University of Latvia

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Diploma Work

Analyzing thyroid nodules by Thyroid Imaging Reporting and Data System (TIRADS) and comparison with Bethesda system

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TABLE OF CONTENT

LIST OF ABBREVIATION

ATC	Anaplastic thyroid cancer
AUS	Atypia of underdetermined significance
Cervical LN	Cervical lymph node/s
CT	Computed tomography
DIT	Diiodotyrosine
FLUS	Follicular lesions of underdetermines significance
FNA	Fine needle cytology
FNAB	Fine needle aspiration biopsy
FTC	Follicular thyroid cancer
LN	Lymph node
LN in neck region	Lymph node/s in neck region
MTH	Medullary thyroid cancer
MEN 2A	Multiple endocrine neoplasia 2A
MEN 2B	Multiple endocrine neoplasia 2B
MIT	Monoiodotyrosine
mPTC	Micro- papillary thyroid carcinoma

MRI	Magnetic resonance imaging
PTC	Papillary thyroid cancer
T3	Triiodothyronine
T4	Thyroxine
TIRADS	Thyroid Imaging Reporting and Data System
US	Ultrasonography

ABSTRACT

Background

Thyroid Imaging Reporting and Data System (TIRADS) is a classification system that stratifies the risk of malignancy in a nodule. Each category is demonstrating the malignancy risk of a thyroid nodule. The usage of TIRADS has lead to better detection of thyroid gland nodules. TIRADS was established to improve management and the cost effectiveness by keeping away from using non needed Fine needle aspiration biopsy in patients that have thyroid nodules. FNA is widely used highly specific, sensitive and precise choice of method for diagnosis of thyroid gland lesion. decreases non needed surgeries for patients with non malignant nodules and gives the possibility to choose accordingly management possibilities to those patient with malignancies by describing the mode of atypia that has occurred. The Bethesda system for reporting thyroid cytopathologies consists of diagnostic categories, indicates malignancy risks and thereby gives appropriate estimations of treatment possibilities.

Objectives

The aim of this study was to analyze the TIRADS classification system for assessment of thyroid nodules by comparing occurrence in gender and age and to compare the different features that can be found. Thereafter, to compare the classification of TIRADS with Bethesda system for Reporting Thyroid Cytopathologies and histopathologies which is a more specific diagnostic method of choice.

Materials and Methods

This is a retrospective study were patient records in Latvia, Riga have been analyzed from May 2016 to February 2017 and thyroid nodule results have been compared. The Thyroid Imaging and Reporting and Data system (TIRADS) as a risk stratification system for classifying thyroid lesions was used to obtain information about the thyroid nodule pattern and risk of malignancy. The Bethesda system for reporting thyroid cytopathologies was used for comparison. IBM SPSS 21.0, Spearman’s rho test and Chi square test was used to analyse results.

Results

The study population included 298 patients. The youngest patient was 16 years old and the oldest 113 years old. The study data was randomly picked, 85.2 % were female and 14.8% were male. The mean age 58.6 (mean age for women 58.5, mean age for men 59.5), median age 59 (median age for women 59, median age for men 60.5), mode for age was 59 (59 for women and 52 for men).

Spearman's rho test for relationship between TIRADS and Betesda classifications shows weak positive correlation (r=0.182).

The largest subgroup of patients, 63.4% had TIRADS classification 3 (95%Cl: 57.8…68.7%) and smallest subgroup of patients 0.3% had TIRADS classification 1 (95%Cl: 0.1%...1.9%).

The largest subgroup of patients, 69.8% had Bethesda classification 2 (95%CI: 64.4%...74.7%) and smallest subgroup of patients 1.0% had Bethesda classification 4 (95%CI: 0.3%...2.9%).

Correlation between TIRADS and Bethesda by considering results as benign vs malignant by deliberating TIRADS classifications 3,4,5 and Bethesda 4,5,6, as positive (malignant) resulted in 100% sensitivity, 9% specificity and 81.4% false positive results.

Correlation between TIRADS and Bethesda by considering results as benign vs malignant by considering TIRADS classifications 4,5 and Bethesda 4,5,6 as positive results (malignant) resulted in 72.0% sensitivity, 78.3% sensitivity and 19.4% false positive results.

Correlation between TIRADS and Bethesda classifications by considering results as benign vs malignant by considering TIRADS 5 and Bethesda 6 as positive results (malignant) resulted in 20.0% sensitivity, 99.6% specificity and TIRADS would only produce 1 false positive result.

Males have more non-homogenous(p=0.045), marked hypoechogenous (p=0.046) and vascular (p=0.01) nodules in comparison with female.

Conclusion

TIRADS has in comparison with Bethesda system lower specificity but higher sensitivity. Many of TIRADS results didn't correlate with the conclusions received from Bethesda. There is a tendency that higher Betesda classifications are observed with higher Tirads classification. The potential reason can be the lack of Betesda 3 and 4 classifications in the studied data. Gender had no influence on TIRADS and Bethesda classification. Marked hypoechogenecity, vascularity and nonhomogeneous were more common in men.

Key words

TIRADS, Bethesda system for reporting thyroid cytopathology, PTC, FTC, MTH, ATC, US, FNA, FNAB, FNAC, MRI, CT, Malignancy, Malignant, Benign, thyroid nodule, risk stratification, prognosis

KOPSAVILKUMS

Ievads

Vairogdziedzera attēlu diagnostikas klasifikācijas un datu sistēma (*Thyroid Imaging Reporting and Data System, TIRADS*) ir klasifikācijas sistēma, kas iedala mezglu malignitātes riskus. Katra kategorija reprezentē vairogdziedzera mezgla malignitātes risku. Tā izveidota ar mērķi uzlabot reaģēšanu un izmaksu pārvaldību, samazinot vajadzību pēc ar tievu adatu aspirācijas biopsijas pacientiem, kuriem ir vairogdziedzera mezgli. TIRADS sistēma ir riska novērtēšanas sistēma vairogdziedzera audu bojājumu klasificēšanai. TIRADS novērtējums sniedz informāciju par vairogdziedzera struktūru, malignitātes risku un klasifikāciju. Bethesda sistēma vairogdziedzera citopatoloģiju novērtēšanai ir vairogdziedzera citopatoloģiju klasificēšanas sistēma.

Mērķi

Šī darba mērķis ir analizēt TIRADS klasifikācijas sistēmu vairogdziedzera mezglu novērtēšanai, salīdzinot gadījumu skaitus abos dzimumos un atbilstoši vecumam, kā arī salīdzināt dažādus nosakāmos raksturlielumus. Pēc tam salīdzināt TIRADS klasifikācijas ar Bethesda sistēmu, kas paredzēta vairogdziedzera citopatoloģiju un histopatoloģiju novērtēšanai un kas ir specifiskāka diagnostiskā metode.

Materiāli un metodes

Šis ir retrospektīvs pētījums, kurā iekļauti pacientu ieraksti no Rīgas, Latvijas, analizējot ierakstus no 2016. gada maija līdz 2017. gada februārim un salīdzinot ierakstus par vairogdziedzera mezgliem. Vairogdziedzera attēlu diagnostikas un apkopošanas datu sistēma (TIRADS) ir riska stratifikācijas sistēma vairogdziedzera patoloģiju klasificēšanai un tika izmantota, lai iegūtu informāciju par vairogdziedzera mezglu struktūru un malignitātes risku. Salīdzinājumam izmantota Bethesda sistēma vairogdziedzera citopatoloģiju novērtēšanai. Rezultātu analīzei izmantotas IBM SPSS 21.0 piedāvātās Spīrmena korelācijas un Hī kvadrāta testa metodes.

Rezultāti

Pētījuma populācija iekļauj 298 pacientus. Jaunākajam pacientam ir 16 gadi, bet vecākajam – 113 gadi. Pētījuma dati izvēlēti gadījuma veidā. 85,2% dalībnieku bija sievietes un 14,8% bija vīrieši. Vidējais vecums bija 58,6 gadi (sieviešu vidējais vecums – 58,5 gadi, bet vīriešu –

59,5 gadi), mediānais vecums bija 59 gadi (sieviešu mediānais vecums bija 59, bet vīriešu – 60.5), ecuma moda bija 59 (sievietēm – 59 gadi, bet vīriešiem – 52 gadi).
Spīrmena korelācijas tests sakarībai starp TIRADS un Bethesda klasifikācijām norāda pozitīvu korelāciju (ρ=0,182).
Lielākajai pacientu apakšgrupai, 63,4%, bija TIRADS klasifikācija 3 ((95%Cl: 57.8…68.7%), bet mazākaijai grupai, 0.3%, – TIRADS klasifikācija 1 (The largest subgroup of patients, 63.4% had TIRADS classification 3 (95%Cl: 57.8…68.7%) and smallest subgroup of patients 0.3% had TIRADS classification 1 (95%Cl: 0.1%...1.9%).
Lielākajai daļai pacientu, 69,8%, bija Bethesda klasifikācija 2 (95%CI: 64.4%...74.7%), bet mazākajai gurpai, 1.0%, bija Bethesda klasifikācija 4 (95%CI: 0.3%...2.9%).
Korelācija starp TIRADS un Bethesda, ņemot vērā rezultātus kā pozitīvus pret negatīvajiem (pozitīvi jeb maligni ir 3, 4, 5 klase TIRADS testam un Bethesda klases 4, 5, 6), uzrādīja 100% jutīgumu, 9% specifiskumu un 81,4% neīsto pozitīvo rezultātu.
Pieņemot par pozitīvu (malignu) TIRADS 4 un 5 klasi, bet Bethesda – 4, 5, 6, tika sasniegts 72,0% jutīgums, 78,3% specifiskums un 19,4% neīsto pozitīvo norma.
Pieņemot par pozitīvu (malignu) TIRADS kalsi 5 un Bethesda klasi 6, tika sasniegts 20,0% jutīgums, 99,6% specifiskums un TIRADS norādīja tikai uz vienu nepatiesu rezultātu.
Tāpat, vīriešiem ir biežāk sastopami nehomogēni (p=0,045), izteikti hipoehogēni (p=0,046) un vaskulāri (p=0,01) mezgli, nekā sievietēm

Secinājumi

TIRADS, salīdzinājumā ar Bethesda sistēmu, ir zemāks specifiskums, bet augstāks jutīgums. Daudzi TIRADS rezultāti nekorelēja ar Bethesda secinājumiem.
Pastāv tendence, ka augstākas Bethesda klasifikācijas atbilst augstākai TIRADS klasifikācijai. Iemesls potenciālajām nesakritībām varētu būt Bethesda 3 un 4 klasifikāciju trūkums pētītajos datos. Dzimumam nebija nekādas ietekmes uz TIRADS vai Bethesda klasifikācijām.
Vīriešiem bija biežāk sastopams hipoehegēniskums, vaskularitāte un nehomogēniskums.

Atslēgvārdi

TIRADS, Bethesda vairogdziedzera citopatoloģijas novērtēšanas sistēma, PTC, FTC, MTH, ATC, US,FNAB, FNAC, MRI, CT, malignitāte, ļaundabīgs, labdabīgs, vairogdziedzera mezgls, risku novērtēšana, prognoze

1. INTRODUCTION

Many millions of individuals are suffering from some kind of thyroid gland disease worldwide. (Tan and Gharib 1997). Goiter is the commonest form of thyroid gland disease and diffuse non-toxic goiter is the reasons for expansion of the entire gland with absence of any nodular growths, while an asymmetric enlargement of the thyroid gland is representative for multinodular goiter (Kumar et al. 2010). Carcinomas of the thyroid glands are not as usual as nodules are (Pacini et al. 2006), it accounts for 1,5 percent of all cancers that endure (Kumar et.al 2010). The rate has augmented in the last ages, mainly in female. (La Vecchia et al. 2016). Cancers of the thyroid gland can be differed into four groups. PTC are the most usual form and the FTC are the next recorded common malignancies of the thyroid glands and befalls frequently in dietetic iodine insufficiency extents. Medullary thyroid cancer, which is the third commonest form originates from cells of the thyroid gland and creates calcitonin. MTC may be heritable and be part of MEN 2A and 2B. ATC are least occurring, utmost aggressive and are considered to be undifferentiated tumours form. (Kumar et al. 2010).

High resolution ultrasound is an important tool for evaluating thyroid nodules and is a universally used device and gives significant information about the thyroid gland. Thyroid nodules can exist as benign or malignant form. Around one third of adult's populace has a thyroid nodule on ultrasonographic examination (Tan and Gharib 1997, Ezzat et al. 1994) and fewer then 10 percent are not benign (Papini et. al 2002). US are essential, safe, nonionizing, cost efficient and certainly accessible imaging instrument for analysis of lesions in the thyroid gland. Studies demonstrate that palpation, ultrasound and biopsies are methods of finding abnormalities. (Dean and Gharib 2008). Thyroid nodules might have highly dissimilar ultrasonographical patterns. (Raggiuniti et al. 2011 and Moon et al. 2008). Usage of ultrasonography has contributed to increase detection of thyroid nodules (Fagin and Mitsaides 2008). Lately, reports advised a reporting data system for thyroid lesions in stratifying the risk of malignancy. (Horvath et. al. 2009). Scientists are evidencing that US is highly trustable although is a less exact method of choice in detection of malignancies (Moon et al. 2010 and Morris et al. 2008). TIRADS have been initiated to sort nodules of thyroid gland (Kwak et al. 2011). It is a is intended to give explanations of all types of lesions that are noticed by the US. Those lesions are including lesions of the thyroid gland that could possibly be both malignant or benign (Papini et al. 2002). According to according to Shin et al. (2016), Cooper et.al (2009) and Gharib et al. (2010). The US is describing the diverse structures that a nodule can

have. Multiple description as echogenicity, form, vascularity, borders and if the nodule is solid or cystic or contains calcification or not. Also detecting nodules before surgery by US gives a better diagnostic accuracy then CT (Ahn et al. 2008). FNAB is the best and the most specific choice for diagnosis of thyroid carcinomas (Pucini et al. 2006). But since FNAB costs more and is not as convenient for the patients, it is of great significance to pick the cases regarding the risk of malignancy. It is vital to find the precise diagnosis, because if not it may affect the therapeutic patterns (Shah et al. 2009). For example, in cases where cytological results are proving PTC, total or near total thyroidectomy is recommended (Pacini et al. 2006) while for ATC there doesn't exist any effective treatment (Colledge et al. 2011).

1.1 Study objective

The aim of this study is:
To study TIRADS and compare its accuracy with the Bethesda classification.

1.2 Tasks

1. The study univariates to detect prevalence of features described in TIRADS
2. To estimate and compare the prevalence of different aspects in female versus male.
3. To assess and describe age related risk groups of having to go through US and FNAB and differences in sex.
4. To study TIRADS correlation with Bethesda

2. LITERATURE REVIEW

2.1 Thyroid Imaging Reporting and Data System (TIRADS)

TIRADS classification systems are grounded on the Breast Imaging Reporting and Data System (BI- RADS) (American college of radiology, 2003). The descriptions for thyroid nodule have been described by Shin et al. (2016). The explanation contains the US characteristics, category and description so we can get an enhanced understanding of the characterization of the nodule and thereby be able to diagnose the nodule more precisely.

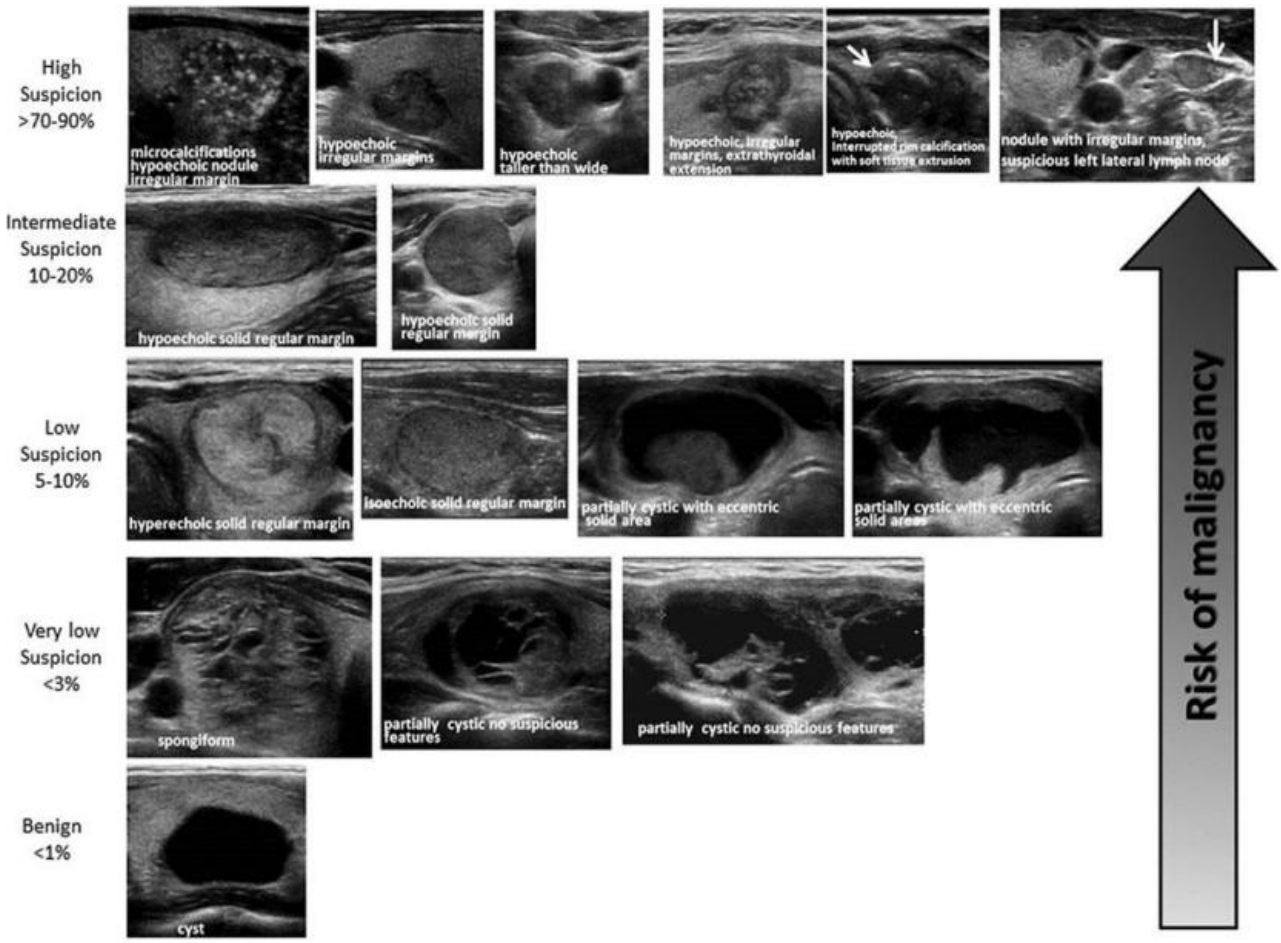

Figure 1. Different US finding of thyroid nodule: In the figure we can se the pattern of the thyroid nodules that have been evaluated by US.
Haugen et al. (2016).

In the US charactaristics either solid, predominantly solid, predominantly cystic or cystic. The echogenicity can be either marked hypoechogenicity, mild echogenicity, isoechogenecity or hypoechogenicity. The shape can be round to oval and irregular. The margin of the thyroid

glands can be smooth, microlobulated or ill- defined. The nodules may contain calcifications that can be either microcalcificated or macrocalcificated. Vascularity of the nodule can be present or absent that can be located in different parts according to Shin et al. (2016), cooper et.al (2009) and Gharib et al., (2010). Newly settled analyses are proposing that bigger nodules have a larger chance of malignancy, (Shinn et al. 2015) but it is still debateable if the size of a nodule could predict the probability of malignancy (Kamran et al. 2013, McHenry et al. 2008 and Shrestha et al. 2012). Because non-malignant nodes can grow slowly, but over an extended period of time and consequently might reach a gigantic volume (Alexander et al. 2003, Ajmal et al. 2015, Erdogan et al. 2006, Asanuma et al. 2001,) Nevertheless, fast growth of a nodule that is solid can be a display of a high grade malignancy. To estimate the accurate growth rate of a nodule is essential especially for the management stratagem (Haugen et. al. 2016).

