CORRELATION OF PREOPERATIVE TUMOR SIZE WITH POST-OPERATIVE HISTOPATHOLOGICAL PROGNOSTIC INDICATORS IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

THESIS

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JULY, 2022 **Dr. Pankaj Kumar**

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DECLARATION

I hereby declare that the thesis titled **"Correlation of Preoperative Tumor Size with Post-operative Histopathological Prognostic Indicators in patients with Differentiated Thyroid Carcinoma"** embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

Certified that the project titled **"Correlation of Preoperative Tumor Size with Postoperative Histopathological Prognostic Indicators in Patients with Differentiated Thyroid Carcinoma"** is the record of research done in this department by **Dr. Pankaj Kumar.** He has fulfilled all the necessary conditions for the submission of this research work.

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IN MEMORY OF MY GRANDFATHER

DEDICATEDTOMYFAMILY, MY TEACHERS AND MENTORS

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LIST OF ABBREVIATIONS

DTCs	Differentiated thyroid carcinoma
ASR	Age Specific Rate
TC	Thyroid Cancer
HICs	High-income countries
LMICs	Low- and Middle-income countries
PTCs	Papillary thyroid cancers
FTCs	Follicular thyroid cancers
FVPTC	Follicular variant PTC
BRAF	B-type Raf kinase
SMR	Standardized Mortality Ratio
HR	Hazard ratio
SNP	Single Nucleotide Polymorphism
FNAC	Fine Needle Aspiration Cytology
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
TIRADS	Thyroid Imaging, Reporting and Data System
AUS	Atypia of Unknown Significance
FLUS	Follicular Neoplasm of Unknown Significance
NIFTP	Non-Invasive Follicular Thyroid Neoplasm with Papillary like Nuclear Features
NED	No Evidence of Disease
RAI	Radio Active Iodine
VC	Vocal Cord
RLN	Recurrent Laryngeal Nerve
DSS	Disease Specific Survival
EMG	Electromyogram
NIM	Neural Integrity Monitor
DSS	Disease Specific Survival

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INTRODUCTION

INTRODUCTION

Neck swellings due to thyroid enlargement have been known to mankind since the dawn of civilization. Byzantine era authors contributed significantly however, not recognized much(1). Thyroid prominences were known to Hippocrates (1st century BC) but he thought it was cervical gland deformity(2). The Chinese scholar Tshui Chih-Thi (85 A.D.) distinguished between solid and soft goitres, He also identified that solid goitres were incurable while the soft ones were benign(2). The earliest recorded thyroidectomy was performed by Abu al-Qassim al-Zawahiri (936-1013 AD) using simple ligature and hot irons(3). At those times it was considered dreaded surgery due to excessive bleeding with a mortality rate of near 40%(4). The discovery of anaesthesia and antisepsis led to drastic change in mortality during and after thyroid surgeries(2), and this was evident by the work of Theodor Billroth, who showed that mortality due to thyroid surgeries has reduced to 8.3% in antiseptic period as compare to 36.1% before that(5). Theodor Kocher, who is considered the Father of Thyroid surgery did many advancements in thyroid surgeries and in 1890 he adopted classical collar incision aka Kocher's Incision, which is still used(6).

Prognosis of Differentiated Thyroid Cancers (DTCs):

The overall prevalence of thyroid swellings is 19-35% as detected by USG of these 5-15% is thyroid malignancy. Thyroid cancer is the 7th most common cancer(7). Thyroid cancer is currently the commonest endocrine malignancy and it is the 3rd most rapidly growing cancer with an average annual rate of increase of 3.6%, however, mortality due to thyroid cancer remained the same(8,9). DTC constitutes >90% of all thyroid malignancies. DTCs constitute Papillary Thyroid cancer and Follicular Thyroid cancers. Every year approximately 95000 new cases are diagnosed globally with an incidence rate of about 3.5-4/100000 in India(10,11). DTC is 3rd most common cause of malignancy among females and the 5th most common among males with male to female ratio of approximately 3, however mortality due to DTCs is equal in both males and females, suggesting poor prognosis in males.

DTCs, the most common thyroid malignancy, has the best prognosis with 10-year survival of > 90%. Among DTCs prognosis of Follicular Thyroid Cancer is poor than that of Papillary Thyroid Cancers. The prognosis of DTCs is dependent on a lot of factors, some of which are patients related and some are tumor related(12).

Table 1: Prognostic factors of DTCs

Patient factor	**Tumor factor**
Age	Grade
Gender	Size
Genetics factors	ETE
Radiation exposure	Capsular invasion
	LNM
	Distant Metastasis

Gender is an important prognostic factor of DTC. Also the different variant of DTC have different prognosis in females with FTCs having poor prognosis as compared to PTCs(13). DTCs are one of the rare cancers in which prognosis is dependent on gender.

Other than gender, age of patient is also an independent prognostic indicator. It is also the only cancer in which age is part of the staging of disease according to TNM classification(14). Apart from prognosis, age is also an important marker for treatment response and even with radioiodine therapy the chances of locoregional recurrence is high in older patients aged more than 45 years(15).

Other than these some genetic factors are also poor prognostic indicators important among these are BRAFV600E, TERT and RAS mutations(16). IL12A expression is also associated with poor prognosis(17). There are multiple genetic mutation which are associated with increased incidence and poor prognosis of DTCs, such as SNPs at 9q22.33, 20q11.22-q12 14q24.3 and 2q35, rs7935 and rs1203952(18).

Size of the tumor is considered an independent prognostic indicator and it is an important part of TNM classification and ATA classification system. There is multiple prognostic system for DTCs and size of tumor is included in every prognostic system. Various studies have concluded that increasing size has detrimental effect on prognosis of DTCs but in our clinical experience we have observed that even small size tumor can be related with poor prognosis. Multiple studies have also stated that chances of ETE, LNM and distant metastasis also increases with increasing size(19). However, some authors have stated that increasing

tumor size doesn't necessarily related to poor prognosis. In some studies it was stated that tumor size is predictive of prognosis only for intrathyroidal nodule however, it is still doubtful if size is indicator of prognosis(20).

Other than these there are multiple histopathological factors which determine prognosis, important among them are LNM, ETE, locoregional metastasis and distant metastasis(21). ETE is an independent prognostic indicator. The chances of recurrence increases by two fold in presence of ETE and there is reduced disease specific survival(22). However, in 2018 TNM classification micro ETE has been removed as a poor prognostic indicator(14). Histopathological variant like tall cell variant, columnar cell variant and hobnail variant have poor outcome as compared to that of classical variant(23).

One of the important modifiable risk factors is radiation exposure. Among DTCs prognosis of follicular carcinoma is poorer than that of papillary carcinoma. There are various modalities for diagnosis but USG and FNAC remain the investigations of choice. Although USG has great inter-observer variability, with various measures such as TIRADS, diagnosis of thyroid malignancy can be easily suspected and accordingly investigated further. USG guided FNAC/ FNAC helps increase the diagnostic probability. There are multiple grading and prognostic systems for thyroid cancer. TIRADS and Bethesda grading systems based on USG and FNAC respectively, are among the most important grading systems and management protocols are also proposed according to these systems. There are multiple prognostic systems of DTCs. Important ones among them are AGES (Age, Grade, Extent and Size), AMES (Age, distant Metastasis, Extent and Size), MACIS (Metastasis, Age, resection Completeness, Invasion and Size), E.O.R.T.C., TNM and Dynamic Risk Stratification(24–29). The role of Computed Tomography and Magnetic Resonance Imaging is limited in DTCs and is confined for extensive disease with vascular involvement, retrosternal extension, neural involvement, distant metastasis and suspected recurrent disease. There are various treatment modalities for thyroid malignancy. Surgical excision with or without postoperative radioiodine therapy is most efficacious. However, the extent of surgery depends on various prognostic factors. However, different studies have proposed that optimal surgery for DTCs are total thyroidectomy except for intraparenchymal micropapillary carcinoma in which hemithyroidectomy/ lobectomy with close follow-up can suffice. Various studies have

shown that increasing age and size of nodule worsens prognosis. Similarly, Metastasis, ETE and worse histological features such as tall cell or hobnail cell variants have poor prognosis. Various studies have found varied correlations between the risk factors and DTC.

Size of nodule is a very important feature in staging and decision making during surgical excision. However, it is still debatable that the size of nodule has independent prognostic value and correlates with post-operative histological features. Various studies have concluded that increasing size has detrimental effect on prognosis of DTCs but in our clinical practice we have observed that this is not completely true and small size also had poor prognosis. Even patients with small thyroid had distant metastasis. However, the overall prognosis of DTCs is excellent so, to determine the prognostic effect of size, long term follow-up is needed, but this study is part of the thesis, so, we are looking for short term prognostic factors or histopathological indicators. The majority of study done to look for prognosis of DTCs are retrospective and we proposed this study as a prospective study to look for prognostic impact of size of tumor. In this study we are trying to establish if there is any correlation between preoperative nodule size as per USG findings with that of postoperative poor histopathological indicators in patients with DTC.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Thyroid tumours were known to humans since the rise of civilization. Earliest documentation of thyroid tumours was during the time of Hippocrates, though evidences of thyroid tumours were present even before that. Byzantine era researchers were among the first who have done a lot of work on thyroid but they understood very less(1). Chinese scholar Tshui Chih-Thi, Leonardo da Vinci and Thomas Wharton had important contribution in understanding structure of thyroid and thyroid tumours(2). Abu al-Quasim al-Zawahiri, William Halsted, Nikolai Pirigoff, Theodor Billroth and Theodor Kocher have very important contribution in development of thyroid surgery(2,5,6). Differentiated thyroid carcinoma (DTC), which mainly includes cancers of papillary and follicular histology, is the most common form of thyroid cancer(30). DTC typically has a favourable prognosis, with an overall 10- year survival rate above 90%. As reported by epidemiological studies, the incidence of thyroid cancer has been on the increase in previous decades.

The incidence of thyroid carcinoma has been increasing in past few decades in India and worldwide. A major proportion is attributed to overdiagnosis, especially in developed countries. Panato et al states that The ASRs for TC in India increased by 37% in women and 27% in males between 2006 and 2014. In both sexes, however, there was a 10-fold disparity in areas. Trivandrum had the highest ASRs (14.6/100,000 women and 4.1/100,000 men in 2012-2014), with a 93% rise in women and a 64% increase in males over 2006-2008. In Indian men, there was no evidence of overdiagnosis. Overdiagnosis, on the other hand, was responsible for 51% of TC in Indian women: 74% in those aged <35, 50% in those aged 35-54, and 30% in those aged 55-64. Trivandrum had the highest rate of TC overdiagnosis in women, at 80%, whereas Kamrup, Dibrugarh, Bhopal, and Sikkim had no or little evidence of overdiagnosis(10).

The rise in thyroid cancer is mainly attributed to increase in incidence in DTC, especially Papillary Thyroid Cancer. Thyroid cancer incidence varies significantly within high-income countries (HICs), and between HICs and low- and middle-income countries (LMICs) and overdiagnosis is likely a major factor. This international comparison verifies the extremely high TC incidence rates in various HICs from 2008 to 2012, as well as high rates in many LMICs, notably in urban regions. Moreover, in the HICs and LMICs with the greatest incidence rates, the papillary carcinomas

accounts for the majority of the increase in incidence and overdiagnoses of TC in multiple nations — is identical. These findings, together with the consistently low fatality rates, suggest that TC cases in LMICs are overdiagnosed(31).

A population-based study done in United States between 1974 and 2013 suggested that thyroid cancer incidence has been increased by 3.6% annually with a major proportion of it has been attributed to papillary thyroid carcinoma. Also, there is a steady increase in mortality due to thyroid cancer at the rate of increase of 1.1% per year. The study also suggested that these are true increase in incidence and are not attributed to mere overdiagnosis(8).

A recent study suggested that incidence of thyroid cancer has been increasing specially in middle- and low-income countries. And the rate of increase is more in males as compared to females, though the mean age at diagnosis among males is 50 – 69 years while in females is 15- 49 years. Though the incidence is increasing but mortality due to TC has decreased in last few decades. Southern and eastern Asia accounts for almost half of TC burden. Death due to TC mainly occurs in elderly patients of age ≥ 70 years. The incidence of thyroid cancer varies greatly between and within the countries. These findings suggest that rising incidence of TC cannot be entirely attributed to overdiagnosis(11).

Thyroid carcinoma is one of the most common malignancies especially in females. It is most common endocrine malignancy. Thyroid cancers are third fastest increasing malignancy in world(9). Among thyroid malignancy DTCs comprise of more than 90% of cases(29). DTCs comprise of papillary and follicular carcinomas. The overall prognosis of DTCs are very good with 10 year survival more than 90%(32). Papillary thyroid carcinoma has better prognosis compared to follicular thyroid carcinoma. The treatment strategy has changed a lot in last decade for DTCs. Many grading scales has been developed to predict the prognosis and individualise the treatment protocol.

