosis of thyroid cancer patients before surgery. Before routine use of FNAB, the percentage of surgically removed malignant thyroid nodules was only 14% whereas now that FNA is routinely used, the percentage of resected malignant nodules is about 50%. (Kocjan et al., 2009)

2.7 Thyroid nodule management

2.7.1 Suppression therapy with I-thyroxine

Suppression therapy with thyroid hormone (levothyroxine) is the most common and easy option. Suppression of TSH in postoperative thyroid carcinoma is considered due to the presence of TSH receptors on thyroid carcinoma cells, so that if not suppressed, TSH can stimulate the growth of remaining malignant cells. (Player TG et al., 2016)

2.7.2 Percutaneous ethanol injection (percutaneous ethanol injection)

Ethanol injection in thyroid tissue will cause cellular dehydration, protein denaturation and coagulative necrosis of thyroid tissue and hemorrhagic infarction due to vascular thrombosis; There will also be a decrease in enzyme activity in viable cells surrounding the necrotic tissue. (Player TG et al., 2016)

2.7.3 Radioactive iodine therapy (i-131)

Radioactive iodine (I-131) therapy is performed on autonomic thyroid nodules or hot (functional) nodules, both euthyroid and hyperthyroid. (Pemayun TG et al., 2016)

2.7.4 Surgery

Through surgery, decompression of vital tissue around the nodule can be carried out, in addition to obtaining specimens for pathological examination. Hemithyroidectomy can be performed on benign nodules, whereas the extent of thyroidectomy to be performed on malignant nodules depends on the type of histology and the level of prognostic risk.

Total thyroidectomy, when possible to remove as much of the tumor and healthy thyroid tissue as possible, is the initial procedure in most patients with differentiated thyroid carcinoma. If regional lymph node (KGB) metastases are found, proceed with radical neck dissection.

Some of the considerations and advantages of choosing this surgical procedure are as follows: (Pemayun TG et al., 2016)

- Papillary carcinoma foci are found in both thyroid lobes in 60-85% of patients

- After unilateral surgery (lobectomy), 5-10% of papillary thyroid carcinoma recurrences occur in the contralateral lobe
- The effectiveness of radioactive iodine ablation therapy becomes higher
- The specificity of triglobulin examination as a marker of recurrence is higher after the reaction of the tumor and thyroid tissue as much as possible.

2.7.5 Radioactive iodine ablation therapy

In healthy and malignant thyroid tissue left after surgery, radioactive iodine 131-I ablation therapy was then given. Doses of 131-I ranging from 80 mCi are recommended to be given in these circumstances, given the specific uptake of iodine into follicular cells, including thyroid malignant cells derived from follicular cells. There are 3 reasons for ablation of residual tissue after surgery, namely:

a) Damage or kill residual carcinoma micro foci
b) Increases the specificity of 131-I scintigraphy for detecting recurrence or metastasis through elimination of uptake by residual normal thyroid tissue.
c) Increase the value of triglobulin as a marker of serum produced only by thyroid cells

Radioactive iodine ablation therapy is generally not recommended in patients with solitary primary tumors less than 1 cm in diameter, unless extrathyroidal invasion or metastasis is found. (Player TG et al., 2016)

2.8 Tumor microenvironment

The tumor microenvironment consists of proliferating tumor cells and several non-cancerous cells (commonly referred to as stroma) present within the tumor, including fibroblasts, myofibroblasts, immune cells, inflammatory cells, adipocytes, endothelial cells, and extracellular matrix components. matrix (ECM). The tumor microenvironment provides the nutritional and metabolic requirements for tumors to grow, as well as extracellular signaling molecules to stimulate and direct metastasis(Mittal et al., 2018; The American Cancer Society, 2018).

This environment is constantly changing as the tumor develops, and can differ between types of thyroid cancer. Stromal cells influence the behavior of epithelial cells by secreting various ECM proteins, chemokines, cytokines, and growth factors, leading to activation of autocrine and paracrine circles. The interactions between tumor cells, stroma, and genetic defects in tumor cells determine the characteristics, morphology, and extent of tumor invasion.

The immune system is known to play an important role in the thyroid cancer response. Cancer-associated inflammatory response helps cancer cell proliferation and survival, angiogenesis, thyroid cancer metastasis. The severe inflammatory response causes the adaptive immune response to weaken, resulting in an imbalance in the immune response and cancer, resulting in cancer development and decreased overall survival. Immune cells have a very large contribution, because they provide growth factors, such as EGF, TGF-ß, TNF-α, and are a source of proteases (metalloproteases, serine proteases, cysteine proteases, etc.) thereby promoting tumor growth, invasion, and metastasis.

Inflammatory cells and their production, namely chemokines and cytokines can trigger cancer growth. A high platelet count is associated with more advanced stages and a poorer prognosis. Platelets promote tumor growth by increasing metalloproteinase-9 secretion, as well as angiogenesis. Malignancy also increases platelet count by producing pro-inflammatory mediators such as interleukin (IL)-1, IL-13, and IL-16 that stimulate platelet progenitors to proliferate.

Peripheral immunity/inflammation indicators such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelet mean volume, and white blood cell-to-lymphocyte ratio have been studied for their correlation with pCR. Low parameter values indicate a systemic background of decreased inflammation and activation of the immune system.