Shin, J. H. et al. (2016) are endorsing that a nodule with minimal cystic changes can be in the group of being predominantly solid nodule since their malignancy probability might be equally to moderately cystic nodules. They are also suggesting that an isoechoic spongiform nodule might be regarded as benign and that the malignancy risk is lesser than one percent. Spongiform nodules are not commonly seen in papillary carcinomas. A nodule which is hypoechogenic or is having microcalcifications might rise the risk of malignancy in a nodule that has a spongiform appearance. (Salmaslioglu et al.2008, Henrichsen et al. 2010, Kwak et al., 2011, Na et al. 2016). Shin, J. H. et al. (2016) are proposing that a nodules echogenicity can be categorized on the basis of the relative echogenicity that is being compared with the reference structures. The echogenicity can be categorized as being either markedly hypoechogenic, hypoechogenic, isoechoic or hypoerechoic. In those particular situations where the echogenicity is heterogenous or is mixed, echogenicity would then be described by predominant echogenic. Furthermost of the malignant tumors result from in the thyroid glands are hypoechoic. It is proven that the risk of malignancy of the nodules which are hypoechoic are higher compared with others, the estimation is approximately 20,6- 70,4 percentage. A nodule can have variety of shapes such as round, ovoid or even irregular. Shin, J. H. et al. (2016) are implying that the margins of a nodule can be labelled as smooth, microlobulated or ill- defined. Those nodules that have a smooth margin is more repeatedly seen in nodules that are hypoechoic, isoechoic with hypoechoic halo and is rarely seen in isoechoic nodules. Smooth margined nodules are not definite for benign nor malignant nodules. A nodule that is irregular doesn’t indicate that the nodule is malignant even though that round to ovoid forms are more regularly seen in benign nodules, still those features can not be used as an exclusive

or indicating marker. (Jeh et al. 2007, Yoon et al. 2008, Kim et al. 2009). Microlobulated margined nodules are suggesting that there might exist malignancy (Na et al. 2016, Moon et al. 2008, Kim et al. 2015). Nodules with ill- defined margin may also be found in hypoechoic nodules. (Langer et al. 2001, Frates et al. 2013). A nodule can be non calcified, microcalcified or macrocalcified. Microcalcification is characterized by a locus of one millimetre or fewer while macrocalcification is characterized by having a greater area of calcification, an echogenic centre of above one millimetre (Malhi et al. 2014 and Beland et al. 2011). Microcalcifications are suggestive of being malignant. However, the malignancy risk is high in solid hypoechoic nodules while it is intermediate in nodules that are isohyperechoic and partially cystic. Macrocalcifications aren't explicit for malignancies even though that they might rise the possibility of malignancy. A nodule which is isolated macrocalcified can concluded as an intermediate doubtful nodule. As there isn't adequately with research there doesn't subsist enough with evidence to confirm and conclude this theory according to many scientists as Na et al. (2016). Regarding Shin, J. H. et al. (2016) the vascularity of thyroid nodule can be evaluated by two main methods, Color Doppler and by usage of power Doppler US thereby the vascularity can be separated into four main categories. The first type is characterized by non-apparent vascularity, type two by perinodular vascularity, there is exist vascularity at the margins. While the third type is distinguished by containing intranodular vascularity with or without perinodular vascularity. The vascularity is characterized by being less then 50 percent. Lastly, the fourth type is discernible by having intranodular vascularity with or without perinodular vascularity and where the vascularity is beyond 50 percent. In 16,7- 91,7 percent of cases intranodular vascularity is present in malignant tumors and 30,7-65,3 percent in benign nodules. (Chan et al., 2003 and Rago et al. 1998). An intranodular vascularity might be predictive value of malignancy in follicular lesions or neoplasm, but this theory is still discussable. (Miyakawa et al. 2005 and Lared et al. 2009). Frates et al. (2003) states as Miyakawa et al. (2005) and Lared et al. (2009) that Intranodular vascularity could intensificate the chances of a nodule to be malignant, but points out that there aren't sufficient with evidence that it could associate intranodular vascularity with the risk of malignancy.

FNAB of the thyroid gland is a precise diagnostic way that is routinely used in appraisal of nodular thyroid diseases (Gharib and Papini, 2007). Additionally, FNA in combination with ultrasonographic evaluations are routinely used to evaluate patients with thyroid malignances (Solomon et al. 1996). FNAB can be give a discomfort feeling or hurt, prices are more in comparison with US and may have some medical risks as infection and bruises. (Ardakani et al. 2015). But, it is established as being a safe, reliable and an effectual technique for

diagnosis of thyroid gland nodules pathologies according to Shin, J. H. et al. (2016). TIRADS classification is magnificent as it depicts all changes being perceived by US, such as lesions including both benign nodules and follicular lesions (Papini et al. 2002). The conclusion whether or not performing a FNA is based on the malignancy and prognostic risk. In case of cervical lymph node metastasis FNA of the nodules would be performed notwithstanding the size of the nodule. The results achieved by US is also a predictive value whether a FNAB should be perform or not (Shrestha et al. 2012). In benign nodular alterations (TIRADS 2), the analytical FNA can be advantageous for spongiform nodules and the size is 2 cm or more. In circumstances where the nodule is of TIRADS-3, the fine needle aspiration is optional when the nodule extents to a size of 1.5 cm or more. A nodule that is TIRADS 4 or 5 and is bigger than 1 cm, FNAB is optional (Na et al. 2016). Na et al. (2016) is also mentioning that FNA is highly beneficial not only in diagnostic purposes but also in therapeutic approaches, as in drainage of cystic contents.

2.2 Fine needle aspiration biopsy

FNAB have the ability to diagnose cancer types as PTC, FTC, MTC and ATC as well as thyroid lymphomas and metastasis situated in the gland. Thyroid carcinomas are tumors that are growing as nodules located in the thyroid gland. The greatest number of carcinomas in the thyroid gland are differentiated and they might appear as normal tissue outwardly. Therefore, the only way to differentiate malignant nodules from benign noldules is by biopsy. (EndocrineWeb.com: http://www.endocrineweb.com/fna.html (Last access: 12 May 2017). FNA can be considered to be implemented in patients with intermediate or low wariness array (Koo et al. 2010 and Park et al. 2011). Indications for fine needle biopsy are findings as a single nodule, firm lump, irregular appearance, rapidly growing pattern or mechanical problems/ complications and hoarseness caused by an enlarged nodule (Source: http://www.internetmedicin.se/page.aspx?id=2780 (Last access 12 May, 2017). Regarding Pacini et al. (2006) all solitary nodules that are 1 cm or larger cm in size should obligatory be submitted to cytology if they haven't been confirmed to have low- supressed serum TSH. Nearby four percent to eight percent of the nodules that are undergoing FNAB are malignant regarding Yassa et al. (2007) and around 10-20 percent of nodules that undergo FNAB are intermediate and doesn't demonstrate any abnormal appearance of the cells. Malignancy conclusion concluded from FNAB is 97- 99 percent specific, substantiating that there might be cases of false results, since the specificity is not 100 percentages. Those intermediate nodules can not be concluded neither as benign nor malignant and might require surgery to define the accurate diagnosis. Benignity of a nodule could be described as not having any abnormal invasions and is surrounded by a capsule. adenoma or adenomatous nodule are exemplars of non malignancy, whereas follicular carcinoma is an example of malignant tumor. (Antic and Taxy, 2013).

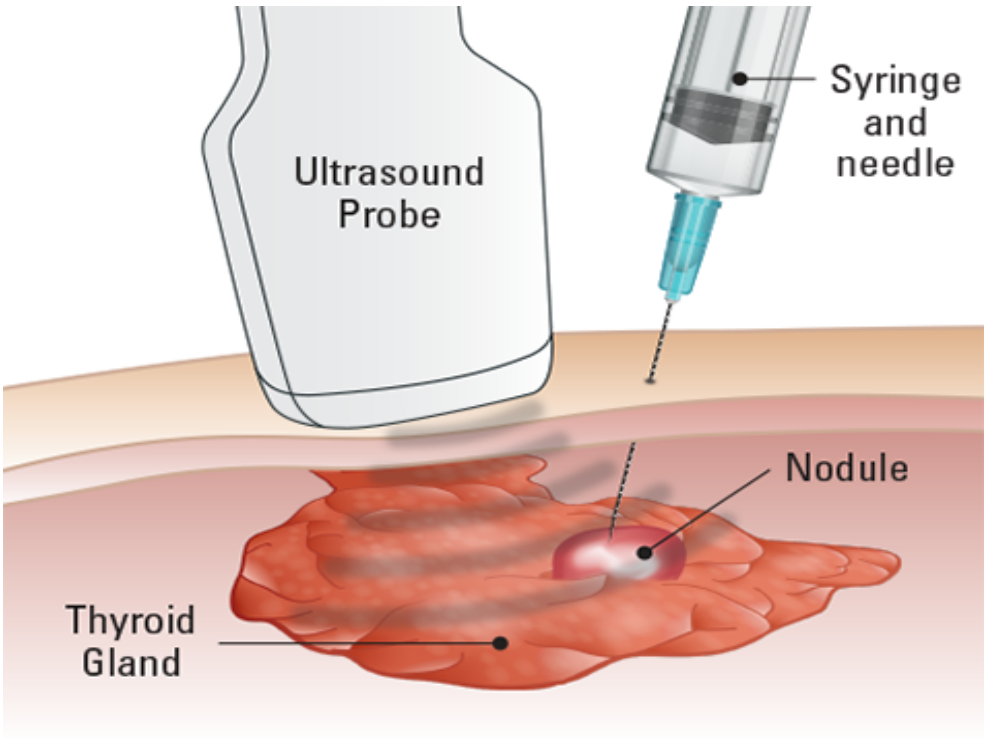

Figure 2. Diagnosing Thyroid cancer:
During the procedure of fine needle biopsy, a small needle is inserted. The needle draws out the content from the nodule that is examined under a microscope.
(Source: https://www.thyrogen.com/patients/Your-Thyroid-Cancer-Journey/Diagnosing-Thyroid-Cancer.aspx (Last access: 14 May, 2017).

Samplings that are containing lesser than six follicular sets is considered as nondiagnostic. Exceptions might for instance befall in circumstances evident of colloid or solid nodule with uncharacteristic appearance, inflamed solid nodule, subacute thyroiditis that is agonizing or thyroid abscess. (Ali and Cibas, 2009). A nodule which is suspicious but undiagnosed should be going through additional analysis, due to the fact that the sample could have been badly stained or another reasonable explanation is that the aspiration of a cystic nodule may have dominance of acellular fluid. Nodule with solid component are necessities to be repeated with FNAB, which is vital due to the fact that papillary thyroid carcinomas might be chiefly cystic says Bongiovanni et al. (2012) and Sohn et al. (2011). Around 60- 70 percent of thyroid nodules that undergo FNAB are benign. Patients that have been identified with a benign nodule should be surveyed with US, due to the consideration that the risk of malignancy isn't zero. Also, a FNAB should be repeated if there is a progression of above 50 percent (Cooper et al. 2010). Benign follicular nodule, colloid nodule, chronic lymphocytic (hashitomo) thyroiditis or granulomatous (subacute, de quervain) thyroiditis are some of the nodules that are considered as benign. A benign result does not conclude diagnosis since up to 3 percent of

nodes that are categorized as benign have been evidenced to be non benign. Therefore, Ali and Cibas (2009) stressed that it is highly vital for the physician to comprehend that there subsist risks of malignancy. Follicular neoplasm that is characterized by having crowded nuclei and absent or scant colloid is an exemplar when nodules are diagnosed with suspicious for malignancy. They have numerous similarities and dissimilarities with malignancy features. Daniels (2011) are describing that follicular types of papillary thyroid carcinomas are characterized by having a particular follicular kind of architecture while having nuclear changes are reflecting those of papillary thyroid carcinoma. Those nodules are requiring surgical interventions as bilateral or total thyroidectomy (Cooper et al. 2010). Post surgically, evaluation of the fibrous capsule is made. A nodule is reflected as benign if there haven't occurred any vascular or capsular penetrations (Yang et al. 2007, Schlinkert et al. 1997 and Kelman et al. 2001). In up to 30 out of a hundred, Hürtle cell neoplasms that are made of a pure, cellular dyscohesion and groups of Hürtle cells are malignant. Confirmation of the diagnosis is made when vascular or capsular invasion is proven (Ali and Cibas, 2009). There are multiple patterns that could be categorized under AUS and FLUS. Bongiovanni et al. (2012) exemplifies some of those situations, as while there occurs a combination of microfollicles and macrofollicles, or circumstances when there is follicular neoplasm that is predominated by microfollicular then while there is a dominating Hürthle cell neoplasia.

2.2.1 Thyroid anatomy

Embryologically the thyroid gland is derivative from epithelial proliferation between the first and the second pouches. Later on the thyroid diverticulum will develop and become bilobulated then travel down until it is reaching the second and third tracheal cartilage. About the tenth embryonic week colloid will be shaped. Noniodinated thyroglobulin is secreted subsequently. T3 secretion will be discharged at the fourth month (Boka et al. 2010). Thyroid gland is a vascular brownish- Red coloured endocrine gland that is situated anteriorly in inferior neck, below larynx, spanning between C5 and T1 vertebra. (Boka, 2010 and Hall, 2011). Thyroid gland is a "butterfly shaped" organ and the form can diverge from H to U and is shaped by two lateral lobes that are elongated with inferior and superior poles that are linked by median isthmus. (Williams et al. 1995). Respectively lobe is approximately 50- 60 mm long. Thyroid weight is in commonly 25 grams in grown-ups (Boka et al. 2010 and Hall 2011). It is vaguely heavier in female compared with men. (Sand, et al. 2006). The thyroid glands are becoming bigger during menstruation and pregnancy (Boka et al. 2010). Pyramidal lobe commonly ascends from the isthmus towards hyoid bone, which attaches it by a fibromuscular band, the levator of thyroid gland. Two pairs of parathyroid glands lie in proximity. The lobes of the thyroid gland are constituted of follicles, that is lined by a simple epithelial layer surrounding colloid filled core. Those closed follicles (100- 300 micrometres in diameter) contain colloid. Major constitution of colloid is glycoprotein thyroglobulin containing the thyroid hormones. (Hall, 2011)

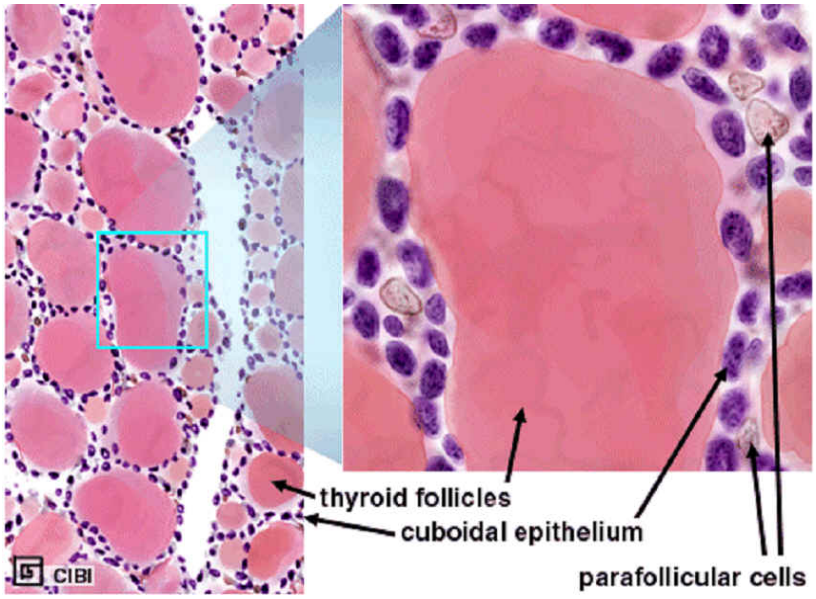

Figure 3. Microscopic appearance of thyroid gland: Microscopic form of the thyroid gland, that shows the secretion of thyroglobin into the follicles.

(Source: http://www.drharper.ca/new_page_12.htm (Last access: 14 May, 2017)

2.2.2 Blood supple and nerves

The thyroid gland is a vascularized organ. It obtains its blood supply from the inferior and superior thyroid arteries. Both of these arteries are located between the fibrous capsule and the pretracheal layer of deep cervical fasia (Cummings et al. 1998). The lower thyroid artery is supplying inferior half of the gland. It is the principal branch of thyocervical trunk that originates from subclavian artery. Superior thyroid artery is the branch of external carotid artery. It supplies the upper half of the gland and splits into anterior and posterior divisions. The right and left branches anastomose with each other on the anterior margin and on the posterior side the right and the left branches anastomose on the posterior side. The lymphatic drainage is very extensive in thyroid glands. Periglandular nodes are were the first drainage flow occurs, then it goes to the prelaryngeal pretracheal and paratracheal nodes alongside the recurrent laryngeal nerve afterwards to the lymph nodes in the mediastinum. (Standring et al. 2005). Innervation of the thyroid gland is mainly by autonomic nervous system (Boka, et al. 2010). Parasymphatetic fibers are originates from nervus vagus. Sympathetic fibers from inferior, middle and superior ganglia of sympathetic trunk (Standring et al. 2005). To consider the surrounding structures of the thyroid glands are important during surgeries, since damage to nervous laryngeus recurrence may occur and for instance may influence the phonation. (Boka, et al., 2010).

2.2.3 Thyroid gland physiology

The thyroid hormones activate the nuclear transcription of many genes therefore the thyroid hormones are often signified as the major metabolic hormones that affects nearly all cells (Hall, 2011). These hormones are involved in differentiation, metabolism, cellular respiration, energy expenditure, growth, as well as function of all tissues in the human body. (Sand, 2006 and Colledge et al. 2011). They are also involved in turnover of hormones, substrates and vitamins. The result is an increase in the functional activity throughout the body (Hall, 2011). The thyroid glands are producing calcitonin and thyroxin (Sand et al. 2006). It is the parafollicular C cells that are producing calcitonin (Colledge et al. 2011). Calcitonin is parathyroid hormone antagonist and is lowering the calcium levels in the body while at the same time it supports bone formation (Boka, et al. 2010). There are two biologically active thyroid hormones, L- thyroxine (T4) and L- triiodothyronine (T3) (Sand et al. 2006). Approximately 93 percent of the metabolically active hormone that is secreted is thyroxine and the remaining 7 percent is triiodotthyronin. T3 is the active hormone, it is three times metabolic potency of T4. T4 is a prohormone that is fragmented in target tissue to form T3

when necessitated. (Hall, 2011). The follicles are the structural, functional and the secretory constituents of the thyroid gland. Thyroidperoxidase is synthetized in endoplasmic reticulum, facilitating formation of T4 and T3 (Sand et al. 2006). Iodine is needed for thyroxine to be formed and it is recommended to ingest 1mg/week regarding Hall (2011). The follicular cells are taking up the iodide ions from blood through active transportation. The follicular cells are synthesising the protein thyreoglobulin that becomes saved in the lumen of the follicles, dissolved in the colloid. The thyroperoxidase is located in the follicular lumen. Around 10 percent of the thyrosin molecules ionized. The enzyme thyreoperoxidase makes sure that iodideions are binding to the thyrosin molecules (Sand et al. 2006). The hormones are released into the blood circulation through a negative feedback system of hypothalamic pituitary thyroid axis. A decrease in serum T3, T4 signals the hypothalamus to secrete a hormone called Thyrotropin liberating hormone. The thyrotropin releasing hormone will further on travel to the anterior pituitary gland where thyroid stimulating hormone is released. When T3 levels in the serum increased the release of of TRH and TSH will be reduced or hindered, to preserve the ordinary metabolic proportion of T3 and T4. Thyroxine binding globulin binds T3 and T4 in plasma (Hall, 2011). In order to keep the body in balance it is important that the hormone production is reaching the ranks of the requirements. Disruption in the thyroid function, may cause too high or too low hormone secretion (Sand et al. 2006). In cases of enhanced excretion, the metabolic process is quicker and is slower in circumstances leading to diminished secretion. Hypothyroidism is characterized by low metabolism while hyperthyroidism is signified by high metabolic rate, euthyroid it the state of normal metabolism. Goiter is an enlargement of all parts of the thyroid gland and doesn't describe the function nevertheless goiter might arise due to hyperthyroidism (Almås, H, 2011).