Table 2: T- staging of DTCs

	T criteria
Tx	Primary nodule cannot be assessed
T0	No evidence of primary tumour
T1	Nodule≤2 cm in greatest dimension limited to the thyroid
T1a	Nodule≤1 cm in greatest dimension limited to the thyroid
T1b	Nodule>1 cm but ≤2 cm in greatest dimension limited to the thyroid
T2	Nodule>2 cm but ≤4 cm in greatest dimension limited to the thyroid
T3	Nodule>4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles
T3a	Nodule>4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a nodule of any size
T4	Includes gross extrathyroidal extension beyond the strap muscles
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a nodule of any size

According to AJCC TNM classification prognosis of thyroid malignancy worsens as the size increases(33). AJCC 8th edition has done some major changes like microscopic extrathyroidal extension has been removed and is not considered as poor prognostic marker. Similarly level VII lymph node involvement has been recategorized into N1a instead of N1b(14,33).

Kramer et al studied 351 patients with DTCs and draw correlation between size and prognosis and stated that: The FTC was substantially bigger than the PTC (3.46 vs 1.84 cm). Patients with pT3b-tumours had considerably smaller tumours (1.9 vs 3.0 cm) than those with considerable extrathyroidal development (pT4a-tumours). Patients with distant metastases in general were affected with tumours > 2 cms. Also, increasing nodule size was associated with a substantial decrease in event-free and overall survival. A pT4a-category and a nodule diameter of 02 cm were found to be independent predictors of survival using multivariate analysis(34).

Reddy et al studied 551 patients with nodule size less than 2 cms and stated that Lymph node metastasis was seen in 45% of individuals. This proportion remains unchanged in comparison of tumours ranging from 0 to 1 cm to tumours ranging from

1 to 2 cm. Logistic regression is a technique for predicting the outcome, although original nodule size was not found to be a predictor of lymph node metastasis in the study, it did demonstrate that positive lymph nodes status was associated with histologic vascular invasion and soft tissue invasion. For the first recurrence, actual estimations revealed there was a significant difference in individuals with positive cervical lymph nodes vs those with negative nodes. In terms of cancer-related mortality, there was no change(35).

Tam et al studied 2323 patient with DTCs and stated that in terms of disease-free survival, patients with tumours larger than 4 cm have worse outcome than those with tumours smaller than 4 cm. Regardless of the existence of minimal extra thyroid extension within each size category, patients did not vary in terms of disease-free survival. Although the size of nodule did affect disease free survival, chances of lympho-vascular invasion and distance metastasis. Hence it can be inferred that size, but not mETE, was an independent risk factor for locoregional failure, and distant metastatic failure(36).

8th edition AJCC TNM classification has increased the age limit of poor prognosis to 55 years from 45 years(14). Due to this there has been significant reduction in stage III and IV disease. Also, as per 8th edition TNM, 10 year disease specific survival for stage III and IV disease are similar (stage III 72.4% vs stage IV 71.9%), whereas as per 7th edition AJCC TNM, there is marked difference in 10 year disease specific survival between stage III (98.3%) and stage IV (82.6%)(37). A similar study has been done by Wang et al in which they have studied 1431 patient with stage III and IV DTCs. They stated that in patients with DTC T4 disease, larger nodule size worsens the prognosis. They also concluded that stage III disease with larger nodule size has worse prognosis as compared to stage IV disease with smaller nodule size. They have studied all nodule size i.e. ≤2 cms; 2-4 cms; >4 cms, and found there was no significant difference in prognosis between tumours of size ≤2 cms and 2-4 cms but tumours > 4 cm have worse prognosis. Disease specific survival was longer in patients with nodule size < 4 cm as compared to patients with nodule size > 4 cm. So they concluded that nodule size is independent prognostic indicator of DTCs(38).

Tran et al stated that nodule size predicted Recurrence Free Survival in the total study group. In a subgroup study, there was no link between nodule size and Recurrence Free Survival in patients under the age of 55. In individuals ≥55 years, however, size

was an independent predictor of Recurrence Free Survival. A size criterion of >2 cm versus ≤2 cm offered the best predictive discrimination in this subgroup. There is no difference in Recurrence Free Survival in patients with nodule size 2-4 cm and >4 cms(39).

Zhao et al, studied prognostic factors of DTCs and stated that the mortality/recurrence rate of DTC has a linear relationship with nodule size. A bigger nodule is usually associated with a worse prognosis. DTC below 1.5 cm has a 30-year specific death ratio of 0.4 percent, while DTC beyond 1.5 cm has a 30-year specific mortality ratio of 7%(22).

In a study done to look for impact of size of nodule on prognosis it was stated that in DTC, the initial tumour's size is described as a predictor of outcome. It's been reported that a greater nodule size is associated with a poor prognosis. In addition, nodule size has been incorporated into a number of grading systems (AGES, AMES and MACIS). The distinction between low-risk and high-risk nodule size, on the other hand, is unclear. These upper limits in sizes were studied for their predictive significance in intrathyroidal carcinomas. It's still unclear whether the tumour's diameter has any bearing on the prognosis(20).

TING‐TING ZHANG et al stated that the vast majority (87 percent) of thyroid cancers discovered in the last 15 years were classified as small DTCs, which are tumours with a diameter of less than 2 cm at their largest diameter(8). Previous research has revealed that tumours larger than 1 cm had a poor prognosis(40). T1a for tumours less than 1 cm and T1b for tumours greater than 1 cm are used in the eighth AJCC TNM staging system. The two DTC populations should be treated differently, according to the 2015 American Thyroid Association guidelines(29). However, smaller DTCs were not associated with a better prognosis in other trials, and there was no difference between the two groupings(41).

In our clinical practice we have observed that nodule size at diagnosis doesn’t necessarily correlates with prognosis and we have seen many patients with small nodule and poor prognosis in terms of extra thyroid extension, lymph node metastasis and capsular invasion. That’s why we aimed our study to see impact of nodule size on prognosis by short term prognostic indicators. This study is a part thesis so long-term follow-up was not possible.

According to AJCC TNM 8th edition, age of the patient is considered an independent prognostic factor. Also, the TNM classification has decided an age cut- off to be labelled as poor prognosis. In 8th edition the cut- off is 55 years, which has been increased as compared to 7th edition in which age cut-off was 45 years. Staging of the disease also change depending on the age as described below

Table 3: Staging of DTCs as per TNM staging

Age at diagnosis	T stage	N stage	M stage	Staging of disease
<55 years	Any T	Any N	M0	I
<55 years	Any T	Any N	M1	II
≥55 years	T1/T2	N0/Nx	M0	I
≥55 years	T1/T2	N1	M0	II
≥55 years	T3a/T3b	Any N	M0	II
≥55 years	T4a	Any N	M0	III
≥55 years	T4b	Any N	M0	IV A
≥55 years	Any T	Any N	M1	IN B

So, according to AJCC age at diagnosis can be considered as an important and independent prognostic factor(14).

Kazaure et al had done a systematic review to look for association of age with prognosis of DTCs and stated that DTC is the only human malignancy to include age as part of the American Joint Committee on Cancer (AJCC) staging system, however, it remains unclear why older patient age is a strong prognostic factor for thyroid cancer mortality. They also noticed that age is an important marker for response to treatment(15). In patients who were risk stratified in the American Thyroid Association (ATA)-high risk category, the influence of age (<55 vs. ≥55 years at diagnosis) on the risk of recurrence and mortality was studied. They discovered that older patients (≥55 years) were less likely than younger patients to obtain an excellent response to therapy (defined as suppressed serum thyroglobulin 0.2 ng/ml, no detectable thyroglobulin antibody, and no structural evidence of disease) (27.5% vs. 40.3%). The disease-specific survival of older patients in the ATA-high risk category who had an inadequate response to therapy was worse than that of their younger counterparts (12% vs. 74%). They also noticed that BRAF mutation is associated with

poor prognosis and increased cancer related mortality, and the probability increases with increasing age(42). Deaths per 1000 person-years were 3.19 and 20.75 in BRAF V600E-positive patients <45 years and ≥45 years, respectively, compared to 0.81 and 4.76 in BRAF V600E-negative patients in similar age categories. Deaths per 1000 person-years were 5.27 and 37.03 in BRAF V600E-positive patients <60 years and ≥60 years, respectively, compared to 1.34 and 9.68 in BRAF V600E-negative patients in similar age categories(43).

Zhang et al did a retrospective analysis to know the effect of age and gender on prognosis of DTCs and found some interesting gender differences in DTC. First, among male patients, PTC, FVPTC, and FTC had similar outcomes. These three subtypes exhibited significantly different results in premenopausal women, with FTC having worse prognosis with respect to DSS as compared with PTC; however, whereas FTC had a worse prognosis than PTC in postmenopausal women, there was no significant difference between PTC and FVPTC. Second, with PTC and FVPTC, women had considerably better DSS than males in patients younger than 55 years old, but there was no difference in patients older than 55 years old. Gender had no effect on FTC outcomes, which was surprising(13).

Yan et al did a retrospective analysis to look for effect of age on prognosis in patients with PTC and FTC and stated that a total of 204,139 patients were found to have DTCs. PTC was found in 92% of the people, while FTC was found in 7.7%. With a median follow-up of 52.7 months, the average age was 48.4 years and the overall survival rate was 96.3 percent. When looking at 10-year mortality in 5-year increments, PTC mortality increased by 30–50% per age group without an evident inflection point. FTC patients, on the other hand, had a more than threefold increase in 10-year mortality from age 40–44 (2.5%) to age 45–49 (3.5%). (7.9%). They also stated that distant metastasis is more common in patients ≥45 years and age at diagnosis is an independent prognostic indicator in patients with FTC. Various studies were done to analyze age threshold for DTCs and some studies found age threshold for poor prognosis to be 55 years(44), whereas according to Kim et al age cut- off for poor prognosis is 57 years(45). However, most of the studies were done for DTCs and different histological type were not considered separately, so, the age cut- off of PTC were decided on the basis of majority of cases of PTCs.

Apart from age, gender also impact the incidence and prognosis of DTCs. The incidence of DTCs is almost 3 times more common in females as compared to males(46). Various studies have been done to know the effect of gender on prognosis. A recent study suggested that recurrence and mortality are more common in males with PTC. But gender has no impact on prognosis of papillary thyroid microcarcinoma. So, they concluded that gender can be an independent prognostic factor in PTC but not papillary thyroid microcarcinoma(47). Various other studies suggested that while female gender is associated with more favorable histological subtypes, more aggressive histology is seen with a fairly even gender distribution(48).

Maino et al, stated that significance of gender as a prognostic factor for PTC is debatable. According to some studies, death in men with PTC may be twice as high as in women. The average PTC size was much greater in men than in women, although there was no significant difference in PTC prognosis. There were no gender differences in terms of patient age or the existence of local or distant metastases(49). In a multivariate analysis, Ito et al. discovered that male gender was strongly connected to having more local recurrences, but not distant metastases or an increased death-specific rate(50). Whereas multiple studies suggest there is no role of gender in prognosis of DTCs.

Recent studies have suggested effect of molecular markers and genetic mutation on the prognosis of DTCs. Subash et al had done a systematic review and stated that there is correlation between BRAF mutation, increasing age and poor prognosis, like disease recurrence and DSS. BRAF mutation is seen only in PTC and not in any other histologic variant of DTCs(51). Although association of BRAF mutation with age and poor prognosis has been seen by many authors. Some work has been done to look for any association of BRAF mutation with gender predilection of DTCs. Among these studies some studies have shown correlation between BRAF mutation and gender. Kim et al states that in 73.4% of cases, the BRAFV600E mutation was discovered. The BRAF V600E mutation was found to be correlated to both male gender and nodule size in men. Although there appeared to be a link between the BRAF V600E mutation and extra-thyroid extension, the correlation was not statistically significant (P = 0062). During the follow-up period, 18% of patients had a recurrence. While univariate analysis revealed that the BRAF V600E mutation was linked to tumour recurrence (21% with mutation vs. 7% without mutation), multivariate analysis

revealed that the mutation was not (45). Xu et al stated that BRAF V600E mutation was found in 64 percent of men with papillary thyroid cancer, compared to 27 percent in women. On the other hand other studies didn't show any correlation between BRAF mutation and gender(53). A meta-analysis of twelve studies found no significant differences in mutation rates by gender, with the BRAF V600E mutant found in 50% of males and 49% of females with papillary thyroid carcinoma(53). Daliri et al studied the prognostic impact and clinicopathological behaviour off BRAF mutation in patients with PTC and stated that the BRAF(V600E) mutation was detected in 40.6 percent of PTC patients, and it was more common in older patients, individuals with advanced tumour stages, and patients who had previously been exposed to radiation. Incomplete response to treatment was linked to a number of clinicopathological factors in PTC patients (follow-up time, distant metastases, advanced stage, first thyroglobulin (fTg) level, history of reoperation and external radiotherapy, and delay in iodine therapy), but not to the presence of the BRAF(V600E) mutation(54).