2.9 The immune system in thyroid cancer

2.9.1 Immune system aging

The incidence of most cancers increases with age. This may be associated with a decrease in immune function called immune senescence. There is a decrease in the amount of lymphoid tissue and its function(Foster et al., 2011; Valiathan et al., 2016). There are three changes in T cell function that occur in the aging immune system (Figure 5). The first is a decrease in the number and proportion of naive T cells, due to a decrease in thymic output. The second is an increase in the proportion of memory

T cells. These cells are still capable of a proliferative response, but there is a defect in normal function. The third is the accumulation of terminally differentiated T cells that are dysfunctional and have a very limited diversity of T-cell receptor (TCR) repertoire.(Foster et al., 2011). Absolute lymphocyte counts are higher in younger healthy individuals, and their numbers decrease significantly with age(Valiathan et al., 2016).

Aging of the immune system causes a decrease in immune function and its capacity to carry out immunosurveillance which plays a role in detecting and eradicating tumors.(Foster et al., 2011; Valiathan et al., 2016).

Tumor suppression by the immune system results from the production of IFN-γ and the perforin pathway used by cytotoxic T cells and natural killer cells (NK-cells). CD4+ T cells play a role in the recognition of tumor-associated antigens through antigen presenting cells (APCs) to naive CD8+ T cells. CD8+ T cells require the help of CD4+ T cells for activation and perform cytotoxic functions(Foster et al., 2011).

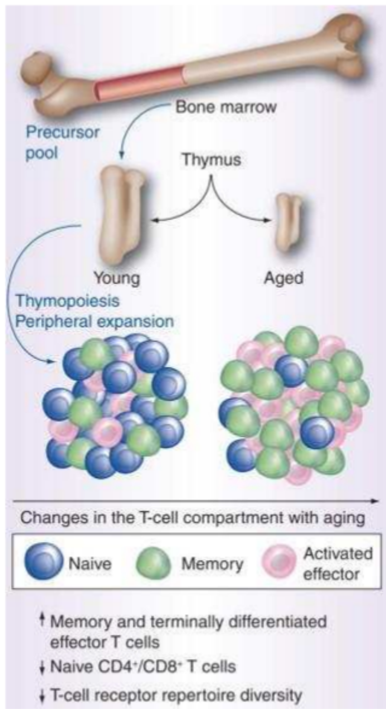

Figure 5. Aging of the immune system that occurs in the population of T . cells(Foster et al., 2011)

2.9.2 Neutrophils in thyroid cancer

Neutrophils are white blood cells of myeloid precursors, are the most abundant type of leukocyte in the bloodstream, and are responsible for the elimination of microorganisms in the host. In patients with advanced cancer, neutrophilia is found. Various cytokines such as granulocyte colony-stimulating factor (G-CSF), IL-1, IL-6 produced by tumors contribute to the development of neutrophilia.(Uribe-Querol & Rosales, 2015)

Tumor-associated neutrophils (TANs)play an important role in malignancy. Neutrophils can promote or inhibit tumor growth, depending on the relative concentration of cytokines in the tumor microenvironment(Mittal et al., 2018). The tumor microenvironment regulates neutrophil recruitment, and in return, TANs promote tumor growth. TANs differ from circulating neutrophils, and may exhibit a pro-tumorigenic phenotype, which is associated with genotoxicity, angiogenesis, and immune suppression.(Polyak et al., 2009; Uribe-Querol & Rosales, 2015). On the other hand, primary tumors can activate specific neutrophils, namely tumor entrained neutrophils (TENs) that can inhibit the process of metastasis in murine lungs.(Grand et al., 2011). TANs in early-stage tumors are mostly found in the periphery of the tumor, are more cytotoxic to tumor cells and produce more TNF-, NO, and H2O2. In contrast, TANs in advanced tumors exhibit a more pro-tumorigenic phenotype. This suggests that neutrophils entering the tumor become more pro-tumor as the tumor progresses(Uribe-Querol & Rosales, 2015).

Tumor cells produce many chemokines, such as CXCL1 (KC), CXCL2 (MIP-2), CXCL5 (ENA-78), CXCL6 (GCP-2), CXCL8 (IL-8), and MIF which is a neutrophil chemoattractant, so that neutrophils are released. from the circulation to the tumor. TANs also produce CCL17 which is a Treg cell chemoattractant. Treg cells produce IL-8, which is a potent neutrophil chemoattractant, resulting in more neutrophil infiltration into the tumor (Figure 6).(Uribe-Querol & Rosales, 2015).

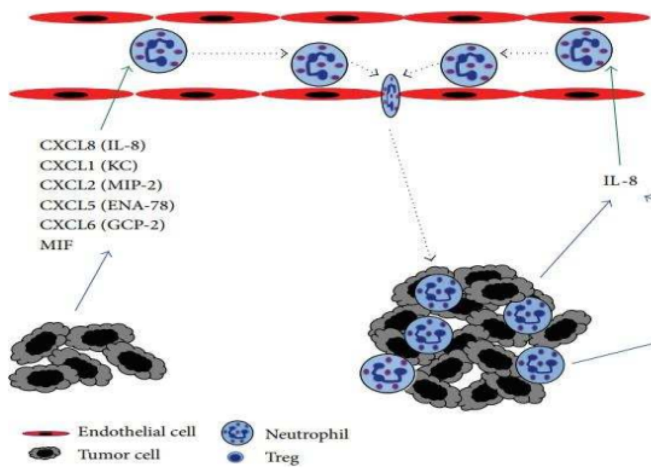

Figure 6. Neutrophil infiltration in tumor cells(Uribe-Querol & Rosales, 2015)