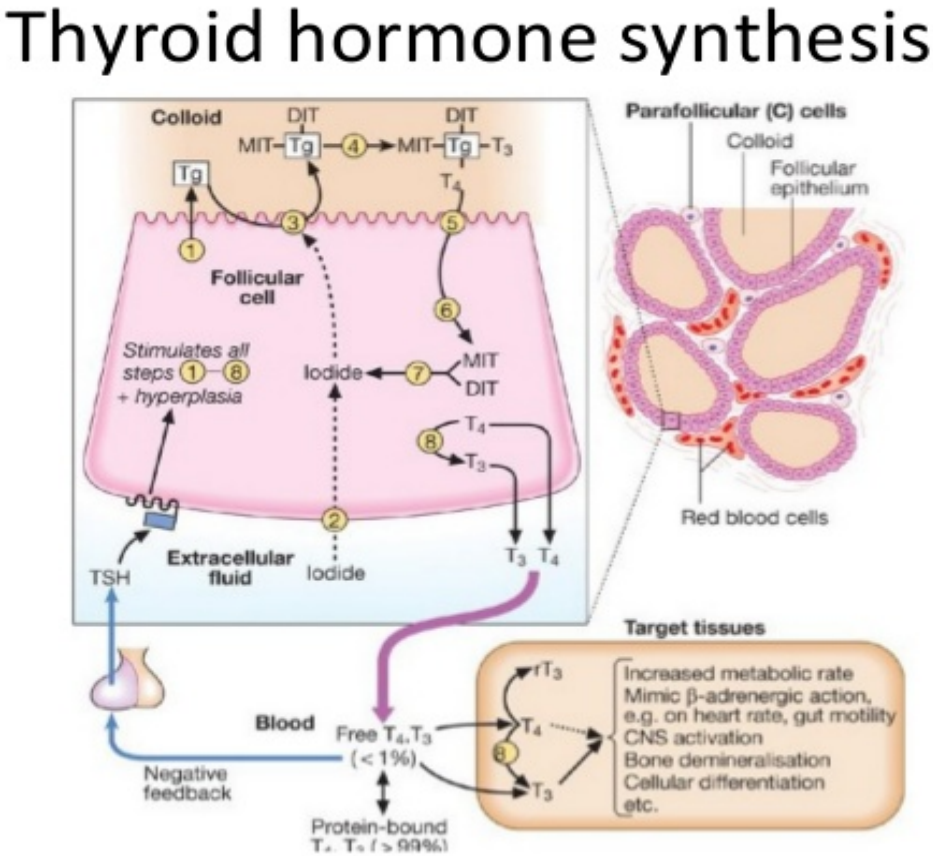

Figure 4. Hormone synthesis pathway.

Thyroglobin is synthetized and then secreted into colloid of the follicles. There is an active transport of the inorganic iodide into the follicular cells. Iodide will further on be conveyed on the surface of the colloid by carriers. They are organified by thyroid peroxidase enzyme to form MIT and DIT. Lateron, the iodinated tyrosine joins to form T3 and T4. Afterwards, the thyroglobulin is being endocytosed and cleaved to form iodinated thyrosine and the thyroid hormones. Thyroxin will become converted into triiodothyronine by monodeiodinase (Colledge et al. 2011).

2.3 Diffuse and multinodular goiters

Goiter is the furthermost form of thyroid gland maladies. Diffuse or multinodular goiters are frequently ensuing due to malfunctions in the synthesis of the thyroid hormones. Typically, this impairment occurs due to lack of iodine. As there is deprivation of the thyroid hormones, a compensatory response occurs that leads to increase in the TSH levels that later on leads to hypertrophy and hyperplasia of the thyroid follicular cells. The final stage of the pathological pathway will cause enlargement of the gland. In this manner the thyroid glands are trying to compensate the deficiency of the hormones (Kumar et al. 2010).

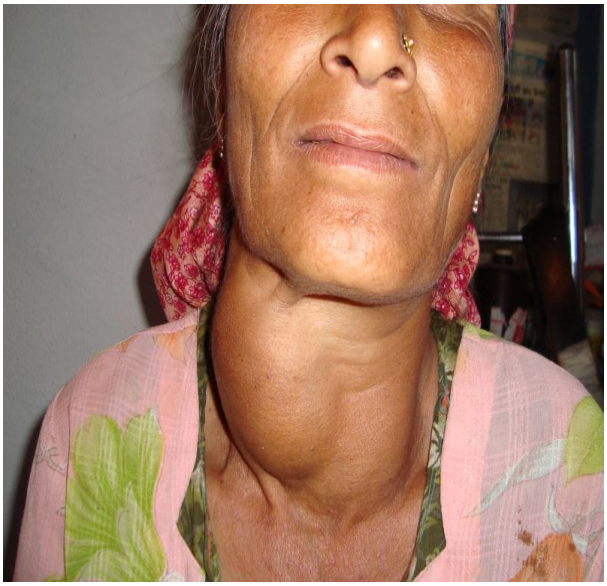

Figure 5. Enlargement of thyroid gland frontal view.
A female patient with a huge goiter. Patients with enlargement of the thyroid glands have a high risk of developing compression symptoms. The degree of an enlarged thyroid gland is equal to the period of deficiency of thyroid hormones. (Source: http://www.saglikvebiz.com/guatr-hastaligi-belirtileri-ve-tedavisi/ (Last access: 14 May, 2017).

Diffuse non toxic goiter is sort of goiter that produces expansion of the entire gland with absence of some nodular creations. Utmost of the patients with simple goiter are euthyroid. Therefore, patients with this ailment have primarily an enlarged nodule with mass effects. The recurrent hyperplasia in amalgamation with involusion might be the source an asymmetric enlargement of the thyroid gland, referred as multinodular goiter. This hypothesis supports that with time all extended simple goiters might become multinodulated goiters, that are producing extreme enlargements of the thyoid gland. Most common clinical courses are caused by the mass effect. Mostly patients are euthyroid but, in some patients plummers syndrome might progress into hyperthyroid state. Approximately 10 percent might develop autonomous nodules. By usage of radioiodine scan a hot nodule can be identified due to uneven iodine uptake. A FNAB is required to approve the diagnosis (Kumar et al. 2010).

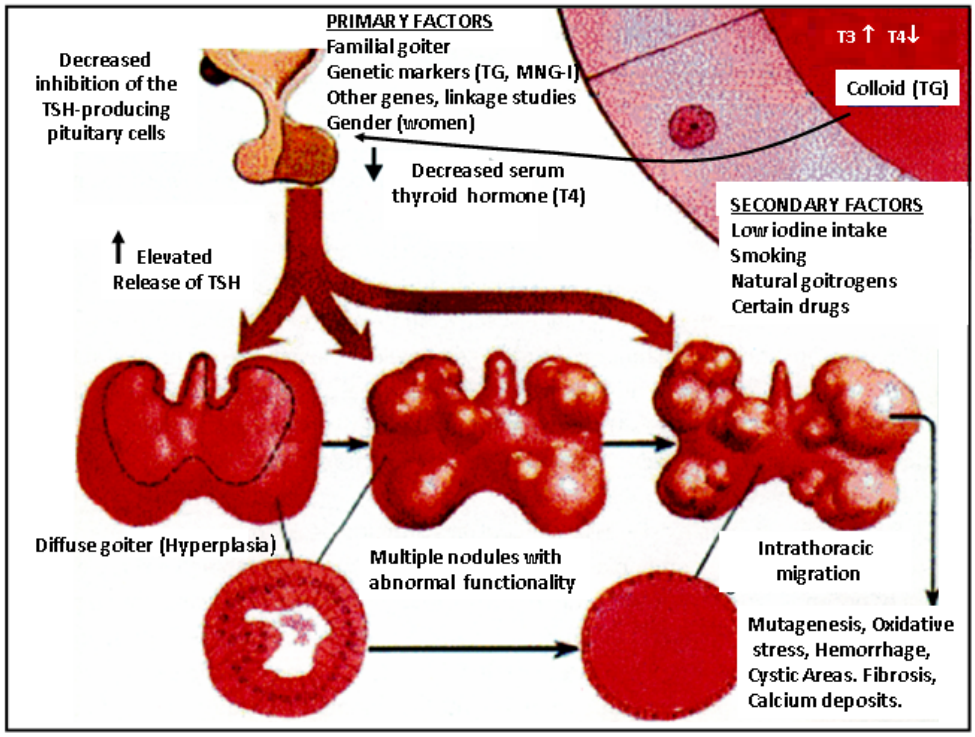

Figure 6. Pathological manner of development of multinodular goiter.

Figure: Dearth of iodine in relation with associated factors leads to inhibitions of serum T4. The increased TSH precipitates to the formation of diffuse goiter. Subsequently, might provoke enlarged multinodular goiter with cystic zones, haemorrhage, fibrosis and accumulation of calcium. (Source: http://www.thyroidmanager.org/chapter/multinodular-goiter/fig3/ (Last access: 14 May. 2017).

Adenomas also known as follicular adenomas are mainly discrete, solitary masses that are derived from follicular epithelium. Majority of the adenomas are non-functional while minority are referred as toxic adenomas due to their pathological secretion of thyroid hormones causing thyrotoxicosis. Less then 20 percent of the non-functioning follicular adeonomas have a mutation of RAS or phosphatidylinositol 3- kinase subunit or contains a bear a PAX8- PPARG fusion gene. While in toxic adenomas somatic mutations of the TSH receptors have been found (Kumar et al. 2010). People who get affected by thyroid neoplasia are presenting with a solitary nodule. Those nodules are usually benign while Toxic adenomas are characterised by secreting high amount of thyroid hormones. Out of all carcinomas, thyroid cancers are accounting for one percentage. Thyroid neoplasia can be classified according to the cell type of origin (Colledge et al. 2011). Toxic solitary nodules are believed to occur in 5 percent of all thyrotoxicosis cases. Toxic solitary nodule is characterized by autonomously secreting hormones of the thyroid gland. It is also characterized by inhibiting endogenous TSH secretion. With time atrophy of the thyroid glands will occur. It is more

common that the T3 levels are high and the malady progression is usually benign and normally the adenoma is greater then 3 cm in diameter. Utmost of the patients that are being established with this particular type of pathology are female elder than 40 years of age. The detailed diagnostic modus is by isotope scanning. Since the atrophic cells that are surrounding the cells wont be capable to take up the iodine the ideal management is by 131I (400- 800 MBq (10- 20 mCi)). Therefore, permanent hypothyroidism isn't as common as in persons that have underwent thyroidectomy. Alternative treatment technique is surgical hemithyroidectomy (Colledge et al. 2011). Regarding Kumar et al. (2010) many scientific criterias may give ideas to the natural development of a nodule that is rendered by several statistical studies. For example, that a solitary nodules occurring in youngers are more common to be of a neoplastic origin when compared with older patients with solitary nodules.

2.3.1 Differentiated carcinoma

Thyroid nodules are usual and differentiated thyroid carcinomas are starting to become frequent as well (Cooper et al. 2006). According Pacini et al. (2006) carcinomas of the thyroid glands are not so common. It accounts for around 1,5 percent of all cancers that happens (Kumar et al. 2010). Thyroid cancer is the commonest endocrine malignancy. The rate occurrence has increased in the preceding times, principally in female (La vecchia et al. 2016). Thyroid cancer may affect persons from any age but it is infrequent in children. Pediatric thyroid cancer accounts for circa 2,4- 9 percent of epithelial origin solid tumors (Samuela and Sharma, 1991). There is a surge in the occurrence of this form of cancer (Pacini et al 2010).

Cancers of the thyroid gland can be differed into four main groups. Papillary cancers of the thyroid gland are the most common form that can develop throughout life but commonest is from 25- 50 years old. Previous ionization exposure is considered as a risk factor. Follicular carcinomas are the second most common malignancies of the thyroid glands with a peak incidence between 40 and 60 years. The carcinoma occurs mostly in dietary iodine deficiency areas. The follicular carcinomas have propensities to grow into blood vessels and make metastasis in the bones and lungs. Medullary thyroid cancer, starts from cells of the thyroid gland and it produces calcitonin. It may be hereditary and be part of MEN 2A and 2B. This type of cancer can metastasize via the lymphativc vessels to the neck and it can also metastasize to the lungs and liver. Anaplastic thyroid cancer are undifferentiated tumors. The

anaplastic carcinomas are the most aggressive types (Kumar et al. 2010). It is proven that patients with cancer with exactly the same cancer form are responding individually to the to the same disease management. Therefore, the clinical course is unpredictable in many cases (Van't veer et al. 2002). According to Van't veer et al (2002), some patients can have recurrency of the disease and develop metastasis. In other hand, some patients may be free from cancer for a long period of time. This is a reflection of the differences that occurs in molecular level. Ultimately, it is imperative to comprehend the molecular mechanism thereby be able to diagnose the patient as precisely as possible. As an accurate conclusion is completed the most appropriate management possibility can be given and unneeded suffering by the patient can be avoided.

2.3.2 Papillary thyroid cancer

PTC is the most common (65- 68%) cause of thyroid cancer and the occurrence is increasing, specifically in the last 10-15 years (Pacini, 2012). According to Colledge et al. (2011) PTC are accounting for 90 percent of all irradiation induced thyroid malignancies. The escalation is frequently seen in papillary carcinomas lesser than 1-2 cm, also called mPTC. The cause could be due to being exposed to ionized radiation or as there is increase rates of autoimmune thyroiditis. PTC is most commonly occurring in individuals being grown-up, older than 45 years old. Reported papillary thyroid cancer from 2003 to 2005 indicates an increase of almost 100 percent in non- Hispanic and black females, whereas it increased 20 to 50 percent in white Hispanics, Asian/pacific islanders and black males, when compared similar cases from 1992-1995. (Enewold et al. 2009). Increase in the incidence might be allied with better analysis, diagnosis and screening methods regarding Pacini (2012). Papillary type of thyroid cancer is predominantly a gradual growing and metastasise locally to the lymph nodes in the neck (Colledge et al. 2011). It is a well differentiated form of thyroid cancer. A follicle cells differentiated tumor that is characterized by particular nuclear morphology. This form of thyroid cancer can be identified by its appearance. Nipple like projections that can be seen when examinating the biopsied tissue is very characterised for papillary thyroid cancer (Thyroid Disease: http://thyroid.about.com (14 May 2017)). Distinguishing the cell nuclei, nuclear crowding, nuclear folds and a ground glass appearance is greatly characteristic. Some of these findings can be benign changes. Columnar cell variant and tall cell cancer is an exception to the characteristic form and is infrequent. In some cases, PTC is multifocal and consists generally of separate primary tumour. The risk classification regarding TNM uses the size of the tumor (LiVolsi et al. 2004).

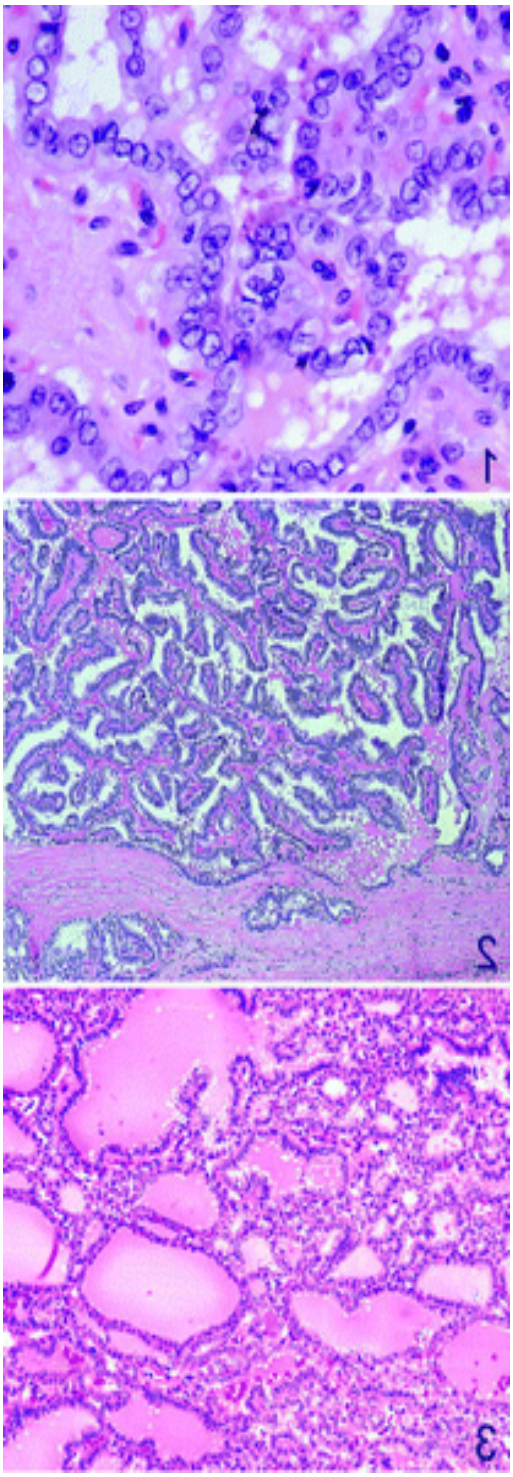

Figure 7.

1.PTC is characterized by expanded; overlapping nuclei that are clear due to peripheral margination of chromafin and due to uneven silhouettes that are creating grooves and cytoplasmic insertions. Stained by: Hemotoxylin- eosin (H&E), magnification is x400.

2.PTC that is shaped by papillae with fibrovascular centres. Stained by: Hemotoxylin- eosin (H&E), magnification os x400.

3. PTC of follicular variant that has scalloping and hypereosinophilia of colloid. Stained by: Hemotoxylin- eosin (H&E), magnification is x400 (LiVolsi et al. 2004).

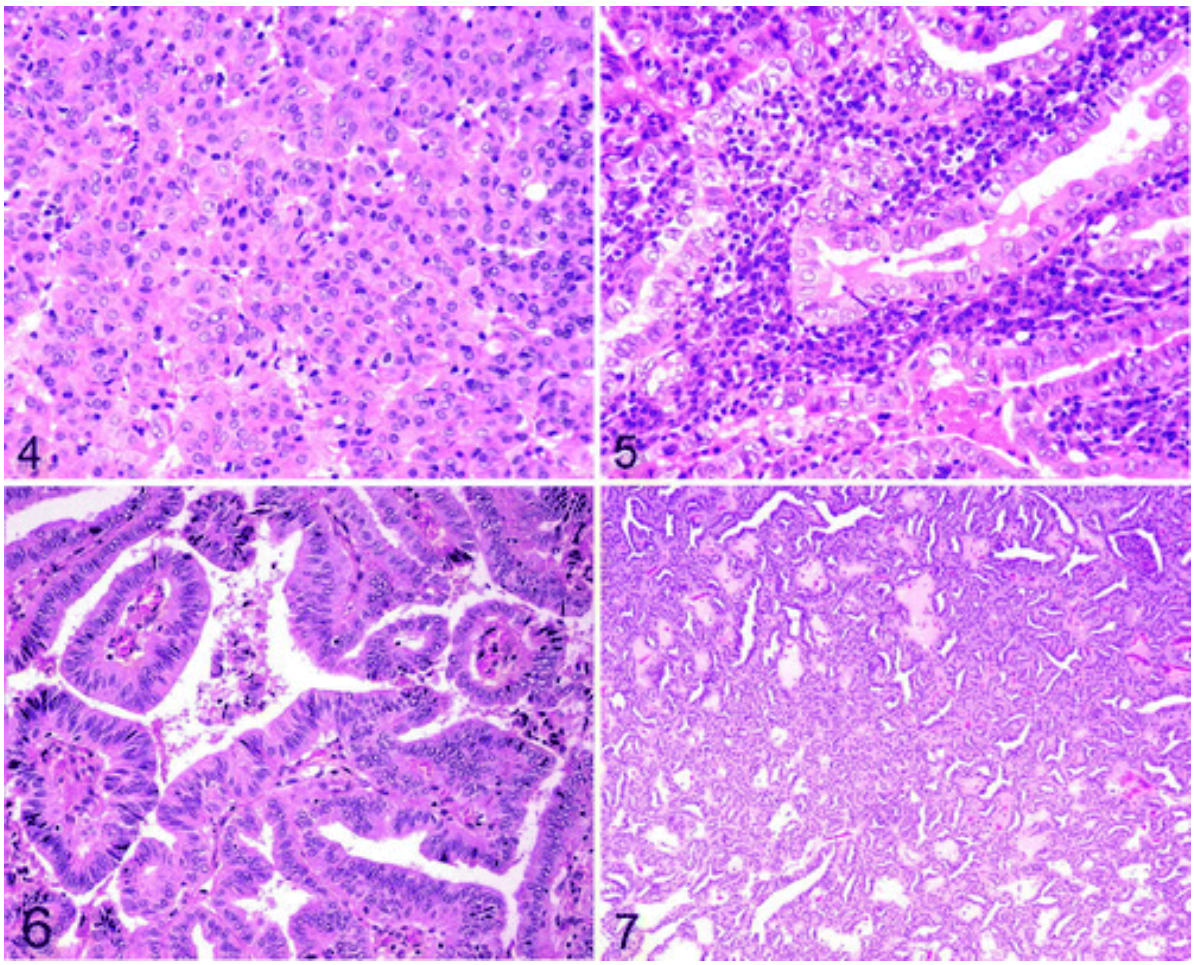

Figure 8.

3. *Oncocytic variant of PTC: composed of cells with mainly eosinophilic granular cytoplasm. Hemotoxylin- eosin (H&E), magnification is x100*
4. *Whartinlike PTC has mainly lymhoplasmacytic stromal infiltrate. Hemotoxylin- eosin (H&E), magnification is x200*
5. *Tall cell variant of PTC has lengthened cells with height to width relation beyond 3:1. Hemotoxylin- eosin (H&E), magnification is x200*
6. *Cribiform- morular variant of papillary thyroid carcinoma. Hemotoxylin- eosin (H&E), magnification is x100 (LiVolsi et al. 2004).*

Many chromosomal rearrangements are proven to be involved. One of the first oncogenic actions is chromosomal reorganisations of the rearranged during transfection (RET). Due to paracentric inversion of chromosome 10. In many cases there have been found RET fusion protein (RET/PTC) which have an underlying oncogenic role. For most of the cases RET/PTC1, RET/PTC2 and RET/PTC3 have been identified (Arighi et al. 2005, and Takami et al. 2002).