Among the molecular factors BRAF and TERT mutation are considered most important for prognosis of PTC. Zhao et al did systematic review and network meta-analysis and concluded that for overall TC outcomes, the BRAFV600E + TERT co-mutation rated first for disease stage, lymph node metastasis, extrathyroidal extension, tumour recurrence, and thyroid capsule invasion. TERT+RAS or RAS rated first in distant metastasis, mortality, and multiplicity, while BRAFV600E + TERT co-mutation ranked second. When the study was limited to patients with PTC, BRAFV600E + TERT consistently ranked first in primary outcomes such as disease stage, lymph node metastasis, extrathyroidal extension, and distant metastasis, as well as secondary outcomes such as tumor recurrence, mortality, and thyroid capsule invasion. They also stated that though individua BRAF and TERT mutation are poor prognostic indicator for PTC but concomitant mutation has much more effect(16).

Prognosis of DTCs is excellent and these are very slow growing tumours. But apart from the above-mentioned factors there are multiple other factors which leads to poor prognosis in patients with DTC, like extra-thyroid extension, lymph node metastasis (LNM), vascular involvement, distant metastasis etc. Zhao et al performed a review of literature to look for prognostic factors and stated that Extra thyroid invasion is found in 10% of DTC patients, and it is associated with a higher risk of recurrence and

mortality. The recurrence rate in DTC patients with local invasion is 2-fold higher than in patients without local invasion. Within 10 years of DTC onset, 33 percent of patients with local invasion are dead. In 35-65 percent of adult PTC patients, lymph node metastasis develops. DTC patients with lymph node metastasis have a much greater 30-year mortality risk than those who do not have lymph node metastasis. In the presence of lymph node metastasis, 15% of DTC patients die of thyroid cancer, however in the absence of lymph node metastasis, patients can survive DTC. These data indicated that distant metastasis and LNM are independent prognostic factors(22).

Chen et al in retrospective analysis studied high risk factors for distant metastasis they also studied the synergistic effect of different risk factors and stated that the size of the tumour, the presence of LNM, the histologic subtype, and ETE were all found to be independent risk factors for Distant Metastasis. In addition, ETE and histologic subtype (RERI=34.097; AP=0.706; SI=3.585), ETE and LNM status (RERI=6.425; AP=0.410; SI=1.781), and ETE and nodule size (RERI=76.973; AP=0.864; SI=7.930) all had a significant additive synergistic effect on DM. thus they concluded that FTC, locoregional LNM have a additive effect on distant metastasis(21).

Gillander et al in their review on factors affecting prognosis of DTCs stated that Extra-thyroidal extension (ETE) is a poor prognostic indicator, with 10-year overall survival rates of 45 percent in ETE patients compared to 91 percent in patients with intrathyroidal tumours. The TNM categorization system of the UICC distinguishes two levels of extension: massive extension involves invasion of the subcutaneous soft tissue, larynx, trachea, oesophagus, or recurrent laryngeal nerve; minimal extension involves invasion of the sternothyroid muscle or perithyroid soft tissue. Aggressive histological subtypes, advanced age, and recurrent disease are all risk factors for invasion. In WDTC, the difference between minimal and large extension has a considerable impact on prognosis, with patients with major extension having a worse relapse-free survival rate. Tumours with extensive extension have a much worse relapse-free survival rate(55). Some authors have suggested a different staging system to guide the surgical management(56,57).

Table 4: McCaffrey et al staging system of DTCs:

Stage 1	Tumour located entirely within thyroid capsule.
Stage 2	Tumour invades aerodigestive tract perichondrium or abuts the muscle.
Stage 3	Tumour invades through perichondrium and into cartilage or deeply into muscle but spares submucosa.
Stage 4	Tumour invades through perichondrium and into cartilage or deeply into muscle and deforms submucosa.
Stage 5	gross transmucosal involvement

Binbin Du et al had done a retrospective analysis to look for cause specific mortality of thyroid cancers and stated that after a median follow-up of 101 months, 23,040 (13.3 percent) people died, with thyroid cancer accounting for 29.1% and cardiovascular disease (CVD) accounting for 21.7 percent respectively. Patients with follicular, Hürthle cell, medullary, and anaplastic histology had CVD SMRs of 1.14, 1.47, 1.21, and 5.66, respectively. As compared to papillary histology, the adjusted HRs for thyroid cancer specific mortality were 1.59, 1.87, and 12.65 for follicular, Hürthle cell, medullary, and anaplastic histology; HRs for CVD-specific mortality were 1.23, 1.27, 1.13, and 1.60, respectively. Older age, male sex, non-white race, unmarried status, and advanced stage were all independent predictors of CVD-specific death, although surgery and radiation were protective(58).

Gillander et al studied prognostic value of thyroglobulin and stated that antibodies to thyroglobulin are often utilised as surrogate indicators for disease recurrence or persistence in thyroid cancer, but their prognostic significance is yet to be determined(55). Thyroglobulin (Tg), serum thyrotropin (TSH), and thyroid autoantibodies have all been mentioned as potential prognostic variables in papillary or follicular thyroid carcinoma(59). Serum Tg, in particular, could be a valuable marker for WDTC. Tg is detected in serum samples even after total thyroidectomy, due to leftover thyroid tissue, either normal or tumour tissue. Tg levels detected in the blood following a complete thyroidectomy for thyroid cancer have also been linked to the presence of metastatic foci. Tg can also be used to predict recurrence in WDTC patients after lobectomy by looking at patterns in Tg levels rather than absolute numbers(55).

Recent studies shows that apart from conventional prognostic marker (nodule size, age, LNM, distant metastasis, etc), there are some newly discovered factors which

affect the prognosis of DTCs. One of the most important among these are interleukin (IL) family specially IL12A. Zhang et al studied the effect of IL12A expression on prognosis of DTC and stated that both normal thyroid tissues and DTC expressed IL-12A, however the amount of expression in DTC was much higher than in normal thyroid tissues. Age, sex, pathological type, multifocality, extrathyroid extension, lymph node metastasis, and distant metastasis were all positively linked with IL-12A. The percentage of disease persistence or recurrence (P&R) was 13/101 (12.9 percent), and IL-12A expression was found to have a positive connection with P&R. Nodule size, extrathyroid extension, tumour stage (T stage), and IL12A expression all influenced disease-free survival. Nodule size 2 cm and high IL-12A expression were found to be independent indicators of outcome in DTC patients in a multivariate Cox proportional-hazards analysis(17).

Apart from the molecular marker like IL12, BRAF, etc, there are multiple genetic mutation which are high risk for DTCs, especially Single Nucleotide Polymorphism (SNP). Mussazhanova et al has done a case control study to look for the effect of SNPs on prognosis of DTCs and concluded that five of the eight SNPs were found to be significantly linked to PTC: rs965513, rs1867277, rs2439302, rs944289, and rs10136427. The rs966423 gene showed a possible link. rs7267944 was linked to a higher risk of PTC in males, rs1867277 was linked to a higher risk in people over 55, and rs6983267 was linked to pT3–T4 tumours. In the examined series, the genetic component (unidirectional independent effects of rs965513, rs944289, rs2439302, and rs10136427 adjusted for age and sex) was estimated to contribute 30–40% to PTC risk. The genetic factors investigated in this study show a strong link(60).

Thyroid malignancy is one of the common malignancies and its incidence is increasing in the last 3 decades. It can be easily diagnosed with simple investigations. Specially in last few decades as the understanding of the disease has been increasing the role of different investigation is becoming evident. The investigation of choice for diagnosis are ultrasonography and FNAC. Serum thyroid profile is a necessary investigation that should be done before any other investigation because it will tell the nature of mass. A hyperfunctioning mass is rarely malignant(61). FNAC specially ultrasound guided is a very reliable tool in diagnosis of thyroid tumour. Even computed tomography and magnetic resonance imaging have low reliability in diagnosing primary thyroid tumours. These are used as adjunctive modalities for

diagnosis. Moreover, iodinated contrast medium can lead to delay in radioiodine treatment. MRI and CT have a role in diagnosis of distant metastasis and lymph node metastasis. CT also has role in post-surgery patient in whom thyroglobulin continues to rise in spite of negative ultrasonography neck(62). In the last decade the use of ^{18}FFDG PET has been increased for the diagnosis. But its use has been limited to recurrent disease, and to identify presence of distant metastasis. ^{18}FFDG PET has high false positivity rate and even some benign disease of thyroid can show increased uptake, but negative predictive value of ^{18}FFDG PET is very high, so, a negative report is almost confirmatory that no thyroid malignancy is present(61).

Ultrasonography (USG) neck is the most commonly and most widely used investigation for thyroid nodule. USG is very helpful in characterisation of thyroid nodule as well as it helps in doing FNAC. TIRADS grading, one of the most reliable grading systems is completely based on USG findings.

TIRADS grading was given by Horvath et al in 2009 with an aim to help in cost effective treatment. It was based on breast imaging, reporting and data system (BiRADS). Horvath observed that prevalence of thyroid nodule is increasing but majority of them are benign. USG characteristics had already been described which were considered high risk for malignancy. These characteristics were microcalcification, irregular margin, hypo echogenicity, echogenic foci and taller than wider nodule. It was suggested that if anyone of the findings are present then FNAB needs to be done. TIRADS grading was done for risk stratification of nodule and also to decide which patient should undergo FNAC(63). Horvath et al classified thyroid nodule in 6 categories.

Table 5: TIRADS grading of Thyroid Tumours.

TIRADS GRADING	DESCRIPTION	RISK OF MALIGNANCY
TIRADS 1	Normal thyroid tissue	
TIRADS 2	Benign condition	0%
TIRADS 3	Probably benign	<5%
TIRADS 4	Suspicious nodule	5- 80%
TIRADS 5	Probably malignant	>80 %
TIRADS 6	Biopsy proven malignancy	

It also stated that in all cases of TIRADS 1and II FNAC is not needed, whereas in cases of TIRADS 3, FNAC may be required depending on clinical profile, whereas for category IV and V FNAC must be done. The TIRADS grading is based on five morphological features which are composition, margin, shape, calcification, transverse and anteroposterior diameter(63). But recently some authors also consider a 6^{th} feature which is blood flow(64).

Apart from TIRADS there are multiple other grading system based on USG features. These grading systems mainly intended to look for any high-risk factor, so that any further investigation and unnecessary management can be avoided in benign tumours. One such grading system is American College of Radiology (ACR)- TIRADS. This categorization is based on the evaluation of many US aspects of thyroid nodules, including composition, shape, echogenicity, echogenic foci and margin. Each of these features has a score ranging from 0 to 3 points. The total number of points assigned determines the probability of malignancy in one of five grades: benign, marginally suspicious, moderately suspicious, or highly suspect for malignancy. The primary purpose of ACR – TIRADS is to identify indication of FNA in patients of thyroid nodule. The ACR-TI-RADS level and the maximum diameter of the nodules are used to determine whether FNA should be conducted or not. For risk categories TR3–TR5, a size threshold at or beyond which FNA should be performed is given. Only 1 cm or bigger nodules should be submitted for biopsy, while nodules with a low risk of malignancy should be explored further only when they are 2.5 cm or larger(65).

Other grading system is European TIRADS, which was first drafted by Russ et al in 2011(66), which after multiple modification was included in European guideline in 2017. This system also has 5 grades: Grade I – no nodule; Grade II – benign; Grade III – low risk; Grade IV – intermediate risk; Grade V – high risk. It also gives the indication for FNA. Category II (benign) with 0% risk malignancy warrants no indication of FNA. Category III with 2-4% risk of malignancy, FNA is indicated only in tumours ≥2 cm. Category IV with risk of malignancy 6-17%, FNA is indicated only for tumours ≥1.5cm and for category V with risk of carcinoma 26-87%, only in tumours ≥1 cm, FNA is indicated. This classification also suggested use of blood flow within nodule as marker of malignancy but it is not included in European guidelines yet(65,67).

The other classification system is Korean TIRADS, which was first given by Shin et al in 2016. Like other systems, it also classifies thyroid nodule in benign, low suspicion, intermediate suspicion and high suspicion. The difference from other systems is that it calculate the risk of malignancy based on combination of multiple high risk factors and not on single high risk factor(68).

American Association of Clinical Endocrinologists (AACE) classification, ATA classification and British Thyroid Association classification are among the other classification systems based of USG findings. The primary objective of all of these systems is to identify the high-risk features and identify the indications in which further investigation and management is needed(65).

The next most common investigation after USG in patient with thyroid nodule is FNAC. Though FNAC has been used in characterisation of thyroid nodule, but it was in 2007, when first FNAC based classification system was introduced – the Bethesda classification system. It was devised with an aim to eliminate the ambiguity of terminology used between different laboratories, pathologist and surgeons. It also provides information about risk of malignancy in different Bethesda category. The classification category and risk of malignancy are listed in table below(69).