Neutrophils inhibit the immune system and support tumor growth by suppressing lymphocyte activity and T cell responses. Neutrophils are potent suppressors of T-cell activation, decrease natural killer (NK cell) cell function, thereby increasing intraluminal tumor cell survival and facilitating metastasis.(Spiegel et al., 2017). Neutrophils are associated with cancer-associated inflammation due to potential mechanisms in response to ectopic IL-8 released during tumor proliferation, progression, and metastasis. Tumor-associated cytokines such as IL-6 and tumor necrosis factor (TNF)-α contribute to neutrophilia in solid cancers. Neutrophils inhibit the cytotoxic activity of immune cells such as NK cells and T cells that act as antitumor(Guo et al., 2019).

TANs play a role in tumor growth in several ways (Figure 7). TANs secrete matrix metalloproteinase (MMP)-9 which secretes vascular endothelial growth factor (VEGF) from the ECM to trigger angiogenesis. TANs also secrete cytokines (IL-1ß, TNF-, IL-6, and IL-12) that induce chronic inflammatory conditions, arginase 1 which inhibits CD8+ T cells, resulting in an immunosuppressive condition, and ROS which can damage DNA, triggering an immune response. genotoxic effects on tumor cells. Elastase and cathepsin G, serine proteases from neutrophil granules have the effect of aggregation and proliferation of tumor cells. Neutrophils are stimulated by thyroid cancer cells to produce oncostatin M, which stimulates cancer cells to secrete VEGF and trigger angiogenesis, as well as increase the attachment and invasive capacity of cancer cells.(Uribe-Querol & Rosales, 2015).

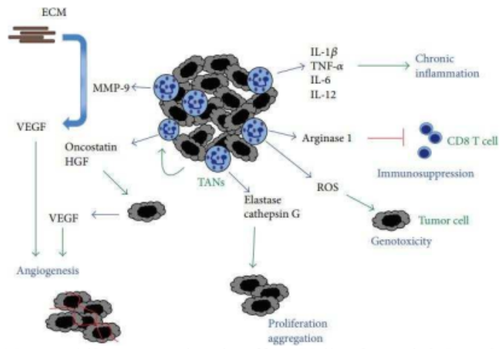

Figure 7. Neutrophil protumorigenic effect(Uribe-Querol & Rosales, 2015)

Neutrophil elastase (NE) is released during cell degranulation. The main function of NE is the elimination of invasive microorganisms. NE also affects tumor proliferation, and is associated with phatidylinositol 3-kinase (PI-3K). NE enters cells, and acts on insulin receptor substrate-1 (IRS-1), which binds to the PI-3K regulatory unit. Degradation by NE increases available PI-3K to enhance the proliferative pathway(Uribe-Querol & Rosales, 2015).

In thyroid cancer, cathepsin G degrades ECM molecules such as fibronectin and weakens the bond between integrins and fibronectin, resulting in E-cadherin-mediated cell adhesion, and is resistant to proteases. The formation of tumor cell aggregates allows tumor cells to disseminate through the circulation and form new metastases. Cathepsin G also enhances signaling and upregulates VEGF to trigger angiogenesis(Uribe-Querol & Rosales, 2015).

Arginase 1 is released from neutrophil granules, and is activated to degrade extracellular arginine, which is an essential amino acid for T cell activation. Thus, neutrophil degranulation can cause an immunosuppressive effect on tumors.

Neutrophils also enhance migration of human thyroid cancer cells MDA-MB-468 via intercellular adhesion molecule-1. Neutrophils suppress CD8+ T lymphocytes and promote metastasis through immunosuppressive mechanisms, and play an important role in the initiation of metastasis by triggering the production of leukotrienes that help colonize tumor cells in other tissues.(Uribe-Querol & Rosales, 2015).

Although neutrophils play a large role in tumor growth, there are also positive effects of neutrophils in carcinogenesis and have antitumor activity. Neutrophils produce ROS and hypochloric acid (HOCl) which can directly damage tumor cells. Neutrophils can also trigger the apoptosis of certain tumor cells either by direct contact or by releasing tumor necrosis factor-related apoptosis inducing ligand/TRAIL. The most effective antitumor mechanism is antibody-dependent cell-mediated cytotoxicity (ADCC). Antibody molecules that bind to tumor antigens are recognized by Fc receptors. This binding activates a cytotoxic response in tumor cells. Neutrophils can be activated to secrete a more potent antitumor phenotype by granulocyte colony-stimulating factor (G-CSF), tumor necrosis factor-α (TNF-α), or inhibit transforming growth factor-ß (TGF-ß). Neutrophils can activate CD8+ cytotoxic T cells, as well as inhibit IL-8, thereby preventing further neutrophil infiltration into the tumor (Figure 8)(Uribe-Querol & Rosales, 2015).