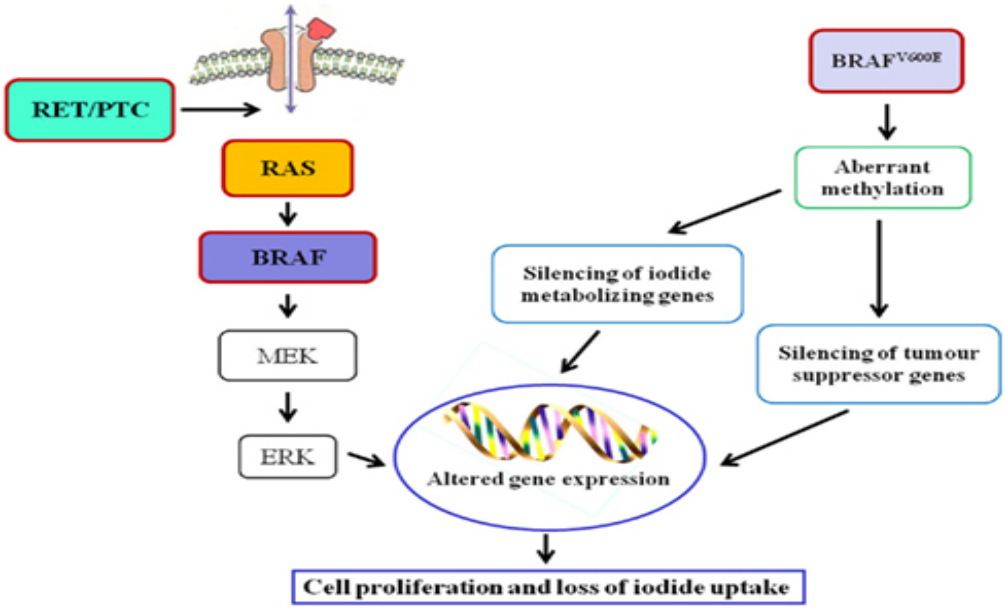

Figure 9. Genetic alterations in thyroid cancer.

Schema shows the possible pathways of development of thyroid cancer. Many genetic abnormalities are involved in development of thyroid cancers that. One of the first oncotic actions are rearrangement in RET and RAS. BRAF gene mutation is commonly seen in thyroid cancers as well. The process finally leads to altered gene expression and cell proliferation. (Catalano et al. 2012)

BRAF gene mutation is usual in cancers diseases appearing in humans. BRAF gene mutation is leading to production of BRAF V60E protein according to Davies et al. (2002). This mutation has an aggressive medical and uncontrolled features such as lymph node metastasis, extrathyroidal invasion and loss of radioiodine avidity. The radioiodine avidity may lead to failure of radioiodine treatments and the disease recurrence can take place according to Nikiforova et al. (2003) while Puexeddu et al. 2004 are not agreeing to this statement. Different investigates have exposed that RET/PTC3 gene rearrangement generally befalls in kids exposed to radiations. This particular gene rearrangement is the greatest commonly association found in pediatric papillary thyroid cancer. (Rivkees et al., 2011).

After the Chernobyl nuclear accident that took place in 1986, the occurrence of thyroid cancer increased in children that had been exposed to radioactive substances. This is especially seen in children that are younger than four years of age (Reinders et al. 2008). It is still not well comprehended if this arises because thyroid glands are more susceptible to the radiation damages in childhood because peak of the thyroid cell mitosis is taking place before an individual is 10 years old or if it is due to the contaminated milk that the children drank or if it is because of combination of both factors (Williams, 2002). Radiation persuaded damage is supposed to be related to chromosomal rearrangement. (Ciampi, et al. 2005). Exposure to radiation has been linked to the danger of developing thyroid cancer, diminished intake of iodine, hormonal factors or lymphocytic thyroiditis is some of the risk factors for thyroid cancer. The radiation may be from high dose external radiation treatments to the neck, especially during childhood (Ron et al. 1995). Regarding Caudill et al. (2005) ionized radiation is the greatest risk influence for developing thyroid malignancies. Radiation exposure from nuclear plant disasters increases also the risk of developing papillary thyroid cancer. As the atomic bombs that occurred in Hiroshima and Nagasaki in year 1945 or the Chernobyl accidents that occurred in 1986 (Williams, 2002).

Lymphocytic infiltrations have been demonstrated to happen, indicating that immunological issues might be involved in the progression of the tumor. Lack of dietary iodine results in compensatory thyroid proliferation also known as goitre. In areas where there is deficiency of iodine there is an increase risk of developing follicular carcinoma compared with iodine rich areas where papillary carcinoma is most frequent (Yumashitda, et al. 1990). Molecular abnormalities that are related embraces genes encoding for thyrosin kinases, RET, NRTK1, as well as two intracellular effectors of the MARK pathway, GTP- binding protein and RAS and serine- threonine kinase BRAF and it is verified that in farther than 70 percent of cases, alteration in one of those genes happens. The RET protooncogene codes for the cell membrane receptor thyroisine kinase. The ligand of the RET receptor are growth factors that are belonging to the glial cell line derivative from neutrophic factor family. Banding of the ligand produces initiation of the signalling cascade. RET can be triggered by rearrangement in the chromosome that will lead to combination of 3’ portion of the RET gene to the 5’, known as RET/PTC rearrangement. (Grieco et al. 1990). More than 40 different changes have been revealed in BRAF gene. T1799A point BRAF mutation is the furthermost. Roughly 90 percent of all mutations that are established in the BRAF gene have been identified to occur frequently in thyroid cancer (Fukushima et al. 2003). Other factors that could have an impacts

in occurrence of thyroid cancer can be the economical, social factors or the level of education. In nations with excessive social and economical position the thyroid cancers have increased radically after late 1990s compared with before 1990s (Li et al. 2013). Mostly patients with PTC have an asymptomatic nodule One of the first manifestations can be a mass located in the cervical lymph noted (Kumar et al. 2010). Certain patients have persistent cough, dysphagia and dyspnea. Seldomly, pain is an initial sign. Symptoms as pain, stridor, vocal cord paralysis, haemoptysis and rapid enlargement are also rare (LiVolsi et al. 2004). The nodule is usually movable during swallowing and is hardly distinguishable from a benign nodule. Usually the carcinoma is a solitary nodule. Palpable nodules that are mostly solitary is the main sign of papillary thyroid carcinoma (Kumar et al. 2010). Patients with lymphadenopathy without any enlargement of the lymph nodes may have primary lesion that is lesser than 10 mm in diameter (Colledge et al. 2011).

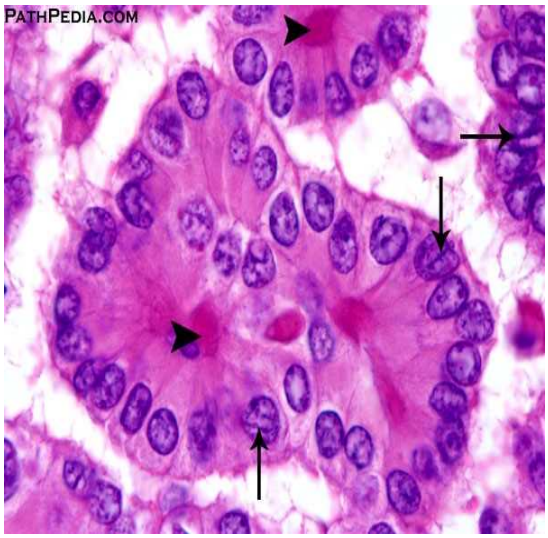

Figure 10. Papillary thyroid cancer with Orphan Annie Eye nuclei.

Papillary carcinoma of the thyroid gland, the long error shows cells that have an empty nucleus also called Orphan Annie nuclei. The shorter error is showing the vascular core. Source: http://www.medrx-education.com/usmle-review/papillary-thyroid-carcinoma (Last access:14 May, 2017)

Multiple analytical examinational methods are obtainable such as ultrasound, thyroid nuclear scans and FNAB. The papillary thyroid cancer nodule is developing as a cold nodule on a scitoscan and the fine needle aspiration biopsy makes it possible to differentiate a malignant nodule from a benign one (Kumar et al. 2010). To evaluate RET proto- oncogene manifestation is a possibility as well (Finn et a.l 2003). The management of PTC is usually by performing total thyroidectomy. Following the thyroidectomy, I 131 in large doses are given to patient in order to ablate the remaining tissue. Life long treatment of Thyroxine is required (Colledge et al. 2011).

Figure 11. Female patient with papillary thyroid cancer

Picture 1. *Patient with follicular thyroid cancer: At time of diagnosis patient had complains caused by mass effect. The complains that she had was dysphagia, difficulties to breath in supine position, cough and cosmetic complains. After palpating the thyroid gland, the physician decided to evaluate her TSH levels, perform an US examination on her thyroid gland and lymph nodes in neck region and finally they performed FNAB that confirmed the diagnosis.*

Picture 2. *Patient post total thyroidectomy. She has no complains at the moment. Patient has to take life long Levothyroxine 175 microgram /day.*

(Picture added with patient consent).

Patient with papillary thyroid cancer have an excellent prognosis (Colledge et al. 2011). According to Yu et al (2011), those people that are more than 45 years old, being a man, African American or being from smaller race, lymph node metastasis, extrathyroidal invasion and distant metastasis affects the largely the survival. Colledge et al. (2011) concluded that those patients that are under age 50 have a close to standard lifetime expectancy if the tumor dimension is fewer than two centimetres in breadth. The consequence of RET/PTC is correlated with the kind and occurrence of RET/PTC comprises the age of disorder discovery and radiation, the variant, sex, metastasis. In the study of Jhiang et al. (1996) concluded that redisposition of RET proto oncogene might be elaborate in progress of distant metastasis. The survival rate depends on the previous health of the patients. Colledge et al. (2011) found that that even individuals with distant metastasis have a 10-year survival rate of circa 40 percent.

2.3.3 Follicular thyroid cancer

The follicular carcinoma is more aggressive then the papillary type of thyroid cancer and is believed to befall due to consequences of the initiation of the point mutation in ras oncogene. As result p21- RAS will become fastened in its functioning conformation that will lead to activation of the protein and growth of tumor. (Kadıoğlu et al. 2015). Follicular thyroid cancer affects elder patients more then it affects younger people. The peak incidence is between 40 – 60 years of age (Kumar et al. 2010). It is supposed to be more invasive than papillary thyroid cancer. This type of cancer has a blood born metastasis meaning that the spread can occur through blood vessels and to distal areas as lungs and bones while spread to the cervical lymph nodes is rare (Colledge et al. 2011). This type of thyroid cancer is occurring more repeatedly in areas of iodine deficiency. Morphologically the follicular carcinomas are single nodules that could be widely infiltrative or cincumscribed. On cross section the apparent colour is gray to pinkish. Microscopically the carcinoma is composed of uniform cells that forms composed of colloid. Some cells are containing Hürthle cells or oncocytic variant of follicular carcinoma. The follicular carcinomas are developing painless enlarged nodules. In scintography those nodules are referred as cold nodules. Some nodules that are more differentiated might be hyperfunctional (Kumar et al. 2010).

The conclusion is chiefly confirmed by microscopical examination of a follicular tumor that has been removed by operation. A complementary lobectomy is performed to be able to perform radioiodide examination and follow up of the patient. Histological examinations are made after surgery to be able to differentiate if the mass is malignant or not. (Ringborg et al. 2008).

Follicular cancers are mostly treated by thyroidectomy and by removal of distended lymph nodes. Muscles, blood vessels and nerves are not being detached (Ringborg et al. 2008). The thyroidectomy is followed by prescription of huge dose 131 I to ablate the remaining tissue. Next step in the disease management is long term treatment with thyroxine supplementations. The dosage of thyroxin should be directed to supress TSH. The dosage should be specific for the patient. Dosage of Levothyroxine is usually around 150- 200 micrograms which patient should take orally every morning. The underlying theory to why patients should use Thyroxine is that growth of thyroid carcinomas is dependent on TSH. The TSH levels should be undetectable. If the thyroglobin levels are noticeable, it could be a reflection of recurrence or metastasis (Colledge et al. 2011).

The prognosis is hugely influenced by the invasion and the stage at time of diagnosis. The patients that have been diagnosed early and have received a proper treatment have an excellent prognosis. (Colledge et al. 2011). The 10- years survival rate is more then 90 percent. Those patients that are present with widely invasive carcinomas with metastasis have worser prognostic values (Kumar et al. 2010).

2.4 Medullary thyroid carcinoma

Medullary thyroid carcinomas are derived from neuroendocrine neoplasms. They are derived from the parafollicular cells (C cells) of the thyroid glands (Kumar et al. 2010 and Pacini et al.2010). Patients that develop MTC are frequently at their middle ages according Colledge et al. (2011). The most usual exhibition of MTC is solitary thyroid nodule. But they can also emerge within the setting of a multinodular goiter (Rosario et al. 2013). Increased size of the LN in the neck is present in the 50 percent of the cases. This form of thyroid cancer is more hostile compared to papillary and follicular carcinomas but less aggressive then anaplastic thyroid cancer. This type of cancer can also be hereditary and typically have a decent prognosis (Hazard et al. 1959). There is a probability that the tumor can secretes 5-hydroxytryptamine, peptides of tachykinin family as well as prostaglanding that can be the reason of development carcinoid syndrome and cushings syndrome. Medullary carcinomas of the thyroid gland can occur as part of MEN 2A or 2B syndrome (Colledge et al 2011). Regarding Kumar et al. (2010) MEN 2A and 2B are more often seen in younger patients and could even develop during the first decades of life, while the sporadic and familial medullary thyroid carcinomas mostly develop during adult life.

MTC cells can furthermore produce hormones as serotonin, corticotropin, melanin and prostaglandins. Medullary thyroid cancer is associated with RET proto- oncogene, receptor protein kinase that is encoded on chromosome 10. (Mulligan, et al. 1995). Activating point mutation in RET protooncogene influences both familial and sporadic forms of medullary carcinoma (Kumar et al. 2010). Regarding Myers et al. 1995 the RET protein consist of three different parts, those include intracellular, transmembrane and extracellular parts. Codon 634 mutations have been seen in both both MTC and have also been associated and found in people suffering from pheochromacytoma and hyperparathyroidism (Frank- Raue et al 1996). MEN 2B is affecting around 95 percent of individuals that are being detected. This happens through an alteration of M918T leading to vicissitudes in the intracellular domain. In familial medullary thyroid cancer patients, the germ line changes occur throughout the RET gene.

Those populations that have M918T mutation have an increased chance of developing an insistent path of illness and have a diminished survival proportion. (Moura et al. 2009).
The most common cause the patient is searching for medical help is due to mass in the neck region sometimes local signs as hoarseness, difficulty breathing and dysphagia may occur. But it is very common that this particular type of thyroid cancer is asymptomatic (Kumar et al. 2010). Paraneoplastic syndromes as cushings and carcinoid might be present but is infrequent. Due to high plasma calcitononin levels diarrhea may occur, due to elevated electrolycte secretion (Ersoy et al. 2003). At time of diagnosis distant metastasis are perceived in 7- 17 percent of cases. Metastasis occurs frequently in multiple sites as lung, liver, bones, brain and skin (Bergholm et al 1989). Distal metastasis to the lung, liver and bone may lead to weight loss, anorexia, fatigue, malaise and pain in bone.
It is important to find the precise diagnosis, because if not it may affect the therapeutic schemes (Shah et al. 2009). Cervical lymphadenopathy is usual therefore; a palpable cervical lymph node is a signal that cancer has spread. (Colledge et al. 2011). US is a valuable tool that specifies information regarding the gland and in predicting cervical lymph node metastasis (Hwang and Orloff, 2011). Detection of nodules before surgery by US gives a better diagnostic accuracy then CT (Ahn et al. 2008). Hypoechogenecity, microcalcifications, irregular margins, central vascularizations and enlarged lymph nodes have a higher possibility of malignancy (Alexander et al. 2004). Neck metastasis occurs early in MTC (Scollo et al. 2003). Huge population of patients with MTC have hypoechoic nodules and intranodular calcification. When MTC is suspected a fine needle biopsy and serum calcitonin levels should be measured. FNAB is one of the most significant diagnostic methods. Common findings are isolated cell groups while cytoplasm usually contains acidophilic granules, with two or more nuclei with an eccentric location (Papaparaskeva et al. 2000) and the calcitonin levels are increasing the confirmation of the diagnosis (Boi et al. 2007). In case of ambiguous circumstances immunochemical studies for calcitonin can be considered as an option. Sensitivity of FNAC is quite high (Essig et al. 2013), but there can still occur some incorrect established cases (Chang et al. 2005). The levels of calcitonin might reflect presence of metastasis and are important for surgical planning and the prognostic features (Constante et al 2007). Following test could be pentagastrin stimulation test in cases where the calcitonin levels are increased for accuracy purposes (Karges et al 2004). Medullary thyroid cancers are managed by total thyroidectomy with elimination of the affected cervival nodes (Colledge et al. 2011) but since individuals with inherited MTC have a higher risk of pheochromocytoma, patients are indicated to be investigated for it before performing thyroidectomy (Kloos et al. 2009). Regarding Nocera et al. (2000) there doesn't exist any effective treatment for distant

metastasis and Colledge et al. (2011) states that the therapeutic 131 I isn't an option since the C cells doesn't have the ability to concentrate iodine. Broekman et al. (2011) supposed that thyrosin kinase inhibitors could be used as a therapeutic option since they are blocking the thyrosin kinase dependent pathways and Verbeek et al. (2011) sees the benefits in usage of thyosine kinase inhibitors as well.
Up to now, it doesn't exist any effective therapeutic management for metastasis in distal regions and chemotherapy has a minimal effect in distant metastasis (Nocera et al. 2000). Roman et al. (2006) made a study where they determined that the important prognosticators for survival are age, stage and extent of the illness. It is believed that patient have approximately 10 years' survival rate of 95,6 percent. Patient with distant metastasis at time of diagnosis have worser survival rate.

2.4.1 Anaplastic thyroid cancer

Anaplastic carcinomas are undifferentiated malignancies of the follicular epithelium (Kumar et al. 2010). This type of malignancy is mostly occurring in elderly female. (Colledge et al. 2011). The mean age of patients who gets affected is more then 65 years. Individuals that get anaplastic carcinomas are older than people who get other types of thyroid cancers (Kumar et al. 2010). This is the least common but the most aggressive thyroid gland malignancy. It has a fast progression and early distribution. Usually anaplastic thyroid cancer appears in individuals living in areas where there is iodine deficiency (Serafettin et al. 1995). Anaplastic thyroid cancer is characterized by rapidly growing neck mass (Ringborg et al. 2008) and invasion to trachea and esophagus occurs. Most usual places of distal spread are in descending order, lung, bone and brain. (Kadıoğlu et al. 2015). The enlargement of the mass can occur during a period of 2-3 months regarding Colledge et al. (2011). Often patient request check-up due to complain as resistance sensation in the neck. Dysphagia and dyspnea could also occur (Ringborg et al. 2008). Stridor may also appear due to compression of the trachea. Those patients that have metastases may possible also experience bone pain, weakness, cough and neurological deficit, depending on metastatic area.

Diagnosis is made by many studies as palpation where a neck mass can be revealed. The goitre is hard and irregular (Colledge et al. 2011). Many patients also have lymph node enlargement which is a sign of metastasis to the lymph nodes. Other methods such as ultrasonography, thyroid scintigraphy, MRI and fine needle biopsy exist. Ultrasonographical examination of the throat region is one of the first method of diagnosis. Around 50- 70

percent of all thyroid nodules that are smaller then 1 centimetre can be recognized thanks to ultrasonography. (Javanainen and Mäenpää, 2002).

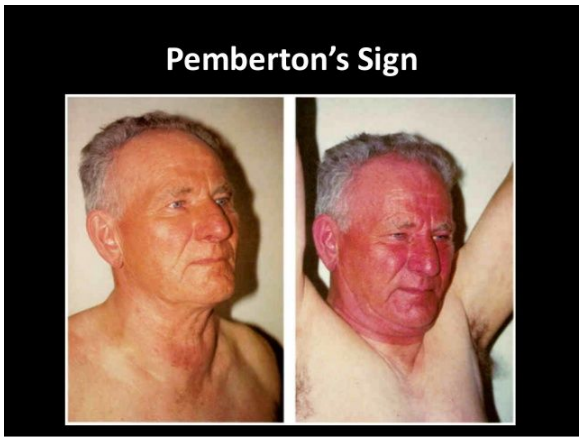

Figure 12. Pemberton sign

For patients suffering from a large thyroid lesion, the pembertons sign is aiding in forecasting the grade of substernal extension. In this picture we can see that the patient is raising his arms over the head. The following is broadening of the mass or airways compression by venous congestion

(Tayde et al. 2014).