Table 6: Bethesda grading of Thyroid Tumors (2006):

Bethesda category	Diagnosis	Risk of malignancy	Usual management
I	Nondiagnostic /unsatisfactory	1-4%	Repeat FNA
II	Benign	0-3%	Follow up
III	AUS/FLUS	5-15%	Repeat FNA
IV	Follicular neoplasm	15-30%	Lobectomy
V	Suspicious for malignancy	60-75%	Near total thyroidectomy/ lobectomy
VI	Malignant	94-96%	Near total thyroidectomy/ Total thyroidectomy

Since its origin Bethesda system have undergone many modifications and last modification was done in 2017. This modification was based on newer data after 2010. Though number of categories remain same i.e., Bethesda I – VI after modification but risk of malignancy has changed due to addition of a newer variant NIFTP into carcinoma. The latest Bethesda classification after addition of NIFTP is as follows(70,71):

Table 7: Modified Bethesda grading of Thyroid Tumors (2017):

Bethesda category	Diagnosis	Risk of malignancy	Usual management
I	Nondiagnostic /unsatisfactory	5-10%%	Repeat FNA with USG guidance
II	Benign	0-3%	Follow up
III	AUS/FLUS	10-30%	Repeat FNA, nuclear testing or diagnostic lobectomy
IV	Follicular neoplasm	25-40%	Nuclear testing or diagnostic lobectomy
V	Suspicious for malignancy	50-75%	Total thyroidectomy/ Hemithyroidectomy
VI	Malignant	97-99%	Total thyroidectomy/ Hemithyroidectomy

Apart from Bethesda system, there are multiple other FNA based grading system for thyroid nodule. These classifications mainly include Italian Reporting System for Thyroid Cytology, which was first proposed in 2007 with 5 tier grading system, but in 2014 it was revised with major differences like addition of category 1C in non-diagnostic group, also category 3 was subdivided into low risk and high risk which corresponds to Bethesda III and IV respectively. The other classification is Royal College of Pathologists, UK, system which also divide thyroid nodule in 5 categories. Thy 3a corresponds to Bethesda III while Thy 3f corresponds to Bethesda IV. Other classification systems include Australian and Japanese system. Both of these are very similar to Bethesda system(72). All these systems are primarily based on Bethesda system with some minor changes. The primary purpose of all these classification systems is to identify high risk patient and help in planning further management for the patient. These systems also help in removing ambiguity in reporting between different laboratories and for better communication between different authors. These

systems also help in devising management protocols by identifying the risk of malignancy.

Both TIRADS and Bethesda classification primarily aim at identifying high risk nodule in which further management is needed. Especially TIRADS which aim at identifying high risk feature on USG so that unnecessary invasive investigation FNA and/or surgery can be avoided in patient with no high-risk feature. Thus, reducing burden on health care system and patient doesn't have to undergo unnecessary surgery. Due to these reasons some authors have done studies to look for reliability of TIRADS in identifying high risk features. There is positive correlation between TIRADS and Bethesda classification and TIRADS grading has been successful in identifying tumours in which further investigation are not required. Here is the result of some studies done recently(73–76):

Table 8: Correlation of TIRADS and Bethesda grading system:

TIRADS BETHESDA	2				3				4				5			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
I	8.5%	-	-	-	2.2%	-	-	-	30.7%	-	-	-	11.1%	-	-	-
II	90.5%	82.1%	93.3%	100%	93.3%	10%	46%	66.6%	30.7%	14.3%	3.2%	33.3%	11.1%	33.3%	6.3%	40%
III	0.8%	15.3%	6.6%	0%	2.2%	60%	51.2%	23.8%	0%	14.3%	22.6%	66.7%	0%	7.7%	3.1%	0%
IV	0%	2.5%	0%	0%	2.2%	20%	2.4%		15.4%	71.4%	53.2%		22.2%	69.3%	21.9%	0%
V	0%	0%	0%	0%	0%	10%	0%	9.5%	15.4%	0%	20.1%	0%	44.4%	0%	68.9%	60%
VI	0%	-	-	0%	0%	-	-		7.7%	-	-		11.1%	-	-	
TOTAL	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

1.Periakaruppan et al; 2. Biswas et al; 3. Uricoechea H V et al; 4 Singaporewalla R.M. et al

All these studies conducted at different time in different regions independently concluded that TIRADS grading is useful in categorisation of thyroid nodule, specially TIRADS 2 which is in good concordance with Bethesda. None of the TIRADS 2 nodule, on FNA had Bethesda V or VI. This suggests that patients with TIRADS 3 can be followed up without doing FNA.

Apart from these diagnostic criteria, there are multiple prognostic criteria proposed for thyroid malignancy. These criteria predict the prognosis of DTCs preoperatively. These are important for treating consultant because they will have an idea about prognosis beforehand and also in counselling the patient before surgery. These are standardised system so they are also helpful in communication between different surgeons or hospitals. Currently most useful and most popular prognostic system is TNM classification, which got recently updated in 8th edition. Apart from this there are other prognostic systems which are used in past, some of them are still used.

The first attempt to prognosticate thyroid malignancy was done in 1979. The European Organisation for Research on Treatment of Cancer (E.O.R.T.C.) Thyroid cancer cooperative group proposed a grading system for prognostication of thyroid cancers. The grading system is as follows:

Age (year) at diagnosis

+12 if male

+10 if medullary or less differentiated follicular

+45 if anaplastic

+10 if T3 category

+15 if at one distant metastasis

+15 additional if multiple distant metastasis

Total score is calculated and patient classified accordingly and 5-year survival in each risk group given as follows(24):

Table 9: E.O.R.T.C. Prognostic Grading System for Thyroid Carcinomas:

Total Score	Risk Group	5-year survival (%)
<50	1	95
50-65	2	80
66-83	3	51
84-108	4	33
≥ 109	5	5

Some authors have tried to prognosticate DTCs on the basis of EORTC system and got a very different survival rate(25).

Table 10: Comparison of 5-year-survival on the basis of E.O.R.T.C. Grading:

Risk Group	Byar et al- 5year survival (%)	Lang et al- 5year survival (%)
1	95	100
2	80	97.8
3	51	85.1
4	33	74.7
5	5	No patient in this group

On further studies some of the author found EORTC system is very good for DTCs, specially for follicular thyroid cancer(25), while others stated that it does not have any added benefit as compared to other grading system(26). The biggest demerit of this system is that it classifies all type of thyroid cancer similarly but in reality, the prognosis of DTCs is much better than other type of thyroid cancers.

One of the earliest prognostic systems of DTCs is AGES classification system, which was proposed by I D Hay in Mayo clinic in 1987. It includes patient **A**ge, Tumour **G**rade, **E**xtent and **S**ize. AGES score is calculated as $score = 0.05$x age in year (if age ≥40Y) + 0 if age <40 years

+ 1 if tumour grade 2 or +3 if tumour grade 3/4

+ 1 if ETE

+3 if distant metastasis

+ 0.2 x nodule size (in cm)

It is interpretated as score ≤ 3.99 considered as low risk and optimal treatment for this nodule is ipsilateral lobectomy. In his study Hay concluded that in low-risk patients who underwent bilateral lobectomy or total thyroidectomy the mortality was more as compared to that of ipsilateral lobectomy. If score ≥ 4, it was considered as high risk and optimum treatment for this is bilateral lobectomy/ total thyroidectomy(77).

Cady et al in 1988 at Lahey clinic developed a new prognostic system, AMES classification. It includes patient **A**ge, distant **M**etastasis, **E**xtent and **S**ize. According to this classification patients are divided into low risk and high risk. In this system age cut off for males and females were different. The nodule size cut off was set at 5 cm. The classification is as follows:

Table 11: Comparison of Mortality at different time period on the basis of AMES Grading:

		Mortality Cady et al 1988	Mortality Lang et al 2007
Low risk	a. All younger patient (male < 41 years, female < 51 years) with no metastasis b. All older patients with intrathyroidal cancer or no/minor capsular involvement or nodule size <5 cm or absent distant	1.8%	3.4%
High risk	a. Patients having distant metastasis b. Older patients with extracapsular involvement or nodule size ≥ 5 cms	46%	22.6%

It has been noted from both the studies that overall mortality of DTCs has decreased due to better treatment but mortality in low risk group has increased because some factors which were considered low risk previously have now been known to cause poor prognosis, also the smaller size nodule has been known to cause poor prognosis(25,78).

In 1993, I D Hay et al, at Mayo Clinic, developed a new grading system, the MACIS prognostic scale to overcome the shortcomings of AGES grading. They stated that the final model includes five variables: metastasis, age, resection completeness, invasion, and size (MACIS). The score calculated as

MACIS = 3.1 (if age ≤ 39 years) or 0.08 x age (if age ≥ 40 years), + 0.3 x nodule size (in centimetres)

+1 if incompletely resected

+1 if locally invasive

+3 if distant metastases present.

Patients with MACIS less than 6, 6 to 6.99, 7 to 7.99, and 8+ had 20-year cause-specific survival rates of 99%, 89%, 56%, and 24%, respectively(28). It is one of the most used grading systems proposed and it was considered as best prognostic system till recently. Lang et al, stated that MACIS grading is equivalent to TNM classification in predicting prognosis of DTCs(25,26).

There are multiple other prognostic systems for DTCs but these systems are barely used now due to either their similarity to this system or their results do not give any further information to affect the treatment process.

Although the above-mentioned prognostic system gives a good insight about preoperative prognosis of DTCs, but these systems predict the prognosis of patient at one point of time. Many times, post operative histopathological diagnosis changes or incomplete resection of disease or there is extensive adhesion present, so, surgeon is not sure about completion of surgery etc, in such scenarios these grading system are ineffective. To overcome these problems, a relatively new concept is given for prognostication of DTCs, in which prognosis of patient is calculated at each follow up. It is called dynamic risk stratification.

A rationale approach was given by ATA in 2009 which was modified in 2015. According to ATA guideline, the first investigation to be done in a patient with thyroid nodule is thyroid profile test and USG neck and thyroid. If serum TSH is reduced then thyroid scan can be considered, however routine thyroid scan is not recommended. FNA is the next investigation and disease is classified and plan for further management is decided according to Bethesda classification. Once the patient is planned for surgery, minimalistic surgery is the new rationale proposed by ATA, stating lobectomy and hemithyroidectomy for intracapsular nodule of size ≤ 1 cm and ≤ 4 cm respectively, while total thyroidectomy is restricted for nodule larger than 4 cm. post-surgery risk of structural disease recurrence is calculated and patient is classified into 3 groups.

1. High risk: Gross extrathyroidal extension, incomplete nodule resection, distant metastasis or lymph node > 3 cm.
2. Intermediate risk: aggressive histology, minor extrathyroidal extension, vascular invasion, > 5 involved lymph node (0.2-3cm).
3. Low risk: intrathyroidal DTC, ≤ 5 lymph node micro metastasis (<0.2 cm)

Depending on the risk stratification the patients are considered for radioactive Iodine therapy. Current indications for radioactive Iodine therapy are(79,80):

1. Patient of high-risk group.
2. Primary nodule>4 cm with microscopic ETE and regional metastasis.
3. Concerning histological type: tall cell, columnar and insular.

Post radioactive iodine therapy to look for response and signs of recurrence the patients are classified into following categories:

Table 12: Prognostic grading Post Radio-Iodine Treatment as per Dynamic Risk Stratification:

Category	Definition	Clinical outcome	Management
Excellent response	Negative imaging and Suppressed Tg <0.2ng/mL or TSH- stimulated Tg<1ng/mL	1-4% recurrence	Follow up with serum TSH, if increased serum Tg level.
Biochemical incomplete response	Negative imaging and Suppressed Tg≥ 1ng/mL or TSH- stimulated Tg≥ 10ng/mL or Rising anti Tg antibody level	30% spontaneously evolve to NED; 20% achieve NED after additional therapy; 20%- structural disease	If Tg level stable or declining – follow up Rising Tg or anti Tg antibody – 18FDG PET and further management.
Structural incomplete response	Structural or functional evidence of disease	50 -85% - persistent disease despite additional therapy	Further investigation with 18FDG PET scan, RAI avidity, Tg and further treatment.
Indeterminate response	Nonspecific finding on imaging. Faint uptake in thyroid bed on RAI scanning Nonstimulated Tg detectable but <1ng/mL. Stimulated Tg detectable but < 10ng/mL OR Anti Tg antibody stable in absence of structural disease.	15-20%- identifiable structural disease during follow up. In rest nonspecific changes either stable or resolve	Follow up with serial imaging and Tg monitoring and if lesion become specific further evaluation with imaging and biopsy

Dynamic risk stratification is an ever-evolving grading system which can be upgraded every time some new investigation or treatment develops. Multiple authors have done study to check for efficacy of Dynamic Risk Stratification and concluded that it is one of the best system for prognostication of DTCs because it allows real time, ongoing re-evaluation of patients during follow up(29,81).