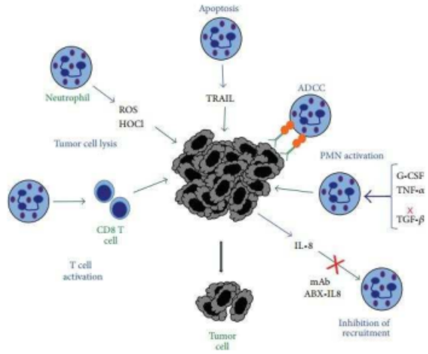

Figure 8. Neutrophil antitumorigenic effect(Uribe-Querol & Rosales, 2015)

2.9.3 Lymphocytes in thyroid cancer

Tumor infiltrating lymphocytes (TILs)is the most common mononuclear infiltrate in the majority of patients with thyroid cancer. A high TIL value is associated with clinical improvement and is associated with a better response to therapy.

1 CD4+ T-helper cells enhance antigen presentation through cytokine secretion and activation of antigen presenting cells (APCs). CD8+ cytotoxic cells play an important role in tumor destruction. (Chi-Yu K., 2017)

Other tumor-infiltrating cell subtypes, such as regulatory T lymphocytes (Treg), and myeloid derived-suppressor cells (MDSC) cause immune suppression in thyroid cancer. Increased Tregs in thyroid cancer is associated with a more invasive phenotype and poorer overall survival. Tregs in the tumor microenvironment restraineffective antitumor response. (Imam et al., 2014)

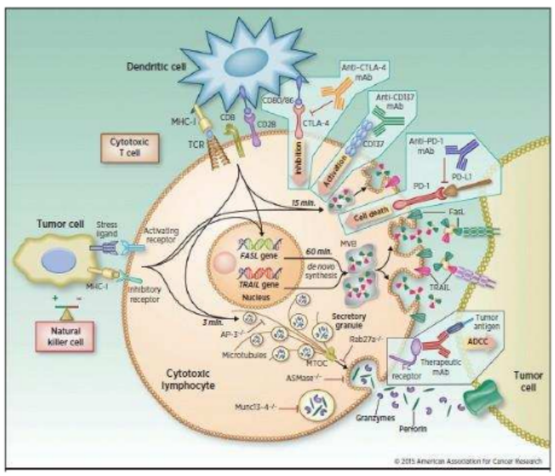

Figure 9. Antitumorigenic effectlymphocytes (Lostao LM, Anel A, Pardo J. 2015)

2.9.4 The ratio of neutrophils to lymphocytes in thyroid cancer

Inflammation-related markers such as leukocyte count, C-reactive protein (CRP), cytokines, platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) are associated with outcomes in cancer patients. NLR is an inflammatory marker that is widely available, easy, and inexpensive to perform(Chae et al., 2018).

The number of neutrophils and lymphocytes can change due to several physiological and pathological processes, but the NLR value can predict the prognosis of thyroid cancer better than the value of neutrophils, lymphocytes, or total leukocytes.(Yamazaki et. al., 2020).

To date, studies examining NLR in well-differentiated thyroid cancer have used a variety of statistical methodologies and most have varied sample sizes (41–3364 PTC cases), resulting in non-uniform results. In general, higher NLR values are associated with larger tumor size, multifocality, lymph node metastases, and higher TNM stages, indicating more aggressive tumor behavior and more advanced disease stage. In one study, high NLR was associated with a poor tumor profile, in terms of extrathyroidal invasion, multifocality, bilateral, and lymph node metastases. (Chae et al., 2018)

A comprehensive meta-analysis, investigating the association of NLR with patient prognosis in a variety of neoplasms (gastrointestinal, gynecological, urological, and pulmonary; head and neck, brain, and breast), did find a median NLR of up to . ratios above the cutoff correlated with poor outcomes and poorer prognosis, in terms of overall survival (median NLR cutoff 4, range 1.9–7.2), cancer-specific survival (median NLR limit 3.85, range 1.9 -5.0), progression free survival (median NLR cutoff 3, range 2.0-5.0), and disease free survival (median NLR cutoff 5.0, range 2.0-7.7). Manatakis et al found a significant difference in PTC lymph node metastases when they set the threshold NLR level as 2.44. Koçer et al in their study compared benign and malignant thyroid nodules and the NLR cut off value was suggested as 1, 91. What is interesting in this study is that the NLR values of differentiated thyroid cancers are relatively low compared to other solid tumors. (Feng et al., 2018)

However, NLR remains largely a nonspecific biomarker of systemic inflammation. Although promising in terms of sensitivity, NLR values could be increased and biased towards all patients with medical conditions affecting the differential white blood cell count (acute infection, allergic reaction, cardiovascular incidence, etc.). This parameter also has some disadvantages, namely that the value can change due to other conditions that increase the number of neutrophils and platelets, such as inflammatory conditions, connective tissue disorders, administration of certain drugs, viral or bacterial infections. Lymphocytopenia can occur due to infection, malnutrition, connective tissue disorders, severe stress, and strenuous physical exercise. However, NLR is readily available from routine blood tests and does not increase the cost of preoperative diagnostics.

The mechanisms linking high NLR values and poor prognosis in thyroid cancer are still not clearly understood. There are several possibilities put forward. First, lymphocytes can decrease tumor progression due to tumor infiltration by a series of lymphocyte subtypes, CD3+ T cells, CD8+, Th1 CD4+, and NK cells, which have shown improved survival in cancer patients. Second, T cells that produce IL-17 can secrete CXC chemokines, such as CCL2 which can recruit neutrophils, resulting in an increase in NLR.(Feng et al., 2020).