Picture source Last access: https://www.pinterest.com/pin/369928556877625722/ (Last access: 14 May, 2017).

Anaplastic carcinomas and lymphomas are problematic to distinguish clinically but can be distinct according to Colledge et al. (2011). Histological studies are made after the surgery to differentiate between follicular adenoma or cancer (Ringborg et al. 2008). Morphologically the neoplasm is containing anaplastic cells. Pathological findings could be large pleomorphic giant cells with osteoclast like multinucleated giant cells, spindle cells with a sacromatous appearance and mixed spindle and giant cells. The cells of the carcinoma are expressing some particular epithelial markers such as cytokeratin (Kumar et al. 2010).

Up to now, there is no effective treatment of anaplastic thyroid cancer. (Colledge et al. 2011). Surgery is seldomly indicated and in few patient's amalgamations of chemotherapy, radiation therapy and surgery could upsurge the survival slightly. (British Thyroid Association and Royal College of Physicians, 2007). It is not always possible to remove the thyroid gland and the lymph nodes (Javanainen and Mäenpää, 2002). By reducing the size of the tumor it is possible to avoid complications and compression that can be so severe that the patient gets

choked to death (Ringborg et al. 2008). When the thyroid gland has been surgically aparted the patient needs thyroxin supplementation in tablet form to replace the thyroid hormones. By thyroxin supplementation, one can avoid symptoms of hypothyroidism and reduce growth of residual cancer cells (Javanainen and Mäenpää, 2002). Prognosis for anaplastic thyroid cancer are very alterable, some patients may endure for 20 years or beyond while other patients are surviving less then a single year (Colledge et al. 2011). While according to Kumar et al. (2010) anaplastic thyroid cancer is almost uniformly fatal and patients with anaplastic thyroid cancers are reaching the mortality rate of 100 percent. The prognosis is worse in anaplastic thyroid cancer compared with the other sorts of thyroid cancer. Roughly 90 percent of individual's decease within six months of diagnosis. Patients may develop lung metastasis or occasionally they have already metastasis in their lung at time of diagnosis regarding Ringborg et al. (2008).

3. MATERIALS AND METHODS

3.1 Study design

The data was collected randomly from Teikas klīnikā in Riga. The analysed cases are from patient that went through ultrasonographical examination and FNAB and was evaluated by TIRADS classification and Bethesda classification.

One patients case history was taken and picture of her photographies was taken.

3.2 Statistical analysis

The collected data was analysed by IBM SPSS 21.0 and Spearman's rho test was used for the correlation between TIRADS and Betesda classifications. Chi square test was used to test the significance of gender in the diagnosis (comparison of two categorical variables). Correlation between TIRADS and Bethesda was also used by Bubble graph, where the bubble size represents number of cases in the subgroup.

3.3 Ethical considerations

The study was approved by The Local Ethics Committee before enrolling the analyzation processes of the patient cases. The entire study was made in accordance by the rules of The Declaration of Helsinki.

Patients case history and photography was taken and added to this thesis with her consent.

4. RESULTS

This study included 298 patients.

4.1 Mean and median age of patients

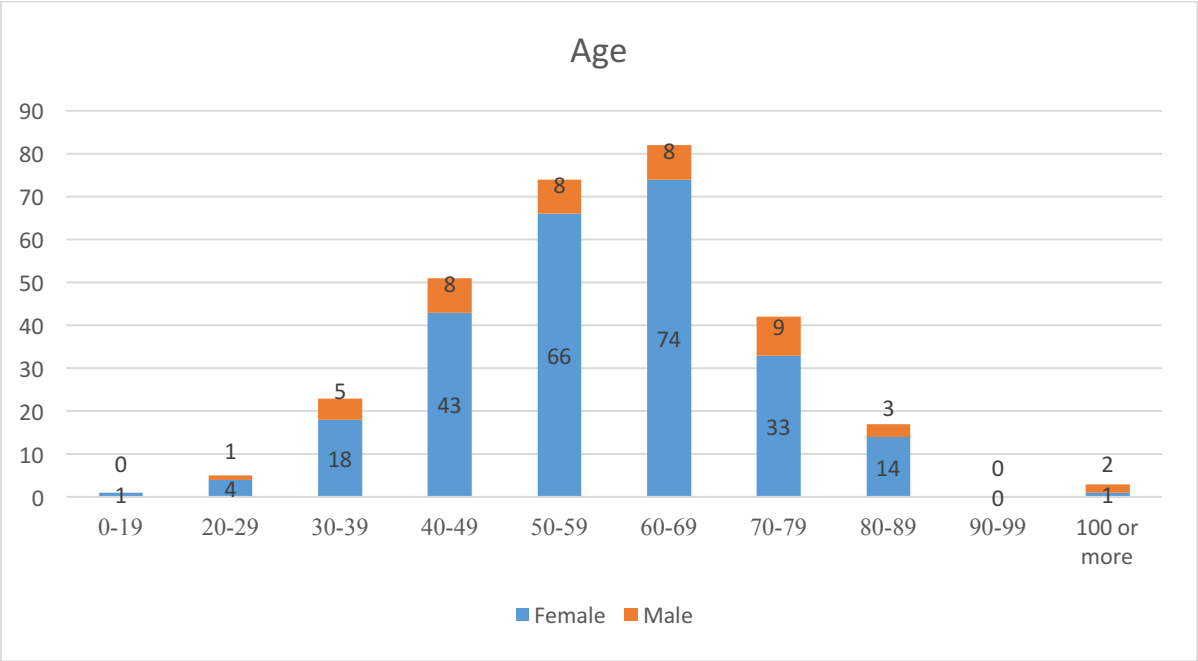

Figure 13. Age distribution in the study group

The patient population were aged 16 to 113

- 85.2% were female
- 14.8% were male.

The mean age was 58.6

- mean age for women 58.5,
- mean age for men 59.5), median age 59

Median age for women 59

Median age for men 60.5,

Mode for age was 59

- 59 for women
- 52 for men.

4.2 TIRADS classification categories among patients

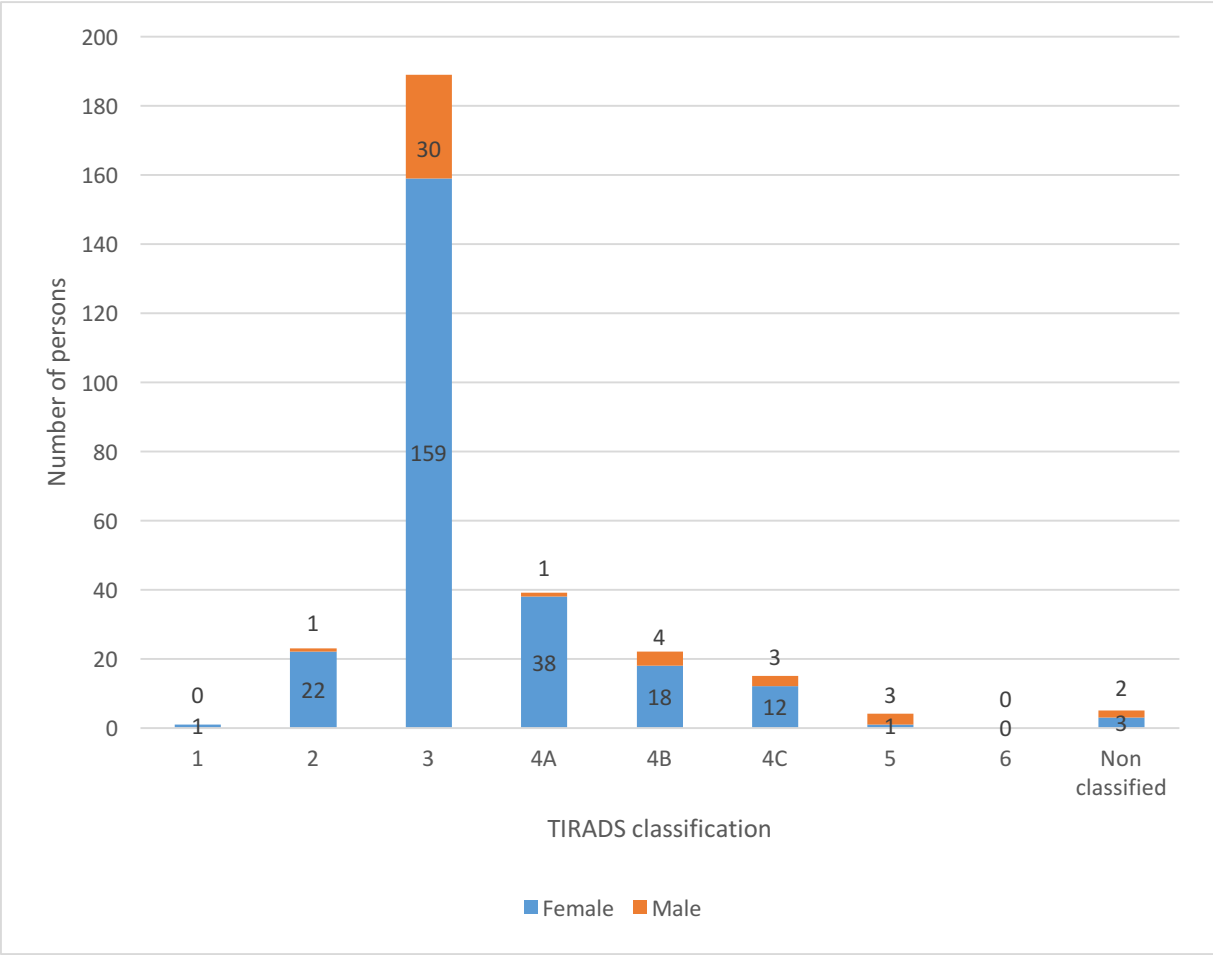

Figure 14. Comparison of patient frequency in TIRADS categories

This same group, when tested using TIRADS approach, showed the following results:

- 0.3% had TIRADS classification 1 (95%CI: 0.1%...1.9%),
- 7.7% had TIRADS 2 (95%CI: 5.2%...11.3%),
- 63.4% had TIRADS 3 (95%CI: 57.8%...68.7%),
- 13.1% had TIRADS 4a (95%CI: 9.7%...17.4%),
- 7.4% had TIRADS 4b (95%CI: 4.9%...10.9%),
- 5.0% had TIRADS 4c (95%CI: 3.1%...8.1%),
- 1.3% had TIRADS 5 (95%CI: 0.5%...3.4%),
- 5 patients were unclassified.

The largest subgroup of individuals had TIRADS classification 3 (low suspicion) with 63.4%. The smallest subgroup of individuals had TIRADS classification 1 (Unchanged Thyroid gland) with 0.3%.

4.3 Betesda classification

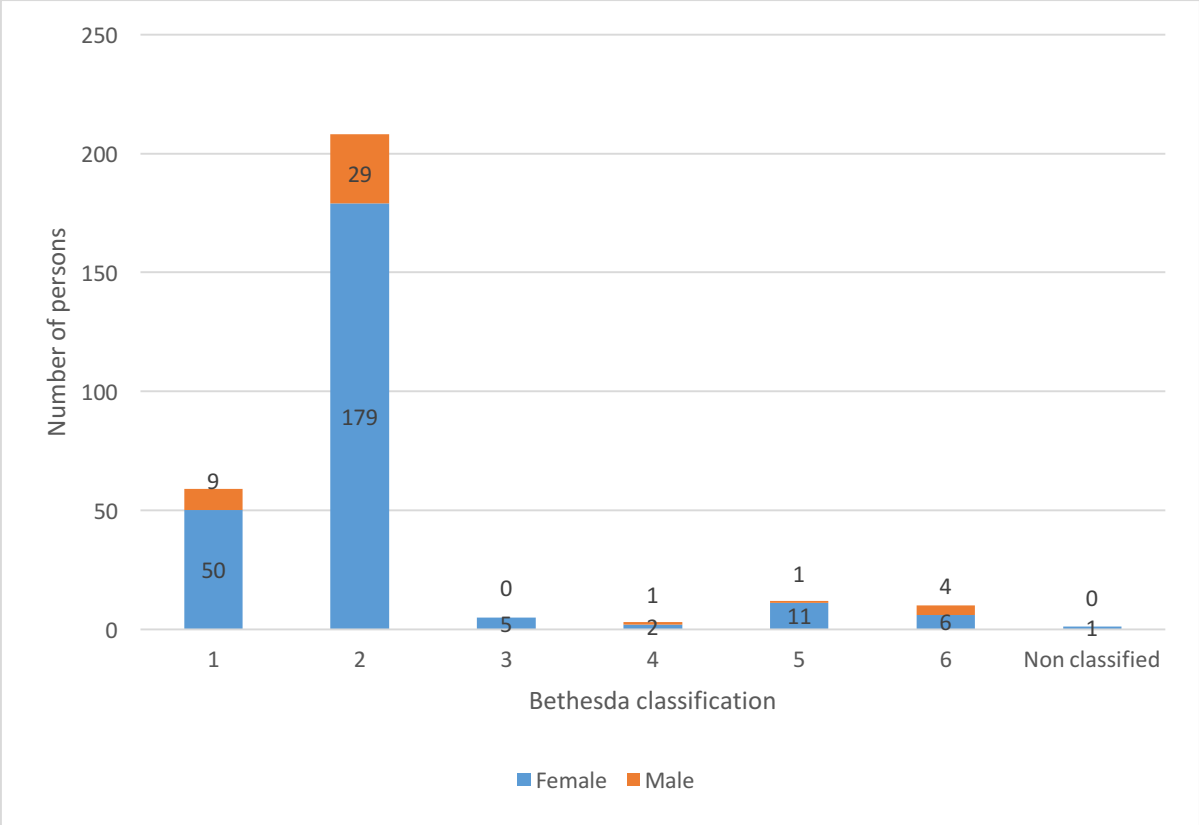

Figure 15. Comparison of patient frequency in BETHESDA categories

The whole patient population have been involved in this analysis where as well

- 19.8% had Bethesda classification 1 (95% Confidence interval (CI): 15.7%...24.7%),
- 69.8% had classification 2 (95%CI: 64.4%...74.7%),
- 1.9% had classification 3 (95%CI: 0.7%…3,9%),
- 1.0% had classification 4 (95%CI: 0.3%...2.9%),
- 4% had classification 5 (95%CI: 2.3%...6.9%),
- 3.4% had classification 6 (95%CI: 1.8%...6.1%)
- 0.3% were not classified (95%CI: 0.1%…1.9%).

This shows that most of the individuals had benign condition and almost 20% needed additional evaluation (classification 1).

Gender had no significant impact on classifications (p=0.28).

Largest subgroups of individuals were in the benign category while largest subgroup of individuals had Tirads classification 3 (low suspicion).

4.4 Spearman's rho test for relationship between Tirads and Betesda classifications

		Bethesda result					
		1	2	3	4	5	6
Tirads result	1	1					
	2	4	19				
	3	35	142	5	3	4	
	4a	6	28			3	2
	4b	5	11			2	4
	4c	4	7			2	2
	5					1	2
	6						

Figure 16. Correlation between TIRADS and Bethesda classification.

Spearman's rho test for relationship between Tirads and Betesda classifications shows weak positive correlation (r=0.182), meaning there is a trend that higher Betesda classifications are observed with higher Tirads classifications. The potential reason can be the lack of Betesda 3 and 4 classifications in the studied data and the high number of Tirads 3 classification (189 cases, which makes up almost 65% of the evaluated cases).

4.5 Correlation between TIRADS and Bethesda by usage of Bubble graph

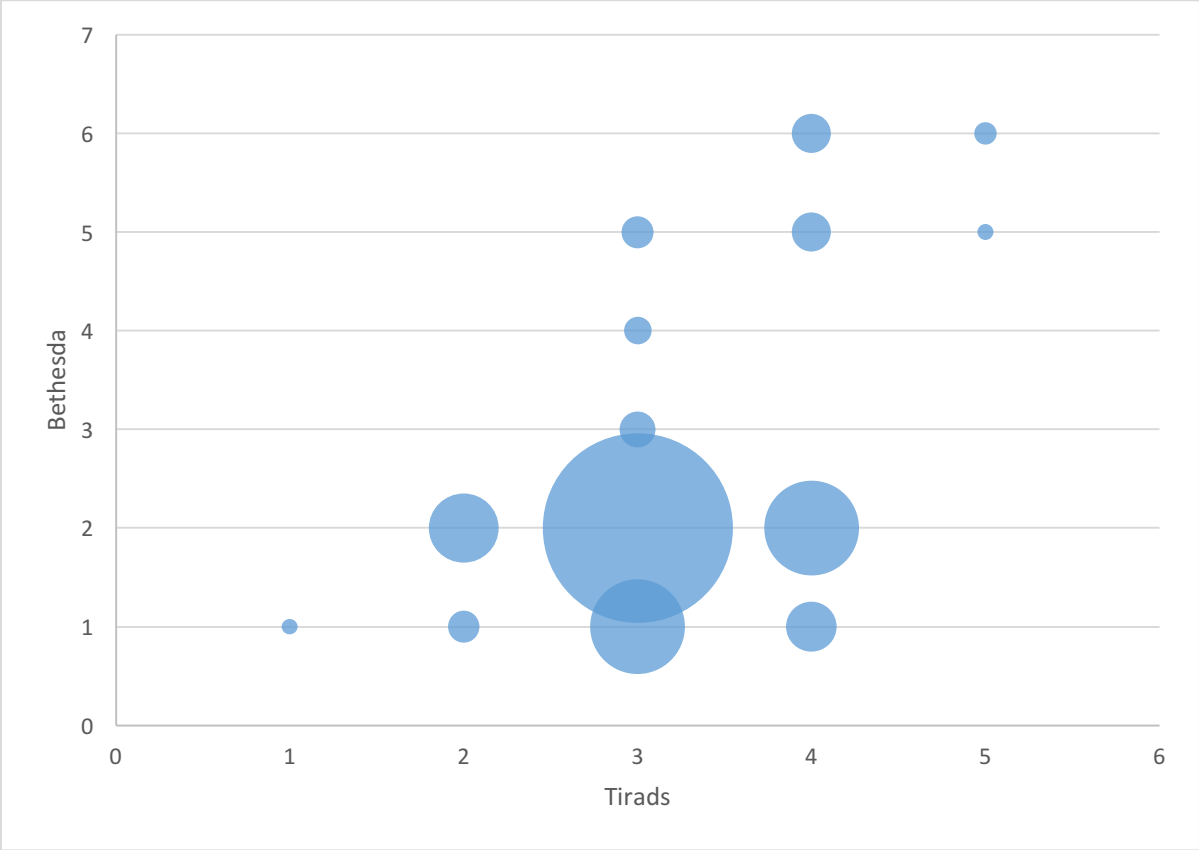

Figure 17. Bubble graph usage for a visual view of the correlation between TIRADS and Bethesda classifications.

The tendency can be seen in the bubble graph – the diagonal from bottom left corner to upper right corner shows the positive correlation trend, while the largest bubble (bubble size represents number of cases in the subgroup) is at crosspoint of Tirads 3 and Bethesda 2.

4.6 Correlation between TIRADS and Bethesda considering results as benign vs malignant

		Bethesda	
		Benign	Malignant
Tirads	Benign	19	0
	Malignant	193	25

Figure 18. Correlation between TIRADS and Bethesda considering results as benign vs malignant by considering TIRADS 3,4,5 and Bethesda 4,5,6 as positive results (Malignant).

This shows that there should be high disagreement between both tests on the benign end of classification spectrum. Therefore, both tests were analyzed for agreement. Whereas Tirads 3 is considered suspicious for malignancy, at first it was assumed to be a positive result for malignancy in the same group with other classifications pointing to malignancy (therefore Tirads 3, 4, 5 or 6 were seen as positive, i.e., pointing to malignancy, and Tirads 1 and 2 were considered negative, i.e., benign). For Bethesda test, the group with classification 1 was not considered for comparison as it was non-conclusive and needed more evaluation. Hence, Bethesda classifications 2 and 3 were considered negative (benign) and Bethesda classifications 4, 5 and 6 were considered positive (pointing to malignancy). The crosstabulation of these results is given in the table. If we consider Bethesda a "golden standard" for this comparison, the Tirads test classifies all malignant (Bethesda classification 4, 5 or 6) as malignant, giving them classification 3, 4 or 5. This means perfect sensitivity (100%) but on the other hand – it classifies almost all of the subjects as having malignant conditions (218 out of 237 who were classified), resulting in very low specificity of 9% and high false positive rate of 81.4%. This would mean high expenses for further evaluation using other tests and many unnecessary tests, which can be unpleasant to the patients. The tests with this cut-off show very differing results and proportions of positive classifications ($p<0.001$).