AIM AND OBJECTIVES

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AIM

Correlation of preoperative nodule size with post-operative histopathological prognostic indicators in patients with differentiated thyroid carcinoma.

OBJECTIVES

1. To assess preoperative size by Ultrasonography neck.
2. To look for postoperative histopathological indicators.
3. To find out the correlation between preoperative nodule size and prognosis of differentiated thyroid cancer based on histopathological examination.

MATERIAL AND METHODOLOGY

MATERIALS AND METHODOLOGY

Study Design: - Cross Sectional Study

Inclusion Criteria:

All patients with cytologically proven, Bethesda III and above thyroid nodule who on histopathological examination postoperatively diagnosed as differentiated thyroid cancer.

Exclusion Criteria:

1. Revision cases or post treatment cases of differentiated thyroid carcinoma.
2. Previously operated for hemithyroidectomy in other hospital, now being planned for completion thyroidectomy.

Sampling Frame:

According to the study by Rajnish Nagarakar et al(82) on Indian population the prevalence of thyroid carcinoma was 0.8%. So, based on this study our sample size was calculated to be 49. In the study we have recruited 57 patients according to our inclusion criteria

Sampling:

All patient presenting to the OPD of the Department of Otorhinolaryngology, diagnosed as differentiated carcinoma thyroid. The sampling was purposive. Our study was proposed to be a prospective study but due to SARS COV2 pandemic and acute invasive Mucormycosis epidemic all surgeries except emergency surgeries were postponed for the time period, so retrospective data of the patients operated for DTCs in Department of Otorhinolaryngology, AIIMS, Jodhpur, has been taken after taking informed consent.

Methodology

We have done a Cross Sectional Study on patients with differentiated thyroid cancer undergoing/ underwent surgery in Department of Otorhinolaryngology, AIIMS Jodhpur by taking retrospective data from January 2016 to October 2019 and prospective data from November 2019 to December 2021.

All patients with a preoperative fine needle aspiration cytology suggestive of differentiated carcinoma (Bethesda III and above) or with a suspicious nodule in USG or with a post-operative histopathology report suggestive of differentiated carcinoma thyroid were included in this study. Patients with post-operative histopathology report suggesting benign nodule of thyroid or recurrent cases of papillary carcinoma thyroid were excluded from the study. All patients with thyroid nodule who presented to the department of Otorhinolaryngology were evaluated as per American Thyroid guidelines, and were operated. Patients were recruited into study as soon as diagnosis of differentiated thyroid cancer was made, after taking an informed Consent. Preoperatively nodule size was assessed and documented, radiologically with ultrasonography of neck, and post operatively based on histopathology report. In patients who were included in the study retrospectively, pre-operative records and post-operative histopathology report were analyzed. All patients included in the study were categorized into three groups based on the size of dominant nodule, according to ATA guidelines and TNM classification i.e.,

Group 1: nodule size <2 cm

Group 2: nodule size 2-4 cm

Group 3: nodule size >4cm

Groups has been made based on Ultrasonography findings and histopathology findings separately and comparison of size based on USG and histopathology report. In patients with multiple nodules, the dominant nodule was selected to measure the size.

Criteria for Dominant nodule based on USG:

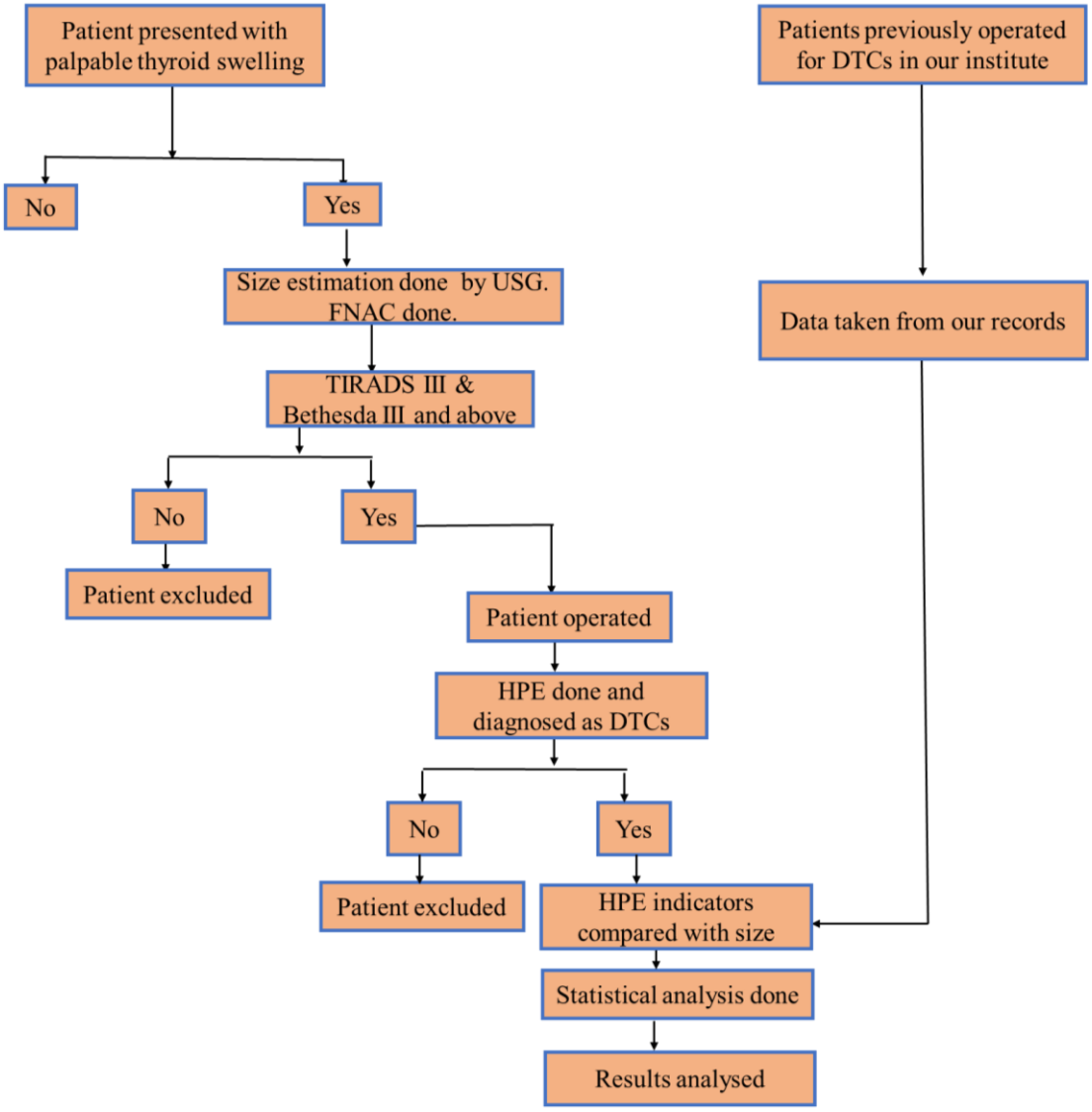
I. The nodule with higher TIRADS grading OR
II. In multiple nodules with same TIRADS grading, the largest nodule was selected as dominant nodule.

Criteria of Dominant Nodule based on Histopathology:

1. The nodule with features of Papillary Thyroid cancer.
2. In multiple nodules with features of Papillary Thyroid cancer, larger size nodule was selected as dominant nodule.

These patients have been subjected to surgery as per preop clinic discussion. After surgery their prognosis is assessed based on histopathological feature, examined by a single pathologist. In this study the parameters included were nodule size, nuclear atypia, tumoural necrosis, vascular invasion, capsular invasion, extra thyroid extension and lymph node metastasis.

Fig: 1 Flowchart of Methodology



Procedure:

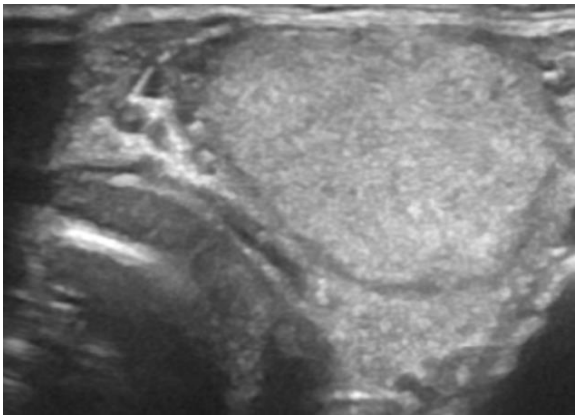
1. All the patients presented with palpable thyroid nodule were assessed clinically.
2. After that all patients underwent USG of neck and FNAC of thyroid nodule.
3. All patients with nodule of Bethesda III and above were enrolled in study.
4. Preoperative size of nodule was evaluated by USG of neck.
5. Apart from markers USG and FNAC, routine blood investigations (complete hemogram, Kidney function test, Liver function test, serum electrolyte, Prothrombin time and INR, viral), Thyroid Function Test, intact PTH and serum Calcium level was assessed for each patient.
6. Preoperative vocal cord assessment was done for each patient.
7. All patients underwent surgery as per departmental preoperative clinic discussion, under GA after appropriate counseling and consenting following a Pre-Anesthetic assessment.
8. Surgical steps:
    a. Patients positioned in supine position with neck in extension (fig. 17.4).
    b. Transverse cervical Kocher's incision was given 2 finger breadth above suprasternal notch, between anterior border both sternocleidomastoid (fig. 17.5).
    c. Subplatysmal flap elevated superiorly till hyoid bone and inferiorly till clavicle (fig. 17.6).
    d. Investing layer of deep cervical fascia incised in midline. Strap muscles identified, separated and retracted laterally.
    e. Middle thyroid vein identified, ligated and cut.
    f. Dissection done in superior pole and superior pole (superior thyroid vessels) ligated and cut.
    g. RLN was identified in Beahr's Triangle or near Cricothyroid Joint at the level of lower border Cricothyroid Muscle and preserved (fig. 17.10).
    h. Parathyroid glands were identified and preserved (fig. 17.10).
    i. Inferior thyroid vessel identified, ligated and cut near to the gland to prevent blood supply of parathyroid glands.

j. Thyroid specimen was delivered (fig. 17.11).
k. Hemostasis achieved and drain placed.
l. Wound closure done in layers.
m. Dressing done.

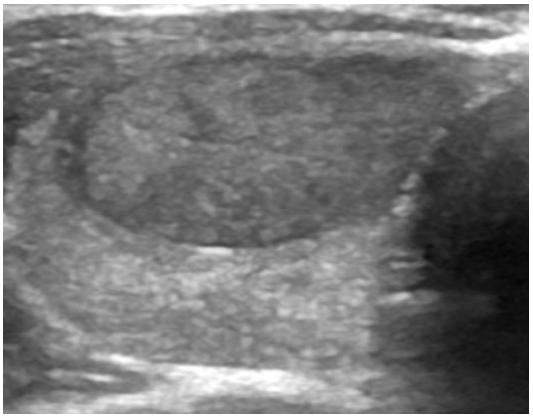
9. Prognosis was assessed by post-operative histopathological examination (nodule size, nuclear atypia, tumoural necrosis, vascular invasion, capsular invasion, extra thyroid extension and lymph node metastasis).

In this study we have taken patients with palpable nodule with Bethesda III and above who on histopathological examination came out to be Differentiated Thyroid Cancer.

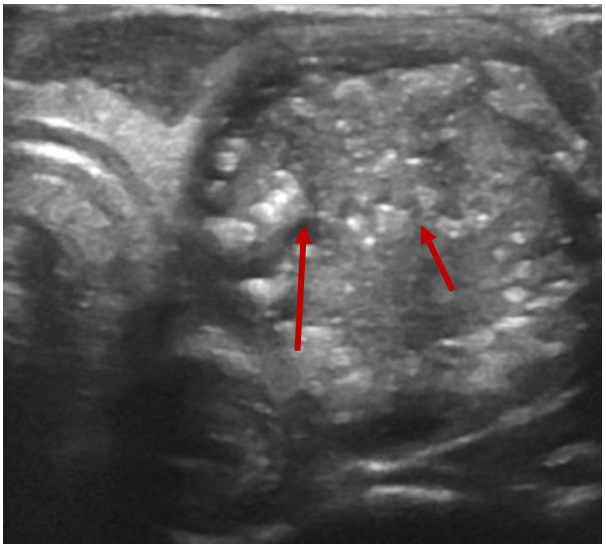
Fig: 2: USG images showing thyroid nodule.



2.1. USG of neck shows a smoothly marginated (0), wider than taller (0), completely solid (2), isoechoic (1) nodule in left lobe of thyroid without any echogenic foci/ calcification (0) suggestive of TIRADS 3 nodule (total point 3).