3. Conceptual Framework and Hypothesis

3.1 Conceptual framework explanation

Thyroid nodules are lesions within the thyroid gland that are radiologically distinct from the surrounding thyroid parenchyma. Malignant status in thyroid nodules can be categorized into benign (follicular adenoma, papillary adenoma, thyroid cyst, adenomatous goiter) and malignant (papillary thyroid cancer, follicular thyroid cancer, Hurthle cell cancer (oncocytic), anaplastic thyroid cancer, medullary thyroid cancer, lymphoma thyroid with or without metastases).

Neutrophils act as markers of inflammation in malignant states. Neutrophils act in several ways to support tumor growth and metastasis: 1) Neutrophil's ability to produce and release growth factors such as PDGF, VEGF, TGF-β, and PF4 which have a role in tumor angiogenesis and tumor growth. 2) the ability of Neutrophils to stabilize the attachment of tumor cells to the endothelium and help the migration of tumor cells through the endothelium out of the vasculature. 3) Neutrophils also support the migration of inflammatory cells to the interstitial space thus supporting the growth of the tumor stroma. 4) Neutrophil ability to inhibit the body's immune system to eliminate tumor cells. On the other hand, lymphocytes have an immune role against tumor cells, in two ways: 1) Lymphocytes play a direct role in the cytotoxic process through the activation of Cytotoxic CD8+ T cells (CTL), natural killer (NK), and NK T cells destroying tumor cells. 2) Lymphocytes play a role in supporting the apoptotic process of the tumor cells themselves. Thus, the higher the neutrophils, it is estimated that tumor growth and metastasis will increase, while the higher the lymphocytes, the less tumor growth and metastasis.

3.2 Research hypothesis

There is a relationship between the ratio of neutrophils to lymphocytes in the blood and the malignant status of thyroid nodules, where the higher the ratio of neutrophils to lymphocytes, the more malignant the nodule's malignancy status is.

4. Research Methods

4.1 Research design

This study is a descriptive study using a retrospective research design.

4.2 Research population

The research population is all patient medical recordswith thyroid nodules undergoing surgerythyroid in the Department of Surgery, RSUD dr. Soetomo Surabaya.

4.3 Affordable population

The affordable population in this study were all patient medical recordswith thyroid nodules undergoing surgerythyroid in the Department of Surgery, RSUD dr. Soetomo Surabaya between January 2018 - December 2020.

4.4 Research sample

4.4.1 Sample size

The minimum sample size is determined according to calculations based on the Lemeshow formula in a retrospective studycross sectionalas follows:

$$n = \frac{Z_{\alpha}^{2}\ p\ q}{d^{2}} = \frac{Z^{2}\ p\ (1\text{-}p)}{d^{2}}$$

(Snedecor GW & Cochran WG, 1967)
(Lemeshowb dkk, 1997)

n = Minimum number of samples required

Z2α= The value of the standard normal distribution of table Z at an error rate of 10% is 1.96

p = Proportion of occurrence of malignant thyroid nodules in patients with high neutrophil to lymphocyte ratio {73%}

q = 1-p (Proportion of benign thyroid nodules in patients with low neutrophil to lymphocyte ratio) {37.5%}

d2 = Limit of error or absolute precision is set to 0.01

From this calculation, the minimum sample size required is 102 samples.

4.4.2 Sampling

Sample takenconsecutively sampling based oninclusion and exclusion criteria ofJanuary 2018 to December 2020.

4.5 Inclusion and exclusion criteria

4.5.1 Inclusion criteria

1. Medical records of patients with thyroid nodules who underwent thyroid surgery from January 2018 to December 2020

4.5.2 Exclusion criteria

1. Medical record data shows that the patient had undergone surgery to remove the thyroid gland and had a tumor other than the thyroid.
2. Medical record data shows that the patient suffers from an autoimmune disease,
3. Medical record data shows that the patient suffers from concomitant infectious diseases, both acute and chronic.
4. Medical record data shows that the patient suffers from hematological disorders,
5. Medical record data shows the patient is undergoing steroid treatment, chemotherapy, or radiotherapy.

4.6 Research variable
4.6.1 Independent variablet: Patients with Thyroid Nodules
4.6.2 dependent variable: Ratio of neutrophils to lymphocytes from the results of laboratory peripheral blood examination

4.7 Operational definition
4.7.1 The value of the ratio of neutrophils to lymphocytes
The value of the ratio of neutrophils to lymphocytes is the number of neutrophils divided by the number of lymphocytes in units of . The value of the low ratio of neutrophils to lymphocytes is the ratio value <1.91. The value of the high ratio of neutrophils to lymphocytes is the ratio value of 1.92(Kocer et al., 2015). Measurement method using electronic (automatic) method with Dimensional Chemistry System, brand Siemens, made in USA in 2011 at the Clinical Pathology Installation of RSUD dr SOetomo Surabaya. The measurement scale is ordinal.

4.7.2 Thyroid nodule malignancy status
Malignant status of thyroid nodules is a classification of thyroid nodule differentiation from histopathological aspects examined from thyroid surgery preparations which are generally grouped into benign and malignant nodules.