		Bethesda	
		Benign	Malignant
Tirads	Benign	166	7
	Malignant	46	18

Figure 19. Correlation between TIRADS and Bethesda considering results as benign vs malignant by considering TIRADS 4,5 and Bethesda 4,5,6 as positive results (Malignant).

Since the previous exploration of data showed high inconsistency in the subgroup where Tirads classification was 3 (and most of the corresponding Bethesda classifications were 2, i.e. benign), the Tirads classification 3 was added to the negative (benign) group. The resulting crosstabulation is given in the table. Again, considering Bethesda as the "golden standard" for this comparison, the resulting sensitivity dropped to 72.0%. This was due to 7 cases considered malignant (or with suspicion of malignancy) by Bethesda were classified as benign using Tirads approach (Tirads classification 3). But in this case the large subgroup of Bethesda 2 / Tirads 3 moved to the true negatives and the specificity of this test increased to 78.3% and rate of false positives dropped to 19.4%. This means that, although we would miss 28% of the malignant conditions (all Bethesda 4 and 5), the percentage of specificity and true positives would greatly increase.

		Bethesda	
		Benign	Malignant
Tirads	Benign	226	8
	Malignant	1	2

Figure 20. Correlation between TIRADS and Bethesda considering results as benign vs malignant by considering TIRADS 5 and Bethesda 6 as positive results (Malignant).

If only the highest score of both tests is considered positive (Tirads 5 due to lack of classification 6 cases), the crosstabulation would look as in table.
Although the sensitivity of Tirads (considering Bethesda the "golden standard" for comparison) would drop to 20%, specificity would be 99.6% and Tirads would only produce 1 false positive result (classified Bethesda 5).

4.7 Incidence and proportion of calcification

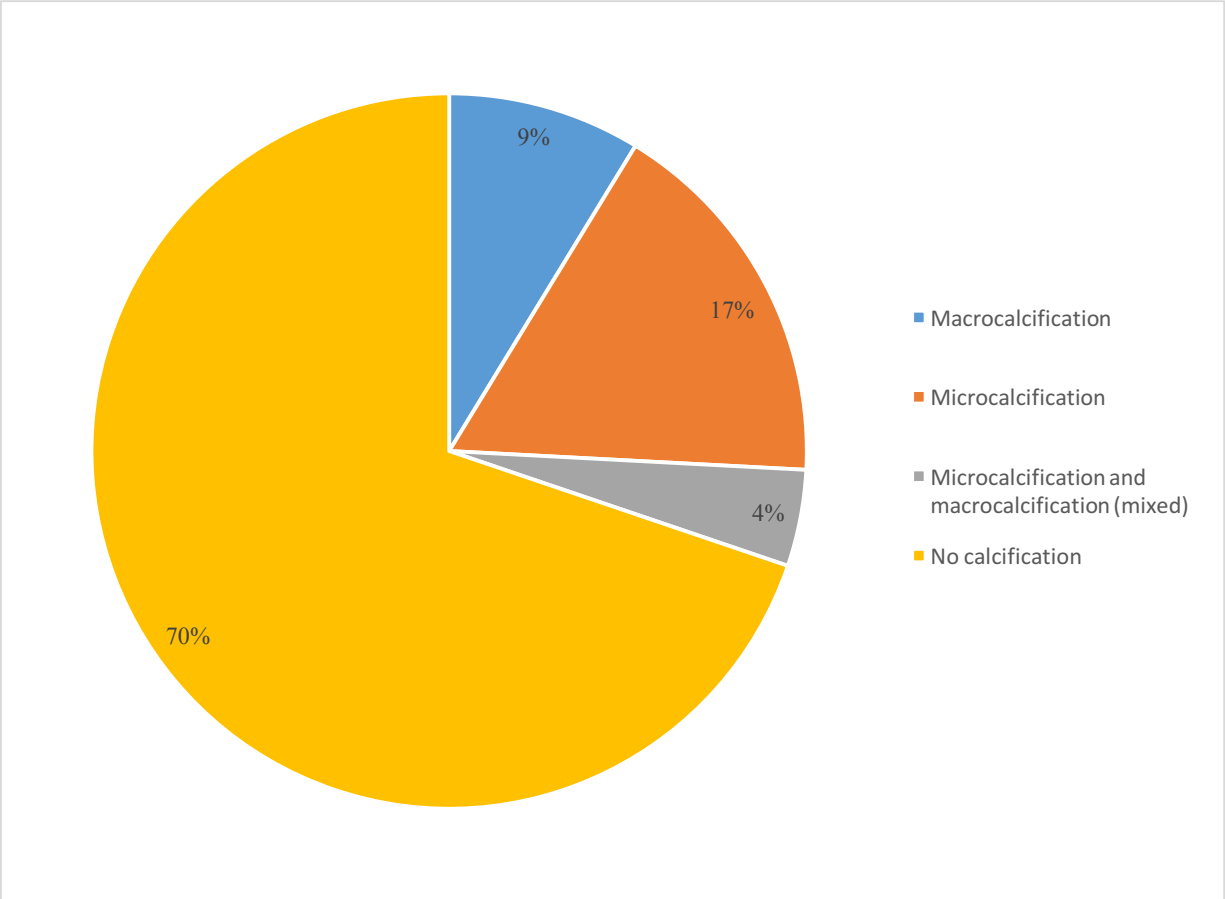

Figure 21. The proportion of calcifications.

When comparing the calcification pattern of a nodule we found that 8.7% of the patients had macrocalcification (95%CI: 6.0%...12.5%) and 17.1% of the nodules had microcalcification (95%CI: 13.3%...21.8%), 4.4% had microcalcification and macrocalcification (95%CI: 2.6%...7.3%) meaning that some parts were microcalcified and some macrocalfied. All detected through ultrasonographical examinations. When studying the the effect or influence of gender, we couldn't find any impact of gender on calcification (p=0.46).

4.8 Incidence and proportion of homogenecity

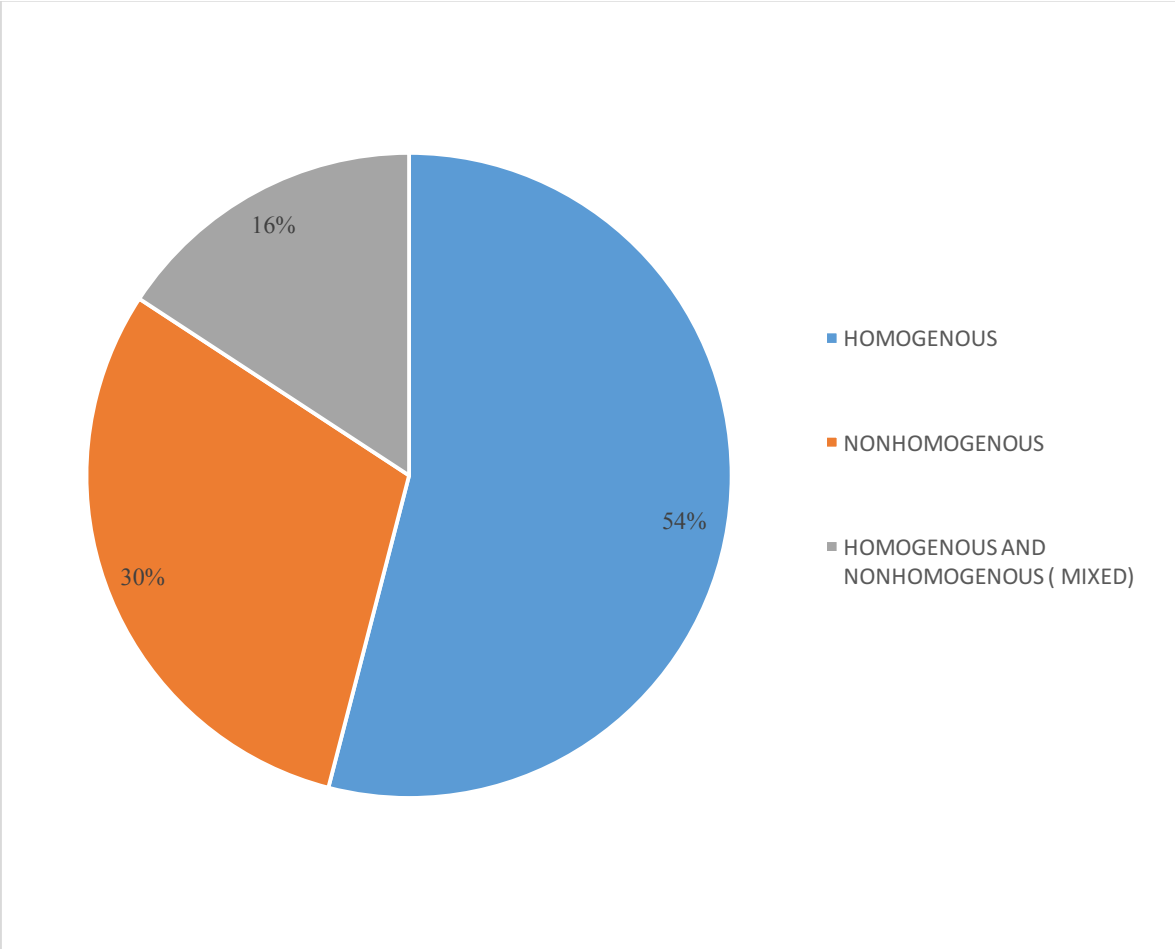

Figure 22. homogenecity and incidence compared in all patient population

Homogeneity is more common the percentage is 54.0 (95%CI: 48.4%...59.6%), 30.2% had nonhomogenous (95%CI: 25.3%...35.6%) least common condition was to have a nodule that is mixed (homogenous/ non homogenous areas) where the percentage is 15.8% (95%CI: 12.1%...20.3%).

4.9 Gender influence on homogenecity

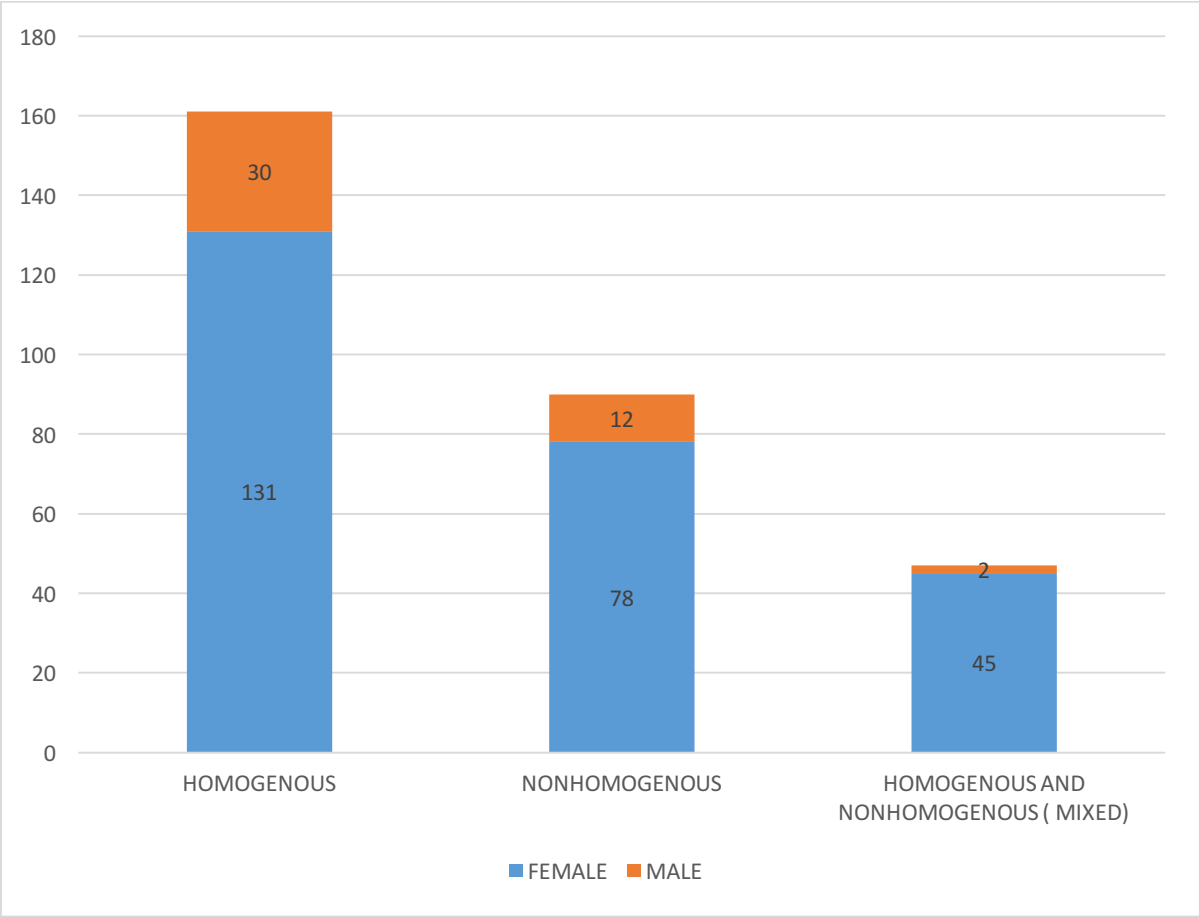

Figure 23. The influence of homogenecity and gender

When comparing the different sexes and the effect of homogenecity. We found that gender has an effect on homogenecity. Men have non-homogenous structure more often (p=0.045). 131 females and 30 male had a homogenous pattern while non homogenecity was seen in 12 male patients and 78 female patient. Considering that the total number of female patients are more in our studied data. The calculated results are proving that nonhomogenecity is seen more often in male compared to female.

4.10 Circumscription and incidence

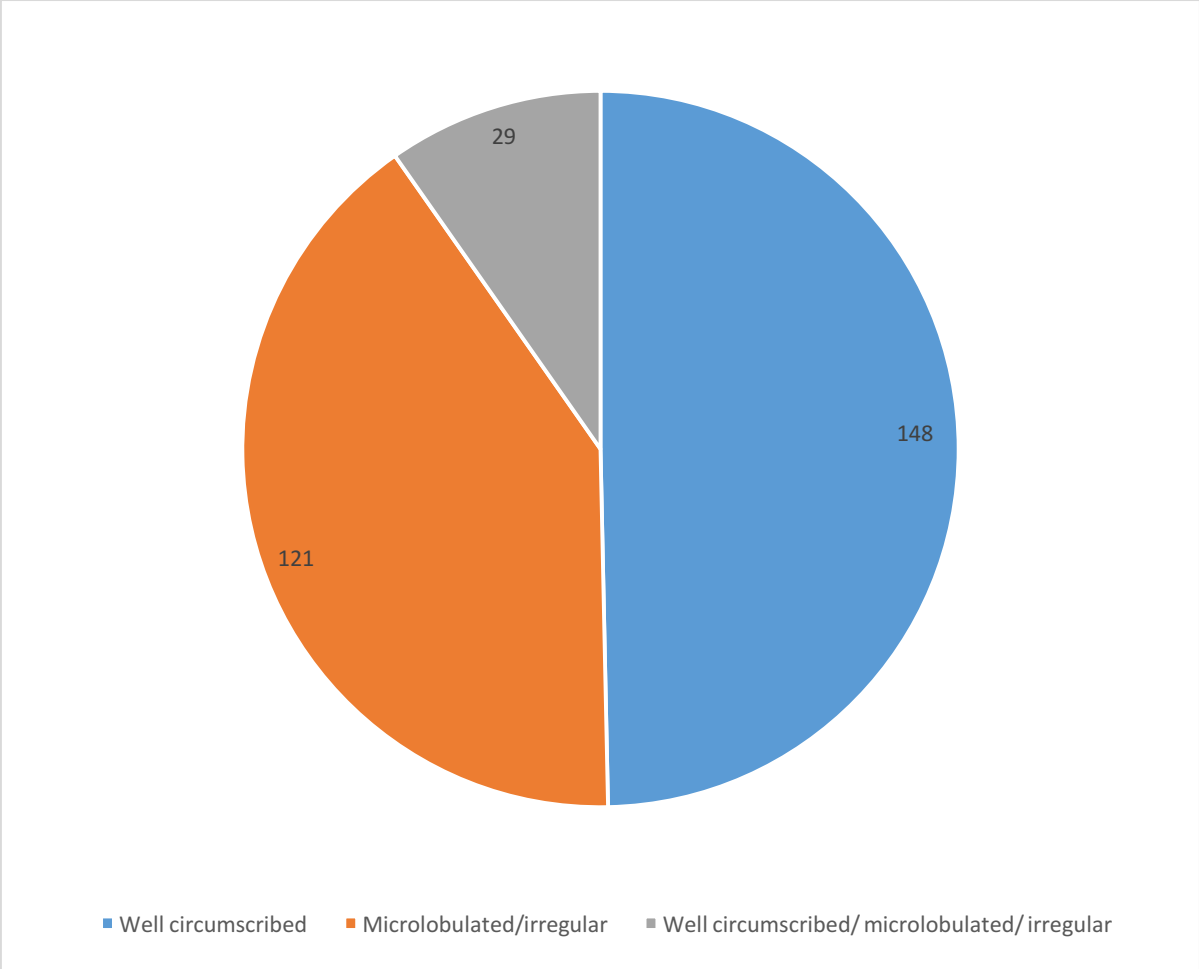

Figure 24. Evaluation of the different circumscriptions that existed in the patient group

Out of 298 patients 148 of them a well circumscribed nodule, so 50.0% had well circumscribed (95%CI: 44.0%...55.3%), while 40.6% had microlobulated/irregular (95%CI: 35.2%...46.3%), only 29 (9.7%) patients had a mixture of well circumscribed/ microlobulated/ irregular nodule (95%CI: 6.9%...13.6%).

4.11 Gender influence on circumscription and incidence

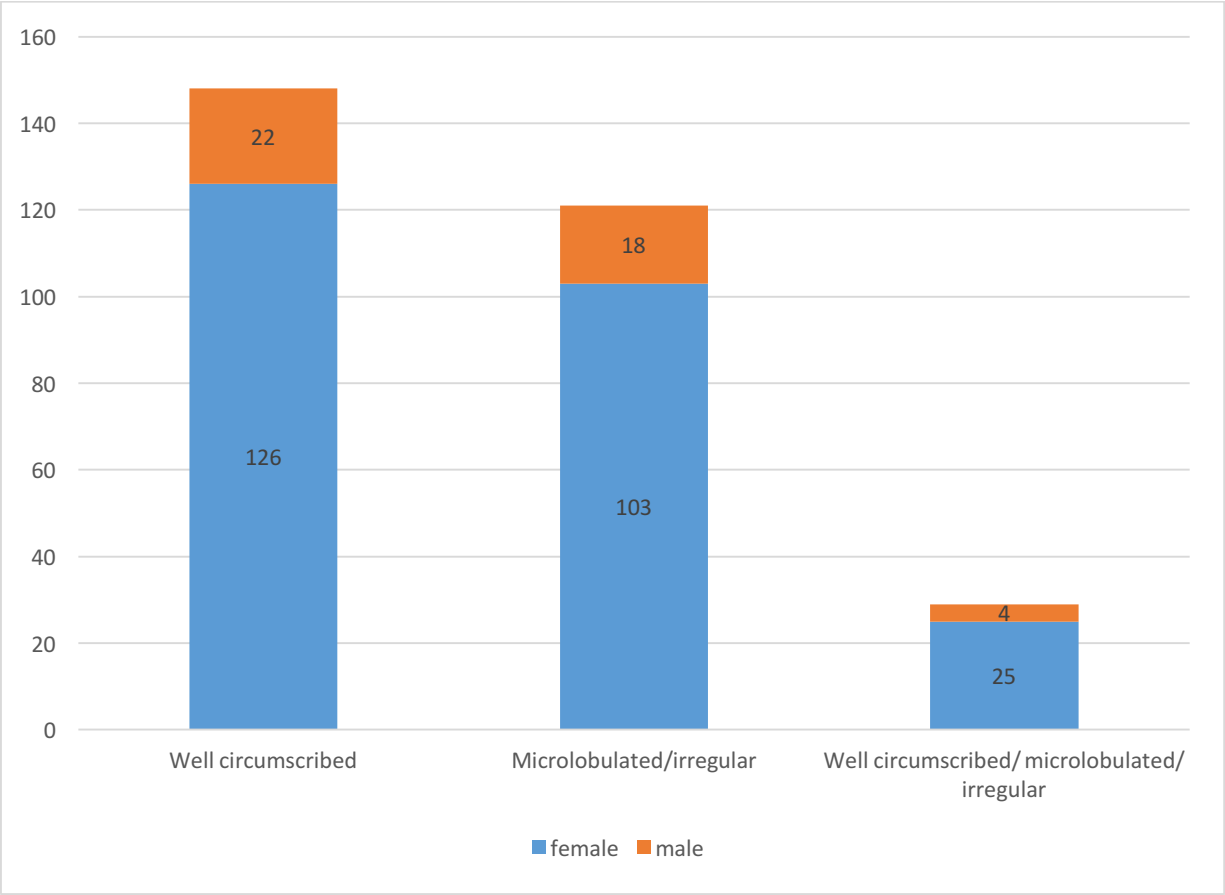

Figure 25. Evaluation of gender influence on the different circumscriptions

Circumscription was the same in both genders (p=0.99). Therefore, we can not conclude out of the results we received from our study that gender has any impact on the circumscription and its representation.