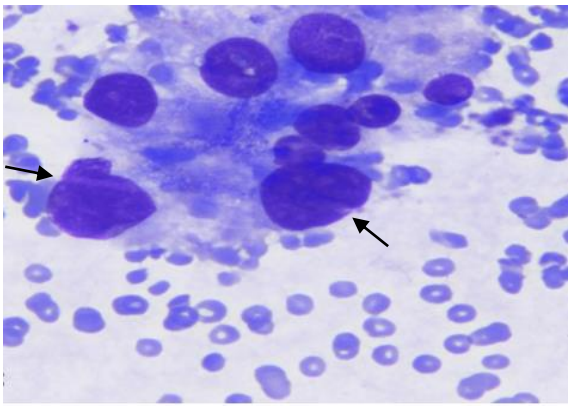


2.2 USG of neck shows a smoothly marginated (0), wider than taller (0), completely solid (2), hypoechoic (2) nodule in right lobe of thyroid without any echogenic foci/ calcification (0) suggestive of TIRADS 4 nodule (total point 4).

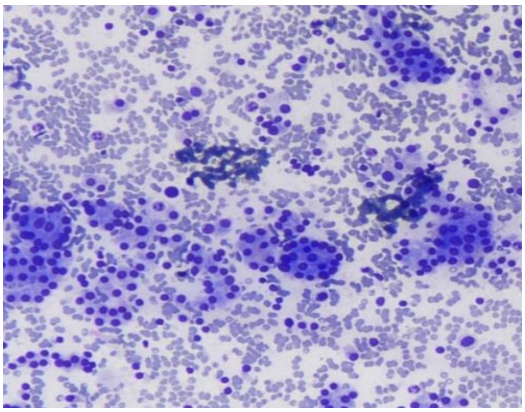


2.3. USG of neck shows a smoothly marginated (0), solid (2), taller than wider (3), hypoechoic (2) nodule in left lobe of thyroid with intralesional punctate echogenic foci (Red Arrows) (3) suggesting a TIRADS 5 lesion (total point

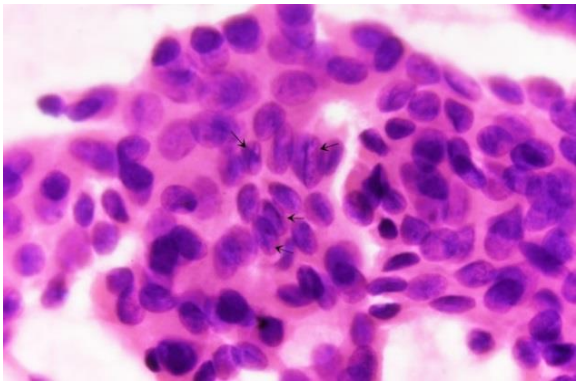
Fig: 3: FNAC images of thyroid nodule.



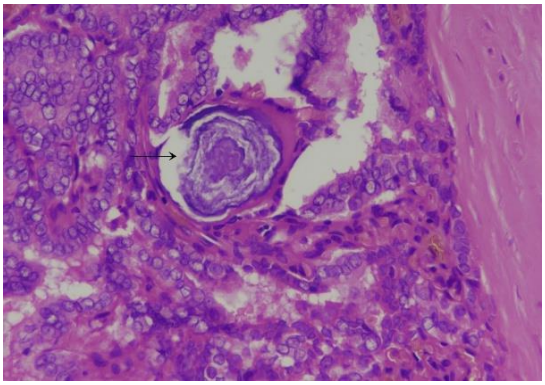
3.1. Cells are arranged in Atypical Microfollicle with atypical cells with occasional nuclear grooving (Black Arrows). Atypia of unknown significance, (Category III, Bethesda system of reporting thyroid cytology)



3.2. Highly cellular aspirate with uniform follicular cells arranged in microfollicles. Follicular neoplasm, (Category IV Bethesda system of reporting thyroid cytology)

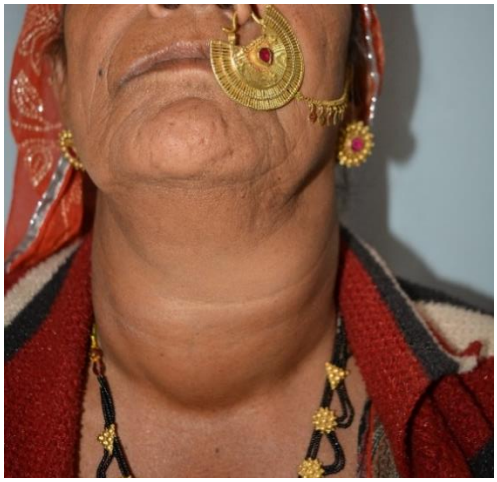


3.3. Sheet of follicular cells with enlarged nucleus and nuclear groove (black arrows) (Category V Bethesda system of reporting thyroid cytology)

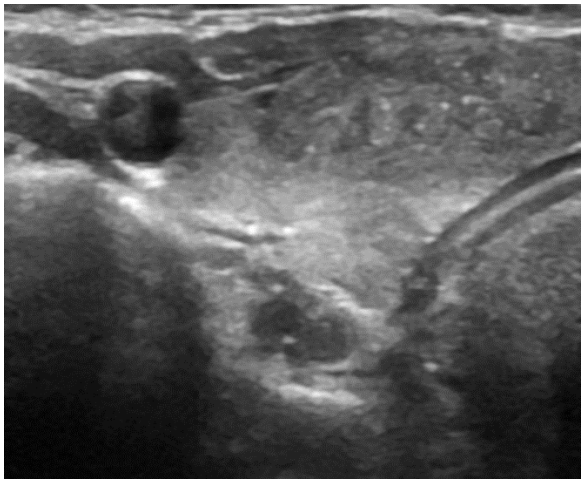


3.4. Psammoma body (arrow) and papillae lined by columnar cells with clear nuclei (Category VI Bethesda system of reporting thyroid cytology)

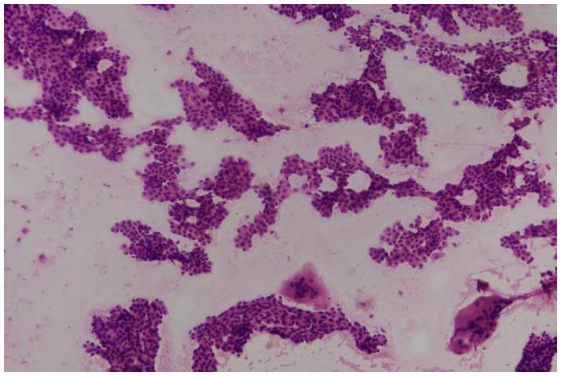
Fig: 4: Patient with a large size nodule (> 4 cms)



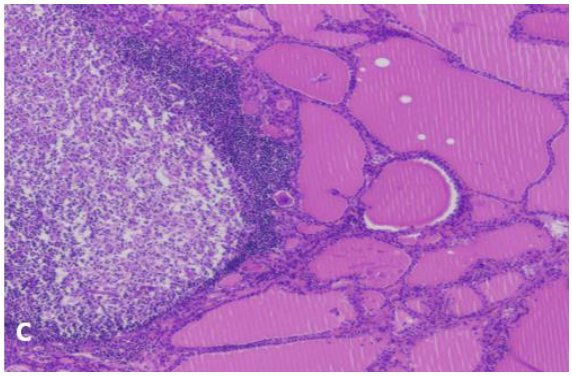
4.1 Patient with large thyroid nodule 4 X 5 cm.



4.2 USG image showing ill-defined solid nodule with multiple echogenic foci (TIRADS V)

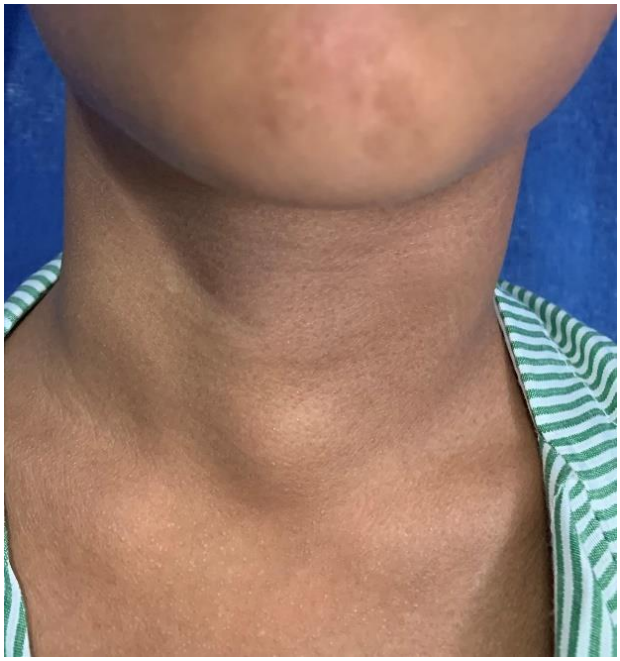


4.3 Multiple papillae of tumour cells with enlarged nuclei, abundant cytoplasm and few multinucleated cells, 10X, H&E stain, Bethesda VI.

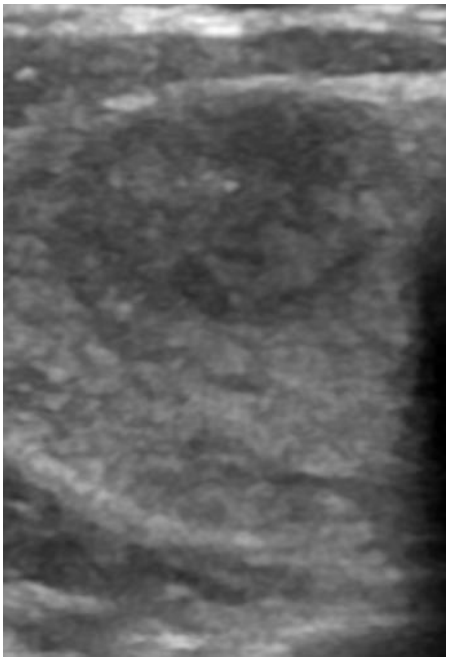


4.4 Classical PTC (4X, H&E stain)

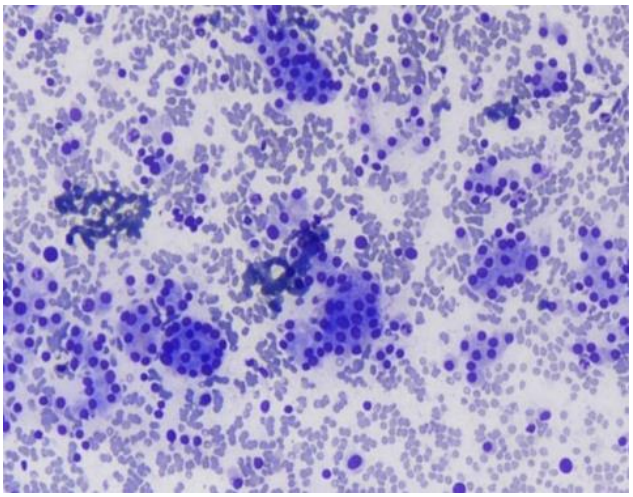
Fig: 5: Patient with small size nodule(<2cms).



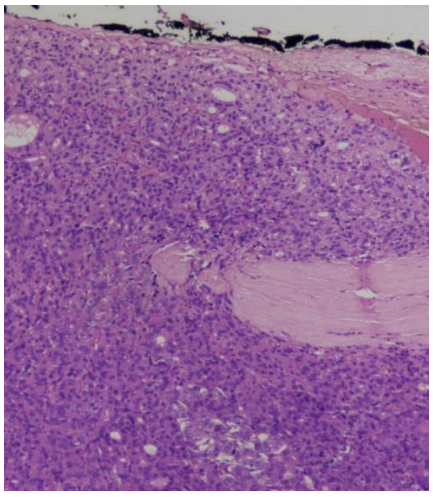
5.1- Patient with small thyroid nodule 1x1 cm.



5.2- Solid, Hypoechoic, TIRADS 4 nodule of Right Lobe



5.3- Follicular neoplasm, Bethesda Category IV



5.4- Follicular carcinoma (4X, H&E stain)

STATISTICAL ANALYSIS

Statistical analysis

Data was entered in Microsoft excel and analysed using SPSSv28 (IBM Corp. released 2021 IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.). Quantitative variables were described using the chi- square test. Nominal Variables were described using proportions and analysed using Fischer Exact test. A p-value of <0.05 s considered as significant.

ETHICAL APPROVAL

Ethical approval and consent to participate

Ethical approval was obtained from AIIMS Jodhpur; Institutional Ethical Committee certificate reference No. AIIMS/IEC/2019-20/981, dated- 01/01/2020 attached in annexure “G”. All patients were informed about the purpose of the study and the benefits of patients in the study. After inclusion in the study, informed consent was obtained from all the participants. The patient's information sheet was given to all patients, and their role in the study was explained before administering screening tools. They were assured of the complete confidentiality of the information and were explained the option of withdrawing from the study at any point in time if they desired to do so. All the data collected were kept confidential. There were no adverse events reported during the course of the study.