4.7.3 Tumor histopathology
Tumor histopathology is a description of the histological type of thyroid tumor cells. Divided into 4 types namelypapillary, follicular, medullary and anaplastic types

4.7.4 Age
Age is a person's age calculated from the date of birth listed on the identity card (KTP).

4.7.5 Autoimmune disease
Autoimmune disease is a disease or disorder that occurs when healthy tissues or organs are damaged by the body's own immune system.

4.7.6 Concomitant infectious disease
Concomitant infectious diseases are infectious diseases that accompany patients with thyroid nodules before thyroid surgery, both acute and chronic.

4.8 Research ethics
The data obtained from medical records were guaranteed to be confidential by the researcher with the approval of the ethics committee.

4.9 Research procedure
4.9.1 Data collection
Medical record data of patients with thyroid nodules who had undergone thyroid surgery and met the inclusion and exclusion criteria of the study were collected. Furthermore, general data from the subject's medical records such as name, age, gender, address, and telephone number and the results of a complete blood count, as well as the results of anatomical pathology examinations from the surgical preparations were recorded. Data recording according to the data collection form.

4.9.2 Data analysis
Data management is carried out using the SPSS 25.0 program. Data analysis was done descriptively.

4.9.3 Data presentation
The data is presented in tabular form accompanied by a descriptive explanation.

4.9.4 Data reporting
The research results are presented in the form of a research report.

5. Research result
5.1 Description of Research Data

This type of research is descriptive using a research designretrospective.Researchers want to see the picture ratio of neutrophils to lymphocytes in patients with thyroid nodules. Medical record data of patients with thyroid nodules with the results of anatomical pathology examinations either benign or non-malignant nodules who have undergone thyroid surgery at Dr. Hospital. Soetomo Surabaya from 2018 to 2020 who met the inclusion and exclusion criteria of the study were collected. From this study, 112 research subjects were collected who met the research inclusion criteria. The medical record data will then be traced to the results of preoperative complete blood tests in the form of neutrophils and lymphocytes. Then calculated the ratio of neutrophils to lymphocytes.

5.2 Characteristics of research subjects

5.2.1 Gender

Based on the research data, the number of research samples was 112 samples selected through consecutive sampling consisting of 26 men (23.2%) and 86 (76.8%) women.

Table 5.1 – Gender of Research Subjects

Characteristics of Research Subjects		Amount	Total
Gender	Man	26 (23.2%)	112 (100%)
	Woman	86 (76.8%)	

5.2.2 Age

Research subjects have an age range starting from the lowest age of 18 years and the highest age of 81 years with the average age in this study was 50.54 ± 13.803 years. The age of the research subjects were grouped into 4 groups, most of which were high risk women (≤ 50 years) totaling 51 (45.5%) people, followed by low risk women (> 50 years) as many as 35 (31.1%) people, high risk men (> 40 years) as many as 19 (17.0%) people, and low risk men (≤ 40 years) as many as 7 (6.3%) people.

Table 5.2 – Age of Research Subjects

Characteristics of Research Subjects		Amount	Total	Min	Max	mean	Std, Deviation
Age	Low Risk Women (≤50 years)	35 (31.1%)	112 (100%)	18	81	50.54	13,803
	High Risk Female (> 50 years old)	51 (45.5%)					
	Low Risk Male (≤40 years)	7 (6.3%)					
	High Risk Male (> 40 years old)	19 (17.0%)					

5.2.3 Neutrophil Count

Based on research data from 113 people, the number of neutrophils was obtained with the lowest value being 1.81 x 103 cells/μl and the highest being 13.63 x 103 cells/μl with the average number of neutrophils being 5.14 ± 2.184 x 103 cells/μl.

Table 5.3 – Research Subject Neutrophils

	N	Minimum	Maximum	mean	Std. Deviation
Neutrophil	112	1.81	13.63	5.14	2,184

5.2.4 Lymphocyte Count

Based on research data from 112 people, the number of lymphocytes with the lowest value was 0.99 x 103 cells/μl and the highest was 4.00 x 103 cells/μl with an average lymphocyte count of 2.22 ± 0.6221 x 103 cells/ l.

Table 5.4 – Research Subject Lymphocytes

	N	Minimum	Maximum	mean	Std. Deviation
Lymphocytes	112	0.99	4.00	2.22	0.6221

5.2.5 Neutophil to Lymphocyte Ratio

The value of the Neutrophil to Lymphocyte Ratio (NLR) is the neutrophil type count divided by the lymphocyte count which is divided into two categories with a cut-off of 1.91, namely low with a

Characteristics of Research Subjects	Thyroid Nodule Status	Anatomical Pathology Results (%)	Amount (%)	Total (%)
Anatomical Pathology Results	Benign	Adenomatous Goiter 51 (45%)	56 (50%)	112 (100%)
		Follicular Adenoma 5 (4.5)		
	Malignant	Papillary Thyroid Carcinoma 47 (42%)	56 (50%)	
		Follicular Thyroid Carcinoma 7 (6.3%)		
		Anaplastic Thyroid Carcinoma 2 (1.8%)		

value of < 1.91 and high with a value of 1.92.

The research subjects had the lowest neutrophil to lymphocyte ratio value of 0.84 and the highest was 9.60 with the average value of the neutrophil to lymphocyte ratio in this study was 2.57 ± 1.728. Based on research data from 112 patients, it was found that the study subjects had a low neutrophil to lymphocyte ratio (NLR) of 39 (34.8%) and 73 (65.2%) of high.