4.12 Incidence and proportion of single nodule versus multiple nodules

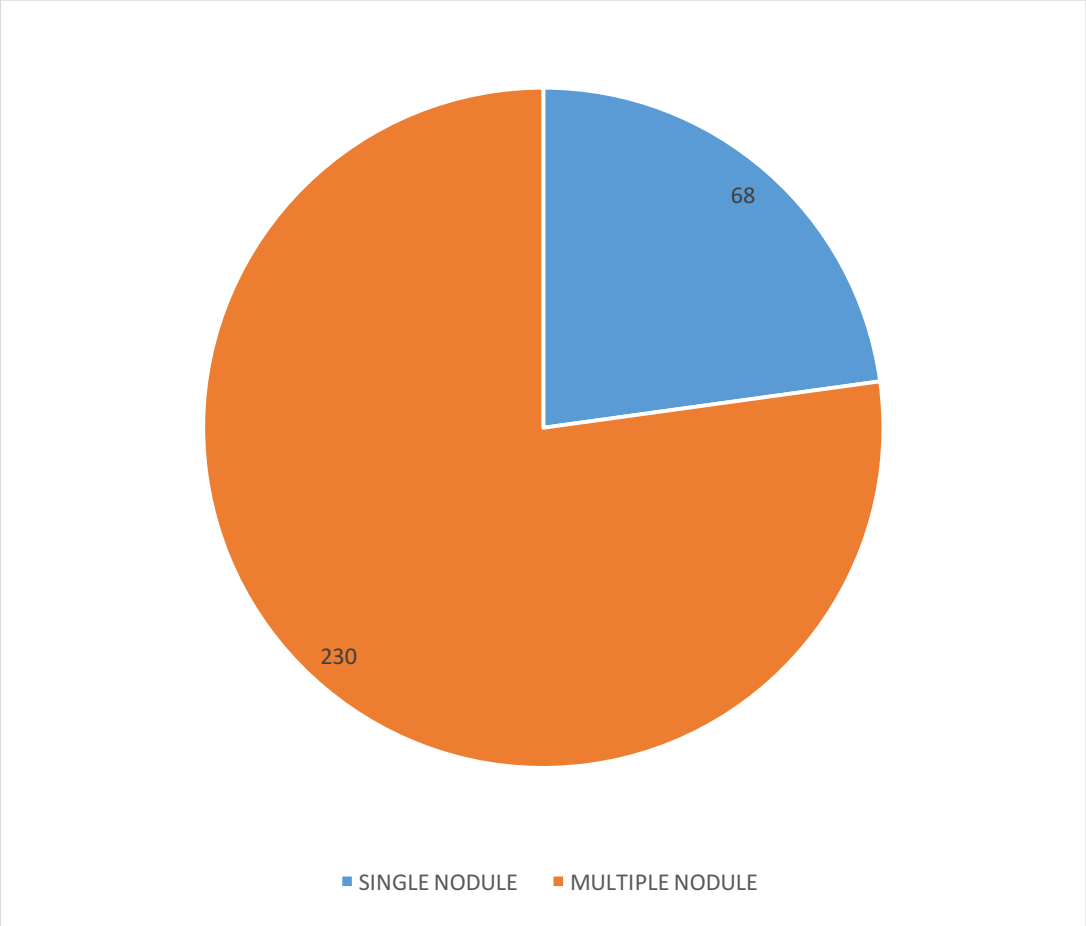

Figure 26. Comparisional incidence of single nodules and multiple nodules.

Most of our patients had multiple nodular pattern on the ultrasonographical features, 77.2% (95%CI: 72.1%...81.6%). 22.8% had single nodule (95%CI: 18.4%...27.9%),
Again, the gender had no potentialities to affect the nodularity since the incidence was the same in both male and female (p=0.99).

4.13 Proportion of size

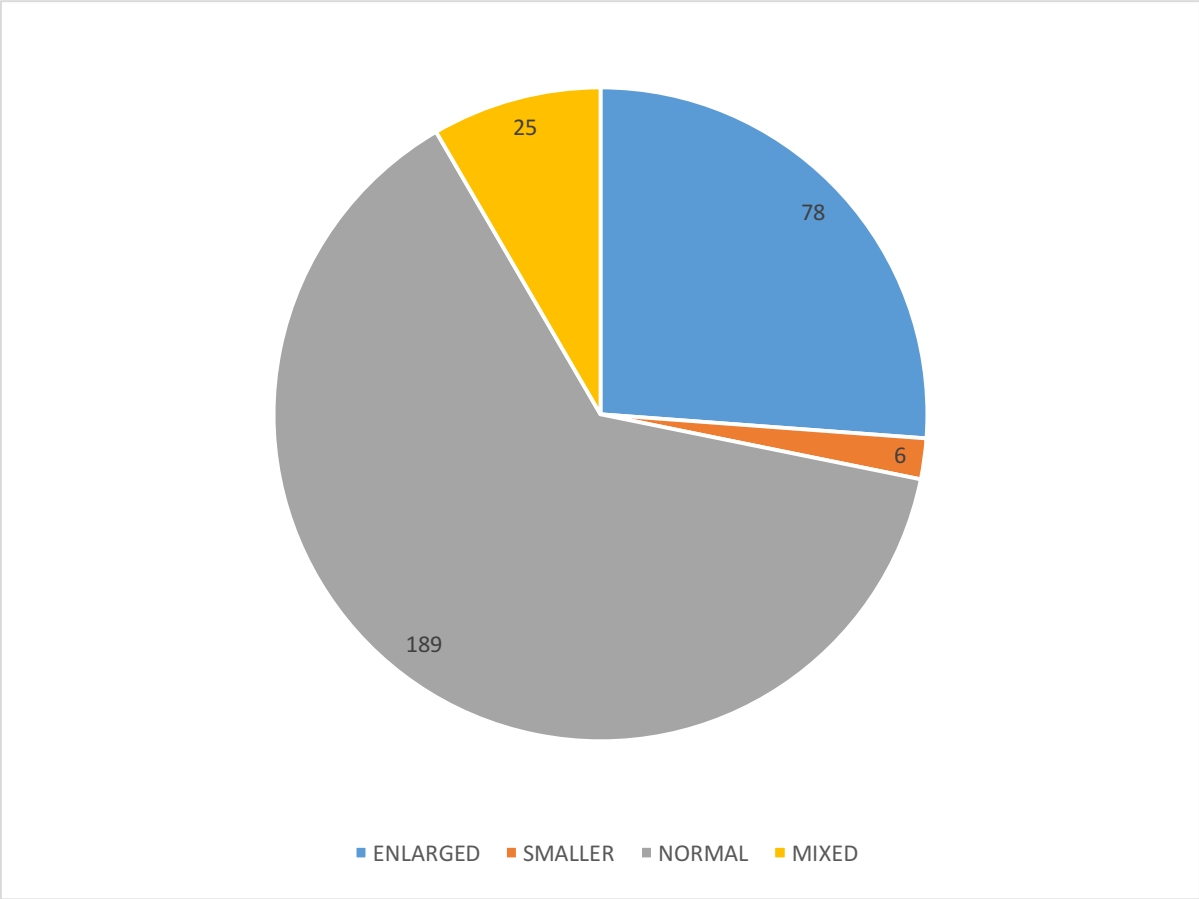

Figure 27. Comparisional evaluation of the proportion of nodule, enlarged, smaller or normal sized nodule.

78 out of 298 patients 26.2% had an enlarged nodule (95%CI: 21.5%...31.4%), while 2.0% had smaller (95%CI: 0.9%...4.3%), which makes it the smallest subgroup in this study. 8.4% had mixed (95%CI: 5.8%...12.1%). 189 out of 298 patients, 63.4% had normal size (95%CI: 57.8%...68.7%), which makes it the larges subgroup, meaning that most of our patients had a normal size.

4.14 Gender influence on proportion of size

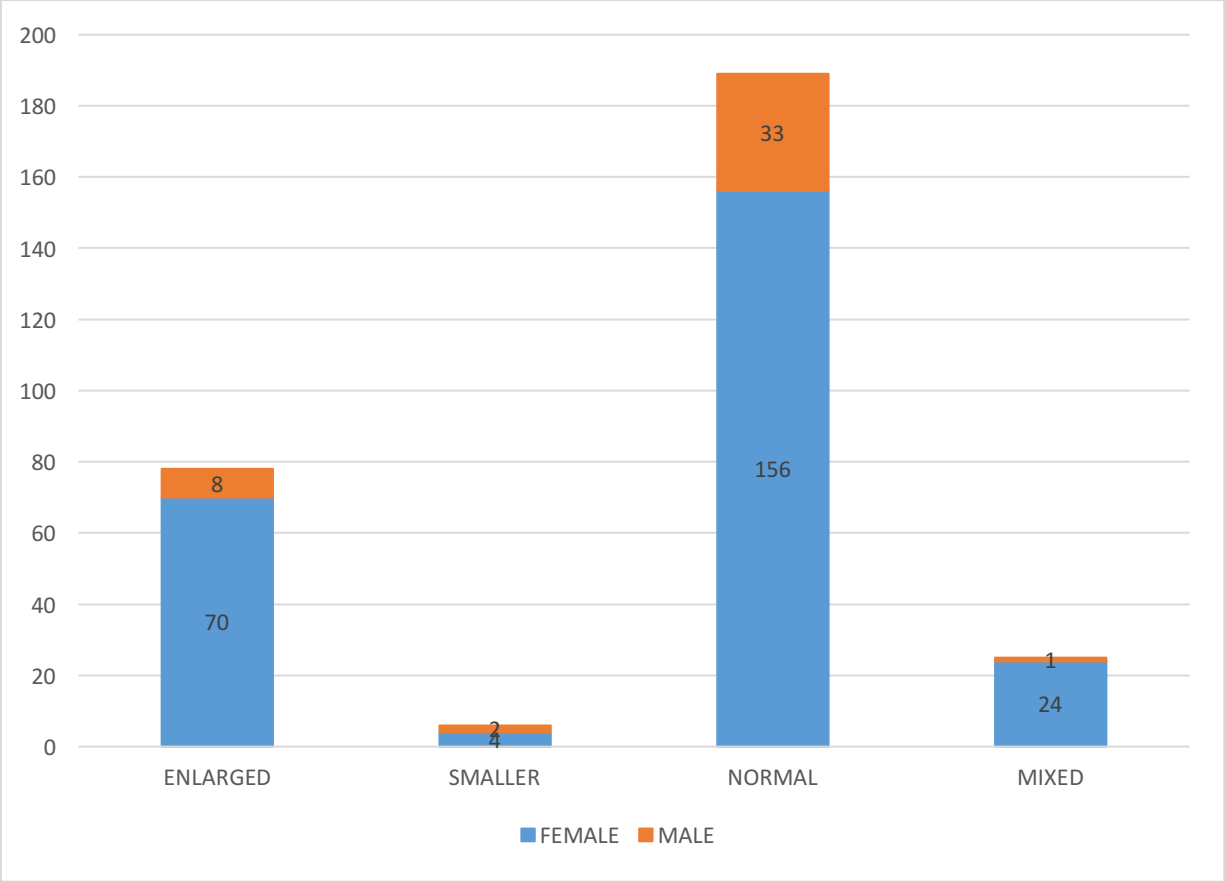

Figure 28. Influence of gender on of the proportion of nodule. Evaluation of Enlarged, smaller or normal sized nodule.

However, size was the same for both genders (p=0.098). Therefore, patients gender does not influence the size.

4.15 Proportion of smoothness

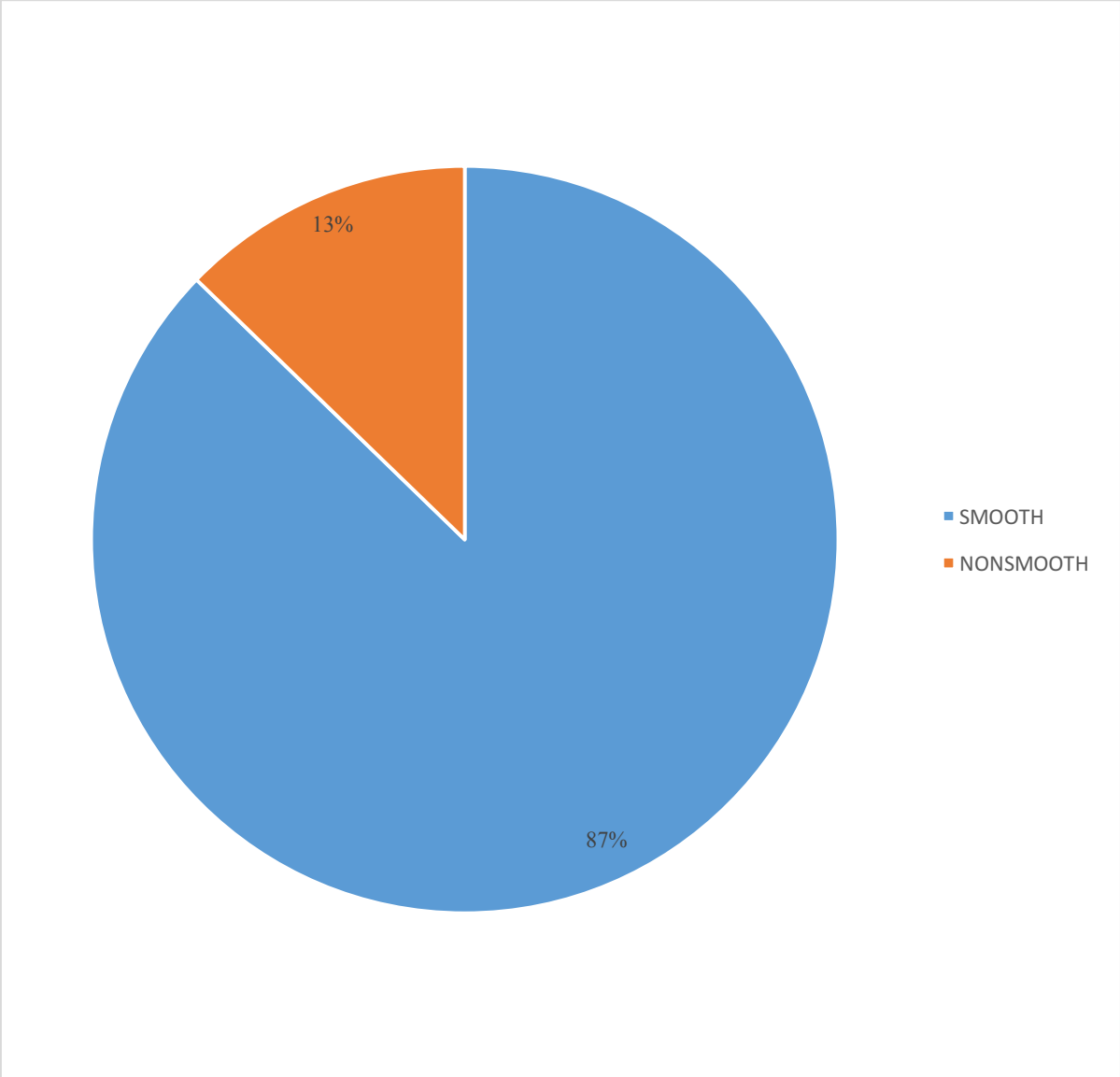

Figure 29. Proportion of smoothness versus nonsmoothnes evaluated in the entire patient populace.

Most of our patient had a smooth pattern. The amount of smoothness is 87.3% (95%CI: 83.0%...90.6%), while only 12.7% had non-smooth (95%CI: 9.4%...17.0%).
Again, Smoothness was the same for both genders (p=0.85).

4.16 Proportion of swollen versus non LN in neck

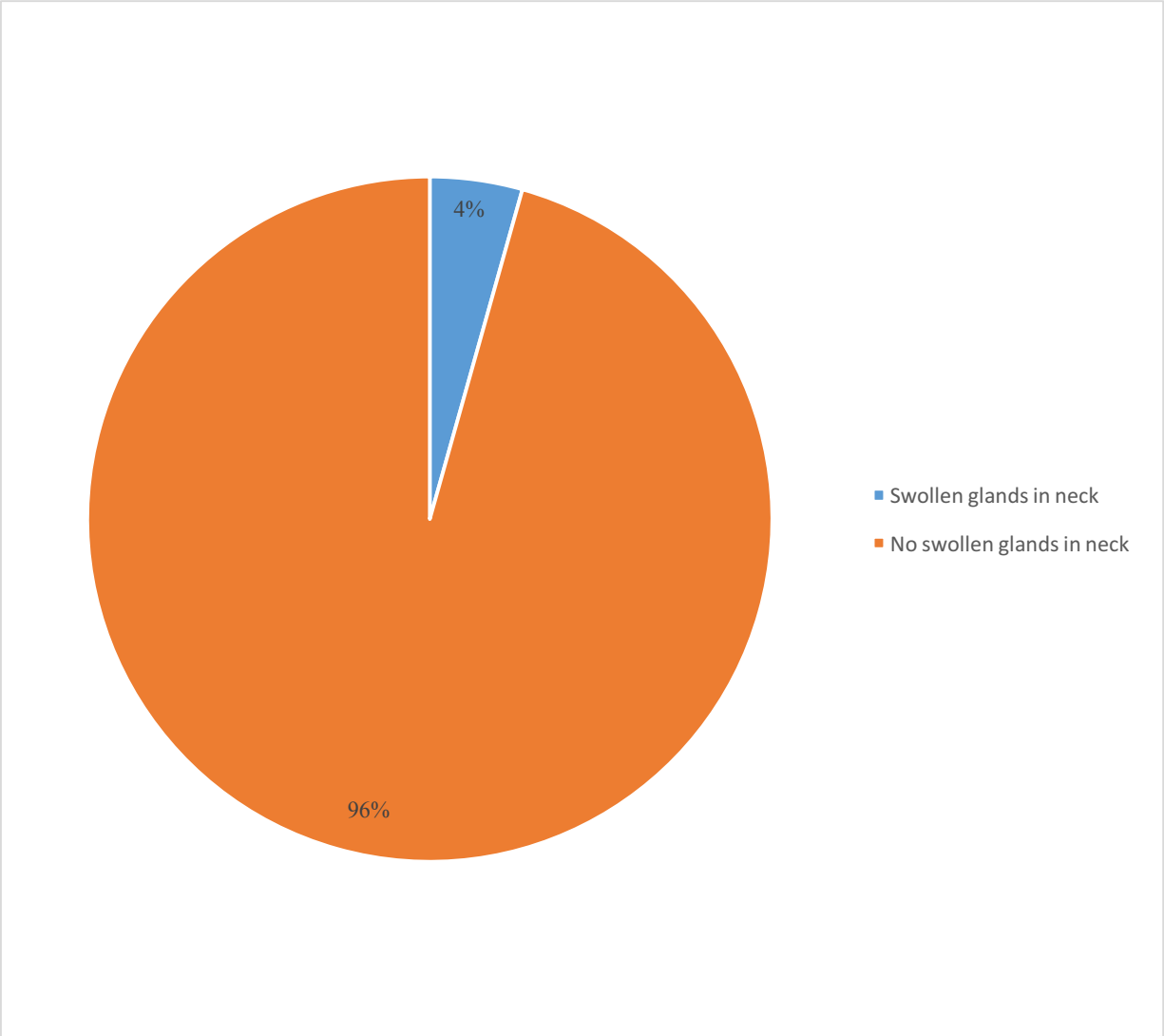

Figure 30. Percentage of swollen versus non LN in neck evaluated in the total populace of patients.

The ultrasonographical results showed that 4.4% had swollen lymph nodes (95%CI: 2.6%...7.3%) while most of the patients didn't have any enlargement.