RESULTS

RESULTS

A total of 57 patients having thyroid nodule who attended the OPD or operated in department of Otorhinolaryngology, AIIMS, Jodhpur, fulfilling the inclusion criteria were studied. After confirmation of histopathology report, the patients were included in study after informed consent.

Among the 57 patients, mean age of patients 35.91 ±1.82 and median age 57 35 years. 49 (86%) patients were female while 8 (14%) were male.

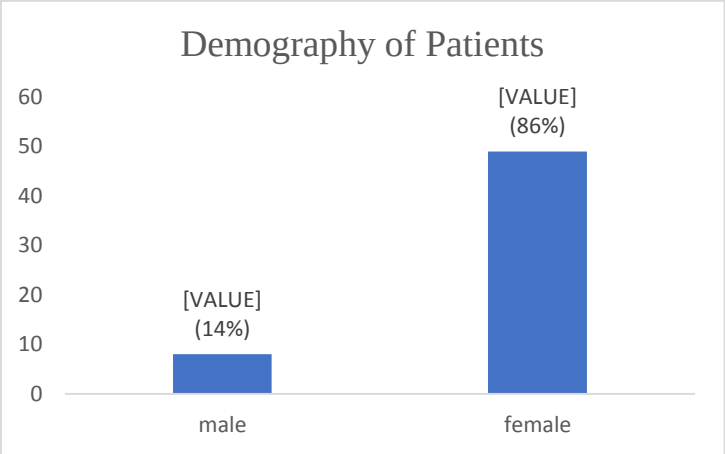
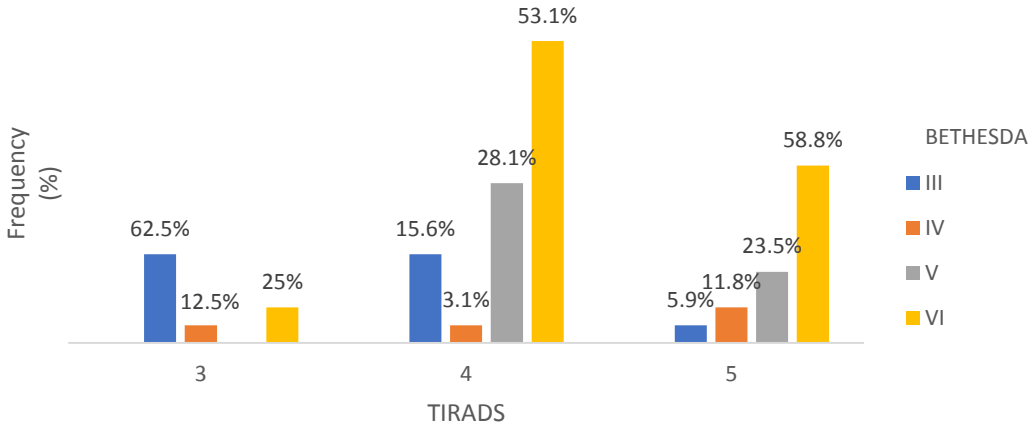


Fig: 6: Gender composition of patients

Maximum patients presented to us after 6 months to 2 years of onset of symptoms. Mean size of thyroid nodule in our patients was 3.34 cm ±0.309.

All patients included in the study were having thyroid nodule with TIRADS and Bethesda III and above and we looked for correlation between TIRADS and Bethesda grading. After FNAC, we found there is significant association (P- value – 0.023) between TIRADS and Bethesda grading. On FNAC of TIRADS 3 nodule, 75% were Bethesda III and IV, whereas none of them were having Bethesda V. Similarly, for TIRADS 4 nodule, majority of the lesion, 81.2% were Bethesda V and VI while only 18.7% were Bethesda III and IV. Similarly in TIRADS 5 nodule, 82.3% were Bethesda V and VI.

Fig 7: Correlation b/w TIRADS and Bethesda Grading



The number of patients in each size group is as follows:

Table 13: Frequency of patients in each size group:

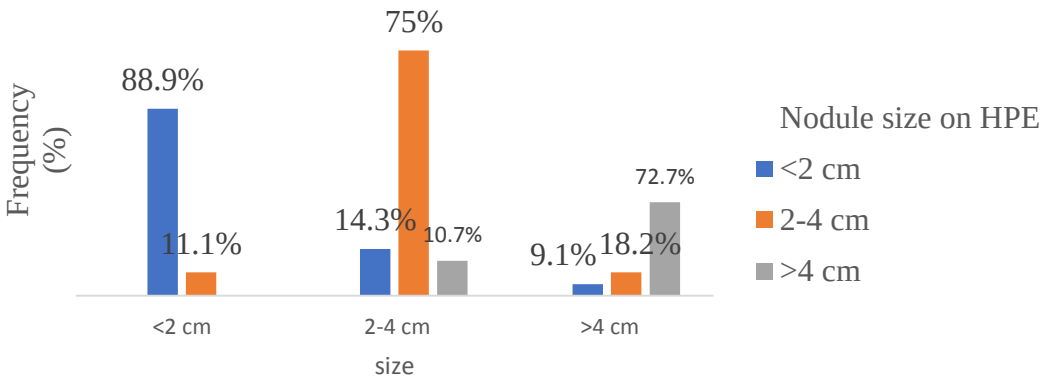
Size	Frequency	Percentage
<2 cm	18	31.6
2-4 cm	28	49.1
>4 cm	11	19.3

Table 14: The frequency of each subtype of thyroid malignancy is as follows:

	Frequency	Percentage
Papillary carcinoma	38	66.7
follicular carcinoma	17	29.9
Medullary carcinoma	2	3.5
Total	57	100.0

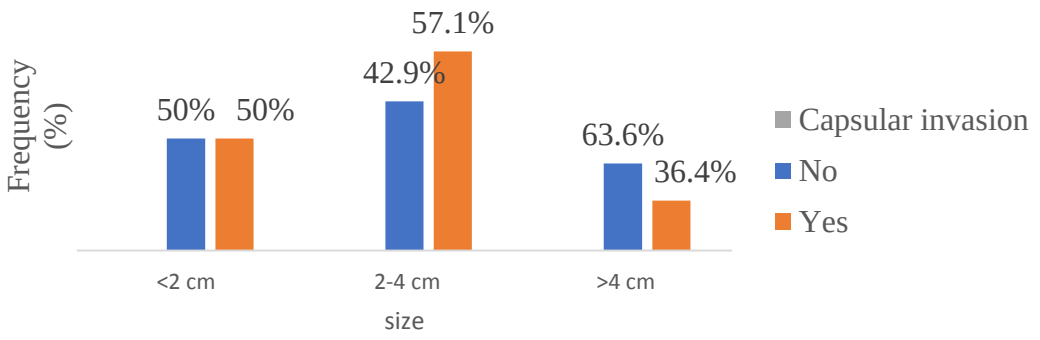
Firstly, the preoperative size of nodule was compared with size during grossing. Statistically significant correlation was found between ultrasonographic size and histopathological size (P- value- 0.000).

Fig 8: Comparison b/w Preoperative Size of nodule by Ultrasound and Histological Size



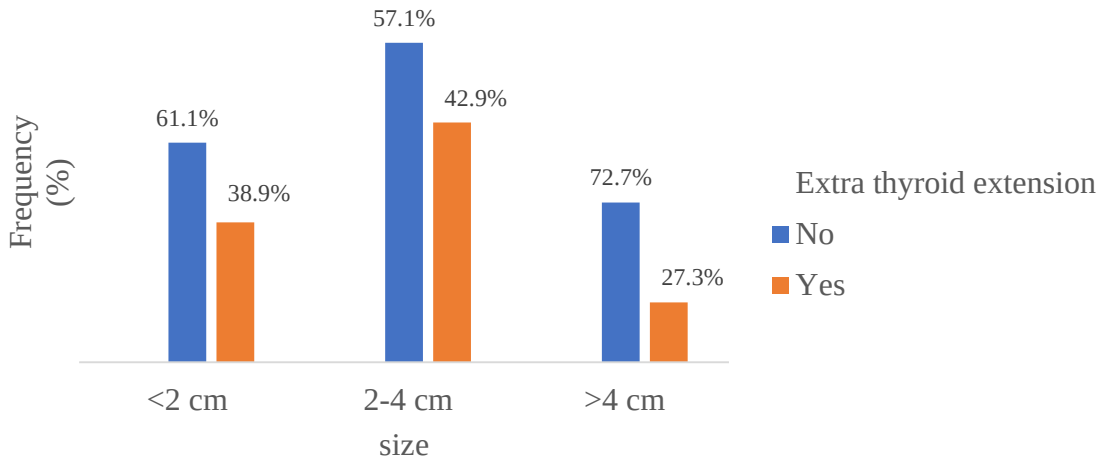
Correlation between size of nodule and capsular invasion was done. Capsular invasion was found more frequently in smaller size nodule (<2 cm and 2-4 cm) 50% and 57.1% respectively as compared to larger size nodule (>4 cm) 36.4% with a P- value of 0.503, i.e. statistically insignificant.

Fig 9: Correlation of Preoperative Nodule Size and Capsular Invasion



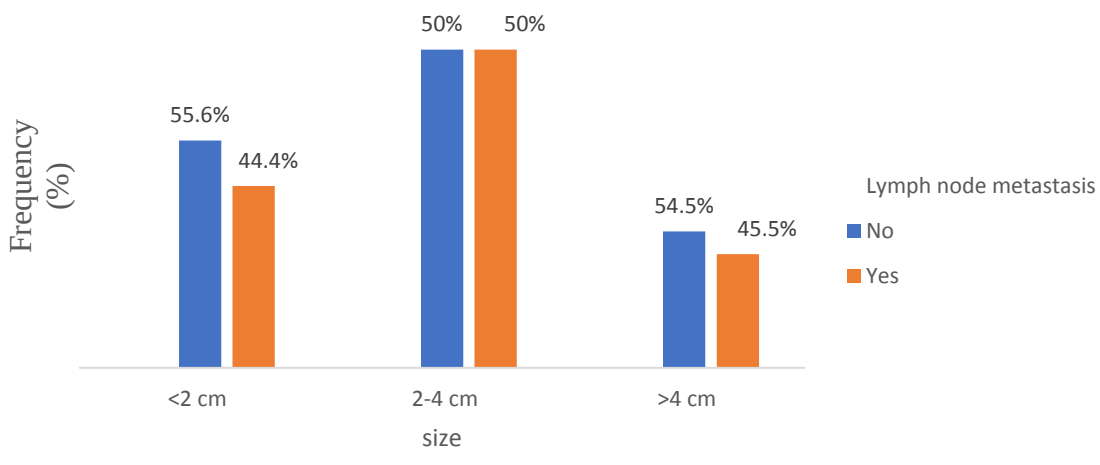
Similar result was found when correlation of size and ETE done, with frequency of ETE in nodule size <2 cm and 2-4 cm was found to be 38.9% and 42.9% respectively, whereas in nodule > 4cm in size, ETE was found in 27.3% with a P value of 0.667, suggesting there is no statistically significant association between tumor size and ETE.

Fig 10: Correlation of Preoperative Nodule Size and ETE



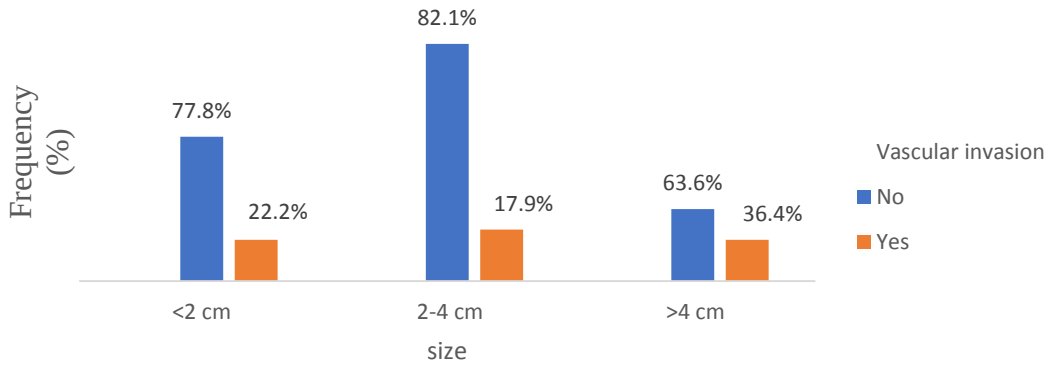
When Lymph Node Metastasis was compared with size, almost equal frequencies were found in each group with 44.4%, 50% and 45.5% respectively in nodule size of <2 cm, 2-4 cm and >4 cm (P value – 0.925).