Table 5.5 – Neutrophil/Lymphocyte Ratio of Research Subjects

Characteristics of Research Subjects		Amount	Total (N)	Min	Max	mean	Std. Deviation
Neutrophil Ratio/ Lymphocytes	Low	39 (34.8%)	112 (100%)	0.84	9.60	2.57	1,728
	Tall	73 (65.2%)					

5.2.6 PA results

Table 5.6 – Anatomical Pathology Results of Research Subjects

Based on the results of postoperative anatomical pathology, thyroid nodules were grouped into 2 groups, namely benign and malignant groups with the same number of 56 (50%) people in each group according to the calculation formula for the study sample with a total of 112 people where most of the results of anatomic pathology Adenomatous goiter in 51 (45%) people, followed by Papillary thyroid carcinoma in 47 (42%) people, Follicular thyroid carcinoma in 7 (6.3%), Follicular adenooma in 5 (4.5%), and Anaplastic thyroid carcinoma as many as 2 (1.8%) people.

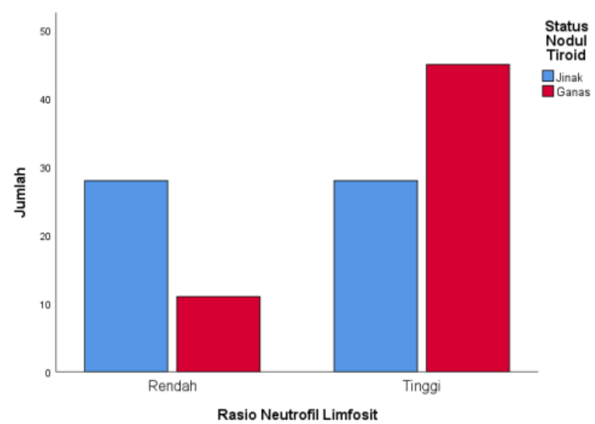

Figure 5.1 Bar chart of Neutrophil-Lymphocyte ratio values by type of thyroid nodule malignancy

5.2.7 Description of the ratio of neutrophils to lymphocytes based on the malignancy status of thyroid nodules

In this study, the value of the ratio of neutrophils to lymphocytes (≥1.92) was 73 (65.2%) people consisting of 28 (25%) people with benign thyroid nodule status and 45 (40.18%) people with benign thyroid nodule status. malignant thyroid nodules, while the neutrophil to lymphocyte ratio was low (<1.91) as many as 39 (34.8%) people consisting of 28 (25%) people with benign thyroid nodule status and 11 (9.82%) people with malignant thyroid nodule status.according to Table 5.7.

Table 5.7 -Description of Neutrophil to Lymphocyte Ratio Value based on Thyroid Nodule Malignancy Status

Characteristics of Research Subjects		**PA Post Operation**		**Total**
		Benign (%)	**Malignant (%)**	
Neutrophil Ratio/ Lymphocytes	**Low (< 1.91)**	28 (25%)	11 (9.82%)	39 (34.8%)
	Height (≥ 1.92)	28 (25%)	45 (40.18%)	73 (65.2%)
Total		56 (50%)	56 (50%)	112 (100%)

6. Discussion

Thyroid nodules are a common occurrence in humans. Findings of nodules in adults are about 4-8% by palpation method, about 10-41% by finding on ultrasound examination and about 50% by pathological examination or at autopsy. Enlargement of the thyroid gland (nodule) can be an inflammatory disorder, hyperplasia or neoplasm, which is clinically difficult to distinguish. Malignancies of the thyroid gland are relatively rare and account for only 1.5% of all malignancies throughout the body, but constitute 90% of malignancies that arise in endocrine organs. This research was conducted at the Department of Surgery, RSUD dr. Soetomo Surabaya examined the description of the ratio of neutrophils to lymphocytes (NLR) in thyroid nodule patients in the range of 2018 to 2020. Based on the calculation of the number of samples for the studyretrospectivecross sectionalobtained a minimum of 112 samples which were divided into 2 groups, namely benign and malignant thyroid nodules. In this study, the sample of each group was 56 so that the total sample was 112.

In this study, based on the gender distribution of the sample, it was found that most of the respondents were women as many as 86 (76.8%) people and men as many as 26 (23.2%) people. This is in accordance with the literature which states that malignant thyroid nodules are 2.9 times more common in women than men (Rahbari et al., 2010).

The AMES classification divides patients into two categories: low-risk and high-risk. Low risk age is patient with age 40 years in male gender and 50 years in female gender while high risk is patient with age > 40 years in male gender and > 50 years in female gender. In this study, the highest sample was in the category of high risk women 51 (45.5%) people and at least men with low risk 7 (6.3%) people with the lowest age of 18 years and the highest age of 81 years (mean age 50 years).). This is consistent with the literature which states that the incidence of malignant thyroid nodules generally increases with age.