4.17 Gender influence on proportion of swollen versus non swollen LN in neck region.

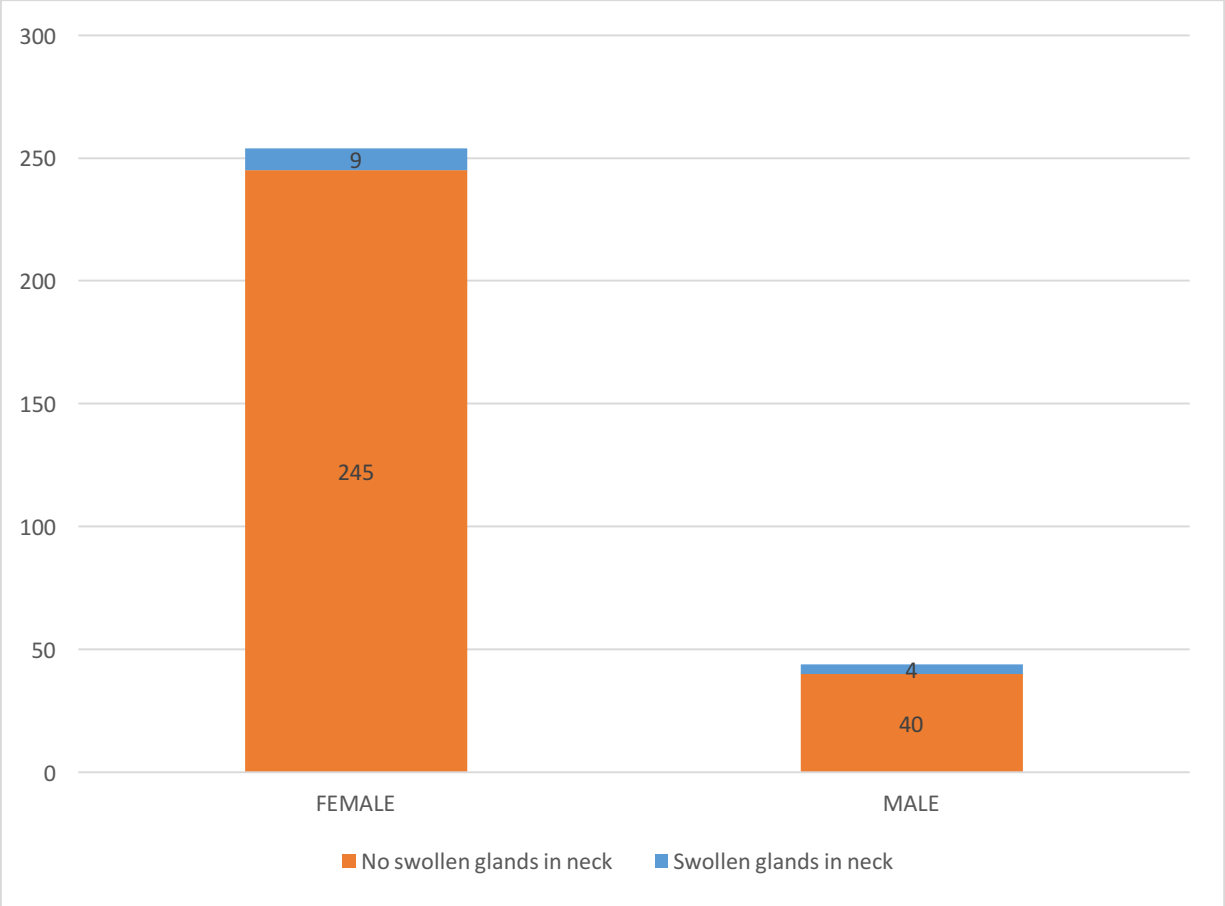

Figure 31. Percentage of swollen versus non LN in neck influenced by gender

There was no difference in the proportion of those with swollen LN, however the difference can be assumed marginally significant (p=0.058) and a study with a larger sample could show that males have swollen LN more often (9.0% of men had swollen LN in neck, while only 3.5% of women had them).

4.18 Incidence of echogenecity among patients

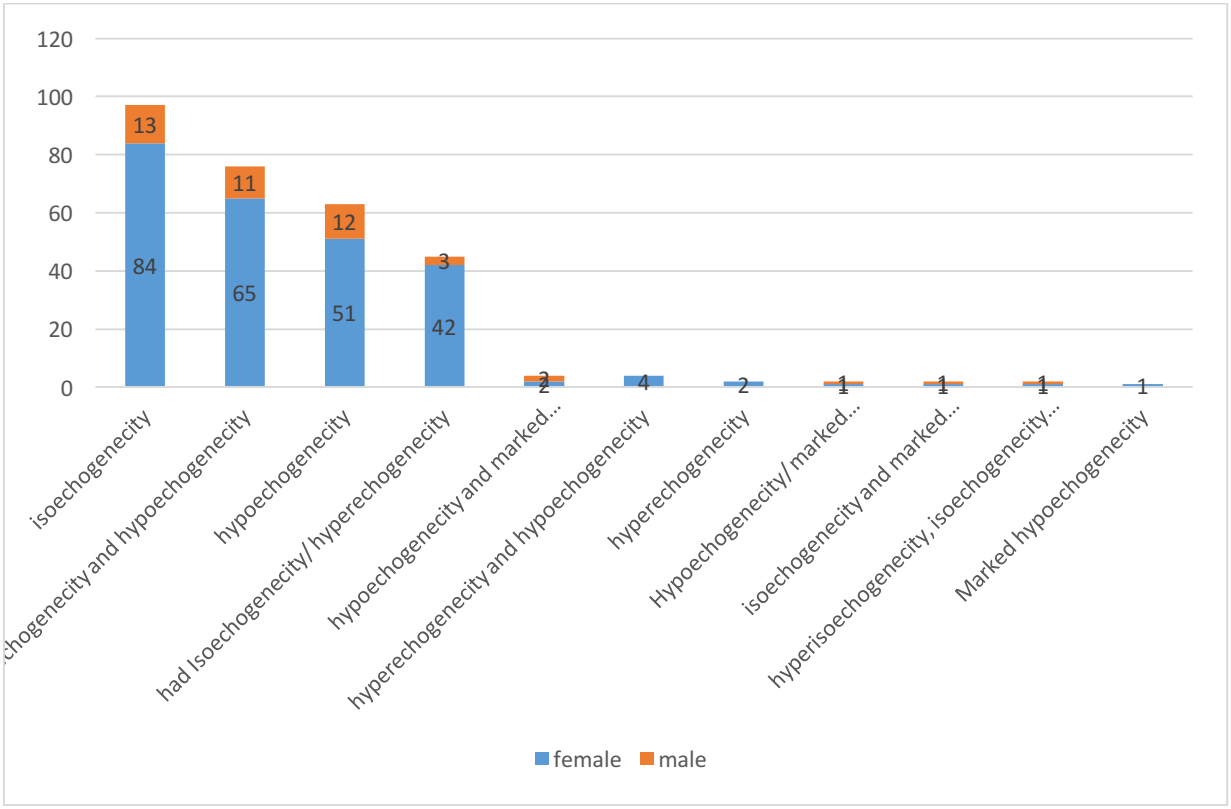

Figure 32. Incidence of type of echogenecity found in the total patient groups and influence of sex.

1. 26% had isoechogenecity (95%CI: 27.5%...38.1%)
2. 25.5% had isoechogenecity and hypoechogenecity (95%CI: 20.9%...30.7%)
3. 21.1% had hypoechogenecity (95%CI: 16.9%...26.1%),
4. 15.1% had isoechogenecity/ hyperechogenecity (95%CI: 11.5%...19.6%),
5. 1.3% had hypoechogenecity and marked hypoechogenecity (95%CI: 0.5%...3.4%),
6. 1.3% had hyperechogenecity and hypoechogenecity (95%CI: 0.5%...3.4%)
7. 0.7% had hyperechogenecity (95%CI: 0.2%...2.4%)
8. 0.7% had hypoechogenecity/ marked hypoechogenecity/ isogenecity (95%CI: 0.2%...2.4%)
9. 0.7% had isoechogenecity and marked hypoechogenecity (95%CI: 0.2%...2.4%)
10. 0.7% had hyperisoechogenecity, isoechogenecity and hypoechogenecity (95%CI: 0.2%...2.4%)
11. 0.3% had Marked hypoechogenecity (95%CI: 0.1%...1.9%).

Men have more of marked hypoechogenecity (p=0.046)

4.19 Vascularity

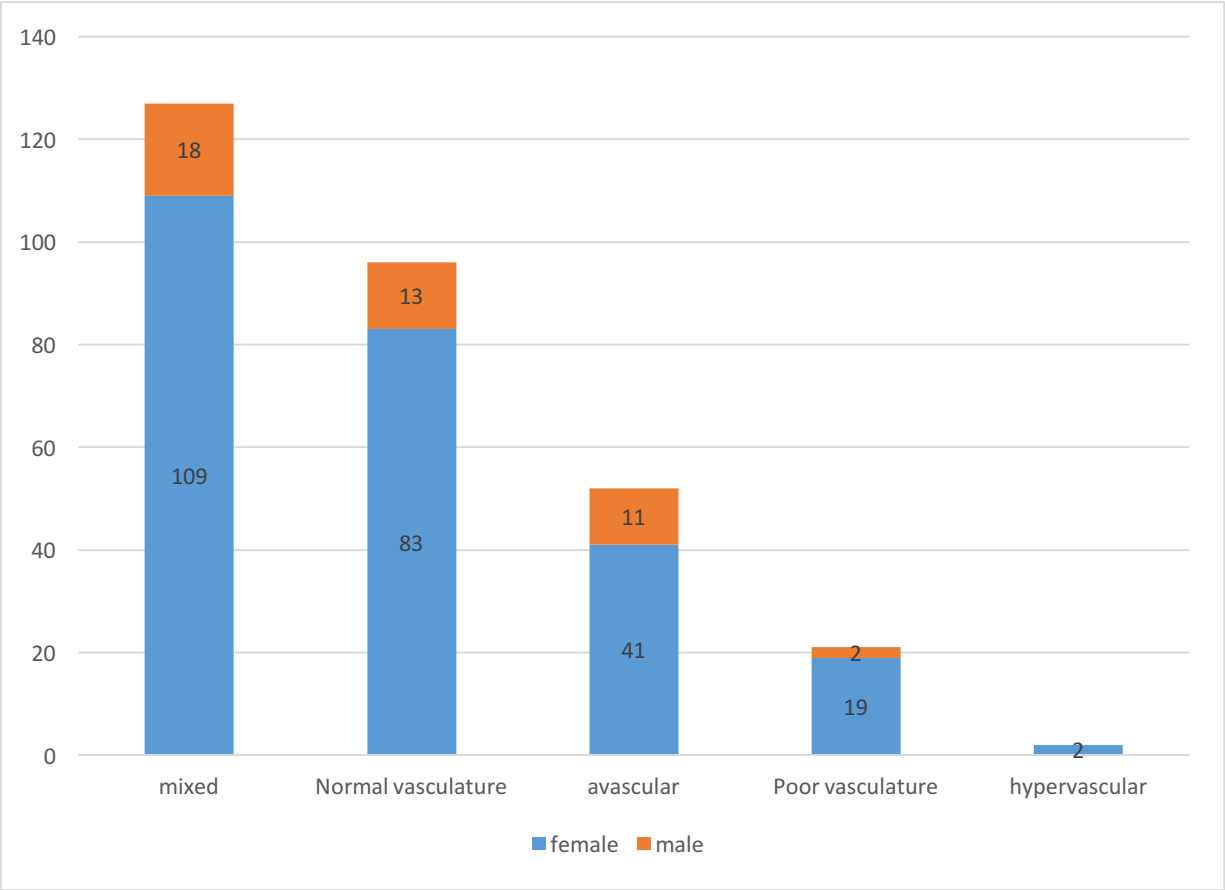

Figure 33. characteristic of vascularity among patients and the influence of sex.

1. 32.2% had normal vasculature (95%CI: 27.2%...37.7%),
2. 17.5% had avascular (95%CI: 13.6%...22.2%),
3. 7.1% had poor vascularization (95%CI: 4.7%...10.5%),
4. 42.6% had mixed (95%CI: 37.1%...48.3%),
5. 0.7% had hypervascular (95%CI: 0.2%...2.4%).

When comparing gender differences and the effect on vascularity, we found out that gender has an effect. The proportion of the conditions are the same for both genders except for vascular, which was more commonly seen in men (p=0.01).

5. DISCUSSION

Worldwide several millions of people are suffering from thyroid gland diseases (Tan and Gharib 1997). Multiple studies have demonstrated the practicality of US and it ability to distinguish benign from malignant nodules. The explanation contains the US features, category and description so we can get an improved understanding of the picture of the nodule and so we can be able to identify the nodule more exactly. The results achieved by US is also a predictive value whether a FNAB should be perform or not (Kamran et al. 2013). FNAB is the best and the most specific choice for diagnosis of thyroid carcinomas (Pacini et al. 2006).

In our patient sample the patients that went through US and FNAB were aged between 16-113. The mean age was 58.6. For female it was 58.5 and for men 59.5. When studying the median age, the results showed us that median age for female was 59 and 60.5 for male. Finally, the mode of age results showed us that female has mode of age of 59 and male has 52. When comparing different age groups, we could see that most common age group that went through US and FNAB was between 60- 69. This age group is the most common age set in both sexes. In total 74 female and 8 male fits in this categorical age group. Only one patient fit in the age group from 0- 19 making it the least conjoint group.
Around one third of adult's populace has a thyroid nodule on ultrasonographic examination (Tan and Gharib 1997, Ezzat et al1994) and fewer then 10 percent are not benign (Papini et. al 2002). While in our study 3.4% had classification 6 (95%CI: 1.8%...6.1%), 6 of those patients were female and 4 of them male and according to Pacini et al. (2006). Carcinomas are not as common as nodules are which our results are agreeing on. In Chandramohan et al. (2016) study out of 238 patients 118 nodules were malignant, 75 nodules in female and 43 nodules in male. In our research gender had no significant impact on the classifications ($p=0.28$). Regarding Tayde et al. (2014) the risk of malignancy is double as common when a thyroid nodule is present. While in the study made by Chandramohan et al. (2016) malignant nodules were more common among male patients ($P = 0.01$). 175 nodules were benign, 119 nodules in female and 35 nodules in male. When they compared different age groups they couldn't find any significant variance in the mean age among benign and malignant variations. Mean age for benign changes was 42.8 ± 12.7 years and mean age for malignant nodules was 43.8 ± 13.8 years ($P = 0.657$). The results we received from our research shows that 69.8% had classification 2 (95%CI: 64.4%...74.7%). In total 179 female nodules and 29 male nodules were benign. The largest subgroups of individuals were in the benign category

while the smallest subgroup was in Bethesda diagnostic category 4 meaning that the nodules were follicular neoplastic or had suspicious to be follicular neoplasm.

FNA in combination with US assessments are regularly used to estimate patients with thyroid malignancies (Solomon et al. 1996). TIRADS classification is outstanding as it describes all changes being observed by US (Papini et al. 2002). The conclusion whether or not performing a FNA is based on the malignancy and prognostic risk. FNAB of thyroid gland is an accurate analytical method that is regularly used in evaluation of nodular thyroid diseases (Gharib and Papini, 2007). FNAB is a safe, trustworthy and a powerful procedure for diagnosis of pathologies according to Shin, J. H. et al. (2016). The largest subgroup of individuals had TIRADS classification 3 (low suspicion) with 63.4% in our studied data which is similar to Moifo et al. (2013) results, who also had a dominance of TIRADS 3 category in their studied populace. The least common subgroup had 0,3% TIRADS classification 1, meaning that the nodule is benign (95%CI: 0.1%...1.9%).

Moon et al. (2015), had in total 7.3% malignant and 92.7% benign nodules. While in our study lower number 3.4% were malignant and we had higher benign outcomes, 69.8%.

When comparing the relationship between TIRADS and Bethesda classifications we found a weak positive correlation ($r=0.182$), defining that there is higher Betesda classifications observed with higher Tirads classifications. When we compared Correlation between TIRADS and Bethesda considering results as benign vs malignant by considering TIRADS 3,4,5 and Bethesda 4,5,6 as positive results (Malignant). The results we achieved was presenting us a perfect sensitivity (100%) but, it categorizes almost all of the nodules as having malignant disorders (218 out of 237 who were classified), consequential in very low specificity of 9% and great false positive rate of 81.4%. The tests with this cut-off show very differing results and proportions of positive classifications ($p<0.001$). In the research study made by Singaporewalla et al. (2017) The accordance with FNAB was 83%. While the sensitivity was 70.6% and the specificity was 90.4%. Since the previous exploration we made showed discrepancy and showed that the risk of malignancy was significantly high, we decided to cut off TIRADS 3 and add it to the negative (Benign) group. So, in the Correlation between TIRADS and Bethesda considering results as benign vs malignant by considering TIRADS 4,5 and Bethesda 4,5,6 as positive results (Malignant) the sensitivity dropped to 72.0% and the specificity of this test increased to 78.3% and rate of false positives dropped to 19.4%. This means that, although we would miss 28% of the malignant conditions (all Bethesda 4 and 5), the percentage of specificity and true positives would greatly increase. These results are giving a better correlation with the reports made by Singaporewalla et al. (2017). Additionally, we studied and calculated the Correlation between TIRADS and

Bethesda considering results as benign vs malignant by considering TIRADS 5 and Bethesda 6 as positive results (Malignant). This crosstabulation leads to drop of the sensitivity of TIRADS to 20% while the specificity would be higher 99.6%. In the latest studied calculated variations TIRADS would give 1 false positive result. When studying the possible differences between women and men and the effect of gender on TIRADS and Bethesda classification, we couldn't discover any significant differences. Scientists are evidencing that US is highly trustable although is a less exact method of choice in detection of malignancies (Moon et al. 2011 and Morris et al. 2008) and Fagin and Mitsaides (2008) states that usage of ultrasonography has contributed to increase detection of thyroid nodules. Our studies are also presenting that it is highly sensitive in detection of changes of a nodule. The sensitivity can even be 100 % when considering TIRADS 3,4,5 and Bethesda 4,5,6 as positive results (Malignant).

The US is describing the varied configurations that a nodule can develop. Various explanation as echogenicity, form, vascularity, borders and if the node is solid or cystic or contains calcification or not. Also revealing nodules before surgery by US gives a better diagnostic accuracy then CT (Ahn et al. 2008). In our study population most of the patients were present with non-calcified nodules while the smallest group of populations were present with a mix of both micro and macrocalcifications. When comparing nodules with micro or macrocalcifications the results proved that nodules with microcalcifications were more common than macrocalcified nodules. In this particular study gender had no impact on the pattern of calcification ($p=0.46$). Isolated macrocalcifications are described in the TIRADS 2 description as a benign aspect while microcalcifications are categorized in the high suspicious nodules. In TIRADS 1 which is described as normal thyroid US, calcifications should not be present. Calcifications that are lesser then 1 mm are considered as microcalcified while larger then 1 mm are regarded as macrocalcified (Chandramohan et al. 2016).

A nodule having an irregular margin is considered to be low suspicious and belongs to TIRADS classification 3. While irregular margined nodule is considered to be highly suspicious and belongs to TIRADS classification 4 and 5. Our statistical analysis is proving that 121 patients had nodules containing microlobulation and irregular margins. While 148 of patients had a well circumscribed margin. According to Moifo et al. (2013) certain finding are increasing the risk of malignancy and irregular margins and micro- calcifications are some of them. Intermediate suspicious nodules are described as containing smooth hypoechogenic

nodules with a smooth margin. In our analysis 87% of patients had a smooth nodule and gender had no influence on the smoothness (p=0.85).
Lymphadenopathy is one of the features that increases the suspiciousness of a nodule being malignant (Moifo et al. 2013). When comparing percentage of swollen versus non swollen LN in neck evaluated in the total populace of our patients 4.4% had LN in neck region (95%CI: 2.6%...7.3%). The influence of gender proved that 9.0% of men had enlarged LN, while only 3.5% of women had an enlargement.

If the echogenicity of a nodule was more than the echogenicity of thyroid gland it was deliberated as hyperechoic. If the echogenicity was equal to the sternohyoid, sternothyroid, thyrohyoid and omohyoid muscles the nodule was considered as hypoechoic. And if the echogenecity was lower than the strap muscles the echohogenecity was considered as markedly hypoechoic (Chandramohan et al. 2016). 0.7% of our patients had hyperechogenecity (95%CI: 0.2%...2.4%) while 21.1% had hypoechogenecity (95%CI: 16.9%...26.1%) and 0.3% had Marked hypoechogenecity (95%CI: 0.1%...1.9%). In our patient group most of our patients 26% had a isoechogenic nodule (95%CI: 27.5%...38.1%).

6. CONCLUSION

1. In our patient sample the US investigation and FNAB were more common among female. The mean age difference between female and male didn't differentiate significantly. Gender didn't have any influence on TIRADS and Bethesda categories.
2. Most of patient had noncalcified nodules. Among patients that had calcification, microcalcification was most frequently seen. Majority of patients had a homogenous nodule. Well circumscribed nodules were slightly more common. Multiple nodules were significantly more commonly seen then single nodules. Normal size of nodules was most commonly seen. Smooth nodules were significantly more common then non smooth nodules. Swollen LN in neck were not common.
3. Marked hypoechogenecity, vascularity and nonhomogenousity were more common in men.
4. TIRADS is highly sensitive bus less specific in comparison with Bethesda.

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