In this study, the value of the neutrophil to lymphocyte ratio was mostly high (≥1.92), namely 73 (65.2%) people consisting of 28 (25%) people with benign thyroid nodule status and 45 (40.18%) people with malignant thyroid nodule status, while the neutrophil to lymphocyte ratio was low (<1.91) as many as 39 (34.8%) people consisting of 28 (25%) people with benign thyroid nodule status and 11 (9.82%)) people with malignant thyroid nodule status. The neutrophil to lymphocyte ratio (NLR) of 1.92 has been agreed to be the cut-off point based on previous studies which are divided into two categories: high (≥1.92) and low (<1.91) NLR(Kocer et al., 2015).

In a study by Kocer et al. It was concluded that the NLR value could be a potential marker in differentiating benign and malignant thyroid nodules. In his study, 232 samples were divided into the multinodular goiter group (n=70), the thyroiditis group (n=97) and the papillary thyroid cancer group (n=65). NLR ranges in the multinodular goiter group (1.74 ± 0.53), thyroiditis group (2.05 ± 0.57) and papillary thyroid cancer group (2.57 ± 0.60). Statistically, the NLR value had a significant difference (p=0.001) in the thyroiditis group and the papillary thyroid cancer group against the multinodular goiter group. Kocer et al. also suggested using the NLR cut-off value of 1.91 which statistically had a sensitivity of 89%, specificity 54.5%, Positive Predictive Value (PPV) 41%,

Seretis et al. also found high NLR values (>2.5) in papillary thyroid microcarcinomas (PTMC). Seretis et al. In his study, 26 patients used benign goiter samples, and 31 patients with Papillary thyroid microcarcinomas (PTMC). The NLR values in benign goiter and PTMC had a statistically significant difference (p=0.001).

In the study of Ceilan et al. concluded that high NLR correlated with tumor size and extrathyroidal extension. NLR can be used as a marker to confirm patients with papillary thyroid carcinoma (PTC). Ceilan et al. collected 201 samples of papillary thyroid carcinoma patients with a mean NLR value of 2.11 ± 0.94 which were then divided into two groups using an NLR cut-off value of 1.92. Patients with NLR <1.91 totaled 100 samples and NLR>1.92 totaled 101 samples. There was a statistically significant difference between the two groups in tumor size (p=0.002) and extra thyroid extension (p=0.028).

Research by Ari et al. studied NLR and PLR in patients with thyroiditis and papillary thyroid cancer compared with a healthy population. The results were significantly higher NLR in thyroiditis patients (mean NLR 2.4±1,4) compared to the healthy population (1.89±0.7), while the PLR was higher in both the papillary thyroid cancer and thyroiditis groups with a mean PLR value of 136.7 respectively.±57 and 139.1±52 compared to the healthy population (107± 22.3). There was no significant difference between the thyroiditis and papillary thyroid cancer groups. Ari et al.'s research results. This concludes that NLR and PLR are strong parameters in both thyroiditis and papillary thyroid cancer, but NLR is superior in diagnosing thyroiditis.

High NLR may result from neutrophilia and/or lymphopenia. Neutrophils play an important role in the process of malignant transformation and metastasis. The role of neutrophils here is to support tumor growth and metastasis, due to the ability of neutrophils to produce and release growth factors such as vascular endothelial growth factor (VEGF) which together with other growth factors trigger angiogenesis and vascularization resulting in an increase in tumor growth rate. Neutrophils also stabilize the attachment of tumor cells to the endothelium and aid in the migration of tumor cells out of the vasculature.In this case, neutrophils act as pro-tumors. While the importance of lymphocytes is emphasized in tumors with a high density of lymphocyte infiltration, they tend to have a better prognosis.Cytotoxic CD8+ T cells (CTL), natural killer (NK), and T NK cells (NKT cells) have important roles in the prevention of tumor growth because of their cytotoxic function and ability to induce apoptosis in destroying cancer cells.In this case, lymphocytes act as anti-tumor.The use of NLR should not be considered as a determining factor but only provides an option in strengthening the diagnosis because histopathology is the gold standard in diagnosis. An elevated NLR indicates an inability of the immune system to respond to a tumor or is a marker of an imbalanced inflammatory response in the growth of a tumor (Liu et al., 2013).

The limitations of this study are related to the retrospective study design. The intrinsic variability of the blood test values should be assessed. When compared to neutrophil counts, NLRs have been found to have superior stability under various physiological conditions and during in vitro handling of blood samples. However, the NLR assessment can have some variability. This variability can be adjusted by conducting large-scale studies or repeated examinations of individual research subjects. To overcome these limitations, further studies with prospective and controlled designs are needed in large numbers.

7. Conclusions And Suggestions

7.1. Conclusion

From the results of the study, the description of the neutrophil-lymphocyte ratio in patients with thyroid nodules in hospitals. Dr. Soetomo period of the year. 2018-2020 got:

1. In all patients with thyroid nodules, there were 34.8% cases with low neutrophil to lymphocyte ratio (NLR) <1.91 and 65.2% with high NLR values.1.92.
2. Low NLR values <1.91 were found in 25% of patients with benign thyroid nodules and 9.82% of patients with malignant thyroid nodules. High NLR value1.92 was found in 25%

of patients with benign thyroid nodules and 40.18% of patients with malignant thyroid nodules

7.2. Suggestion

1. Further research is needed to see the picture of NLR with a larger sample to examine more specifically for each type of thyroid nodule.
2. Further studies are needed to see a significant difference in NLR values based on the type of thyroid nodule.
3. Further research is needed to see the correlation of NLR values based on the type of thyroid nodule.

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