Fig 11: Correlation of Preoperative Nodule Size and LNM



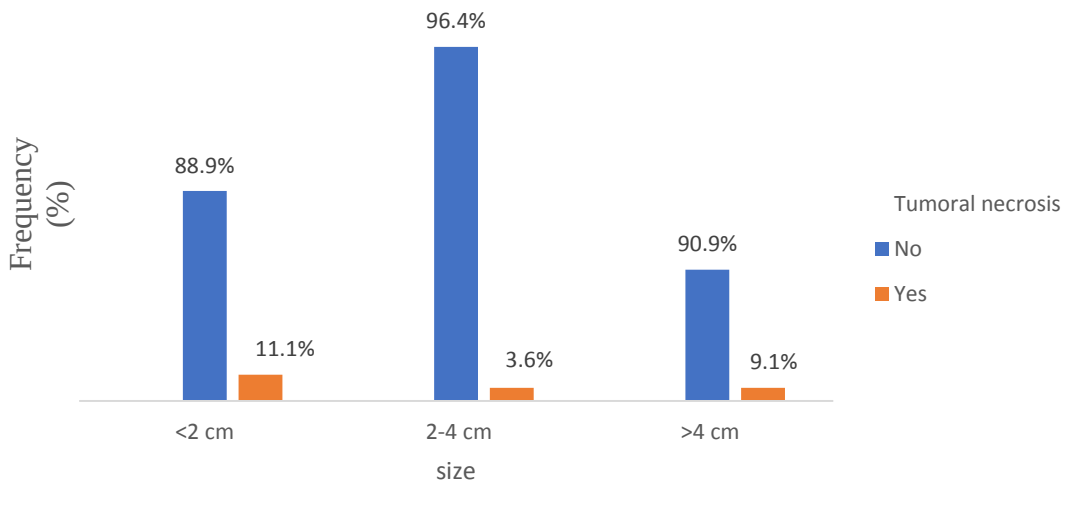
On comparing nodule size with vascular invasion, we found no statistically significant correlation between preoperative nodule size and vascular invasion (P -value- 0.463)

Fig 12: Correlation of Preoperative Nodule Size and Vascular Invasion



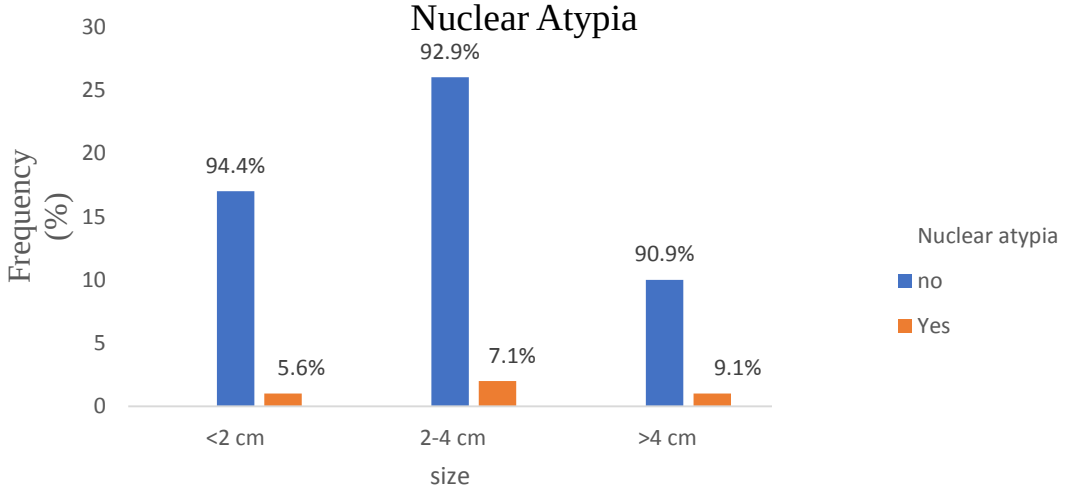
When preoperative nodule size was correlated with intra-tumoral necrosis, maximum frequency was observed in nodule size <2 cm, followed by nodule size >4 cm and 2-4 cm respectively (P – value – 0.593).

Fig 13: Correlation of Preoperative Nodule Size and Tumoural Necrosis



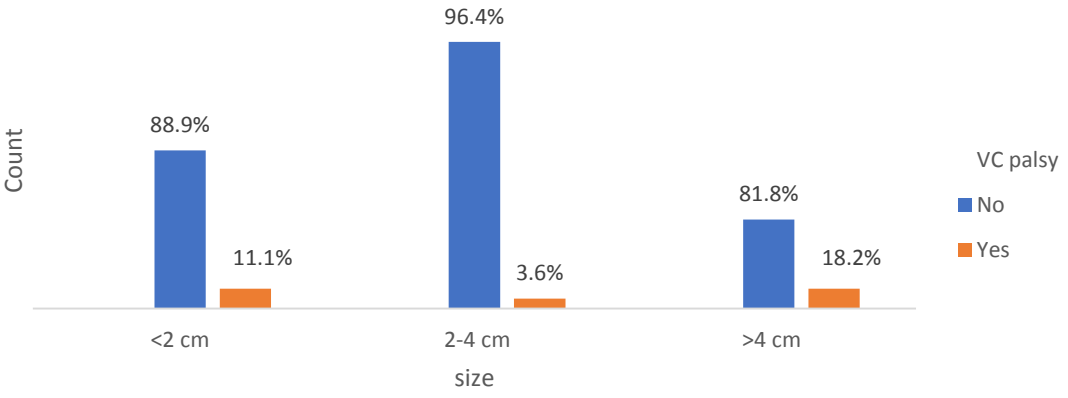
Nuclear atypia was found to be more frequently associated with larger size nodules (5.6% in nodules < 2 cm in size, 7.1% in nodules 2-4 cm in size and 9.1% in nodule > 4 cm in size) which was statistically insignificant (P- value – 0.936)

Fig 14: Correlation of Preoperative Nodule Size and Nuclear Atypia



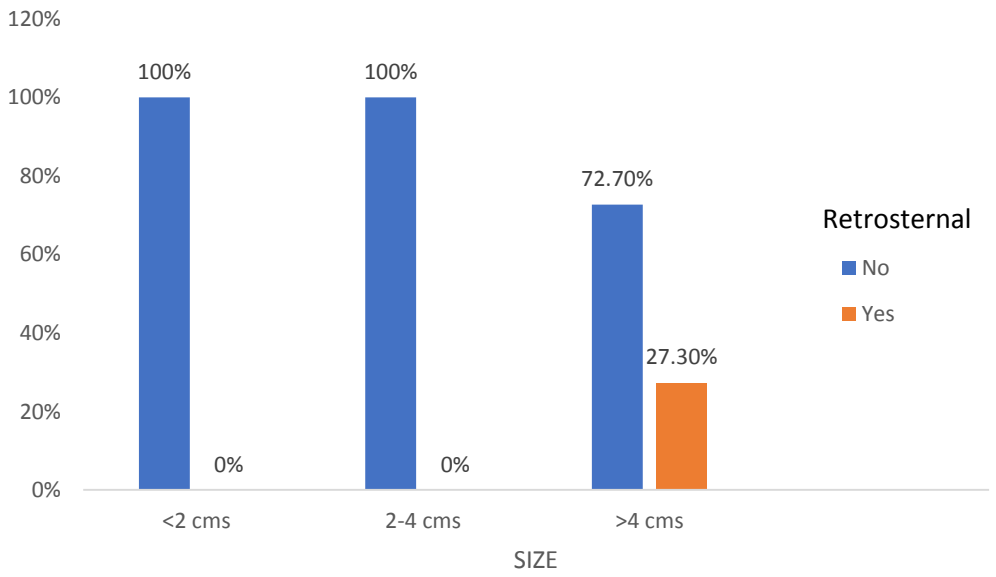
Similarly, when involvement of Recurrent Laryngeal Nerve or preoperative VC Palsy was investigated the frequency was observed to be equal i.e., 2 each in nodule size < 2 cm and > 4 cm. we could not find any statistically significant correlation between nodule size and preoperative Vocal cord palsy (P- value – 0.319). Thyroid tumours cause RLN palsy by either direct involvement of RLN or by mechanical compression. The small size nodule is less likely to cause compression. So, we can interpret that even small nodule can have ETE.

Fig 15: Correlation of Preoperative Nodule Size and Preoperative VC Palsy



Retrosternal extension was seen only in 3 patients, all belonging to group 2 (i.e., nodule size > 4 cm)

Fig. 16: Presence of Retrosternal Extension



In our study, two female patients were found to have distant metastasis and both patients were belonging to group 3 (i.e., nodule size > 4 cm). Both the patients were operated and after radioactive Iodine treatment they survived well.

The summary of the results we found during the study are tabulated in the following table.

Table 15: Summary of results

Prognostic Indicators	Ultrasonographic Size of Nodule			P- value
	< 2 cm	2-4 Cm	> 4cm	
Capsular Invasion	50%	57.1%	36.4%	0.503
ETE	38.9%	42.9%	27.3%	0.667
LNM	44.4%	50%	45.5%	0.925
Vascular Invasion	22.7%	17.9%	36.4%	0.463
Tumoural Necrosis	11.1%	3.6%	9.1%	0.593
Nuclear Atypia	5.6%	7.1%	9.1%	0.936
RLN involvement	11.1%	3.6%	18.2%	0.319

Apart form these there were 3 patients who had retrosternal extension and all of them belong to nodule size > 4 cm. Also, in our study 2 patients had distant metastasis and all belong to nodule size > 4 cm.

DISCUSSION

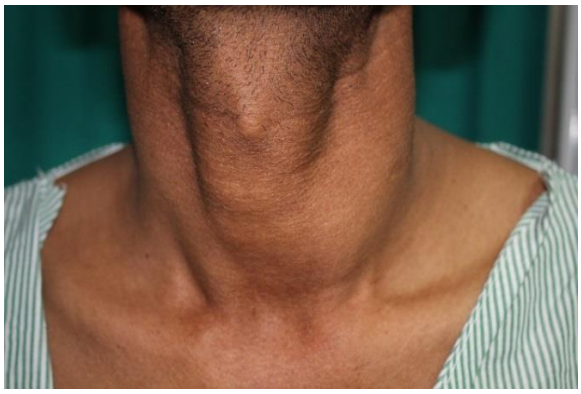
DISCUSSION

The present study is a Cross – sectional study conducted in 57 patients of DTCs worked up and operated in Department of Otorhinolaryngology, AIIMS, Jodhpur. The cases were selected by purposive sampling method. This study aimed at verifying if size of nodule is an independent prognostic factor of DTCs.

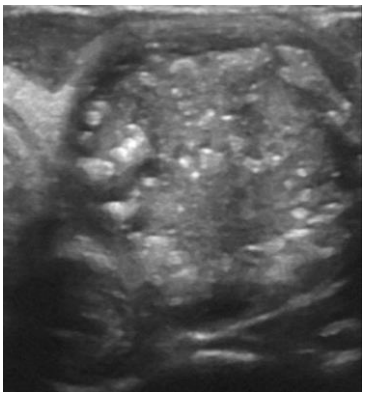
In this study, patients of DTC of all age were included, the youngest one was a 14-year-old girl and oldest was 61-year-old lady. For each patient, similar protocol has been followed. First the patient was clinically examined for thyroid nodule and neck nodes and clinical size was determined. The patient was then sent for USG neck and FNAC from the nodule. Nodule size on the basis of USG was determined. TIRADS and Bethesda grading was done and all patients with TIRADS 3 and above and Bethesda III and above was selected and underwent surgery as per ATA guidelines and as discussed in our departmental preoperative clinics. Histopathological features were studied post operatively. In all cases Neural Integrity Monitor (NIM) was used to check the integrity of recurrent laryngeal nerve.

Fig: 17: Papillary Thyroid Carcinoma in 50-year-old male.

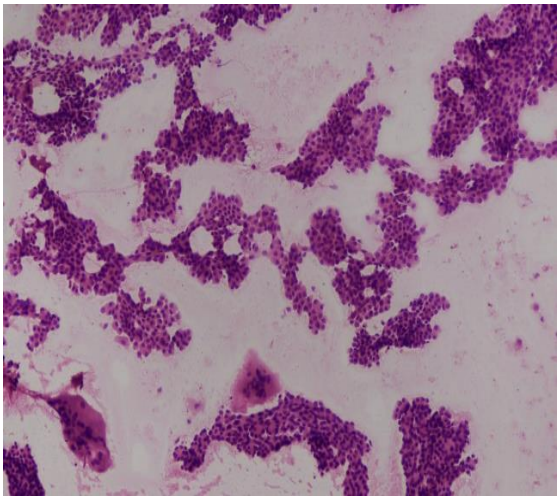
SUPERIOR



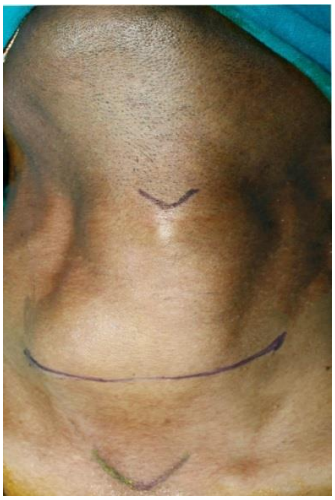
17.1- A 3x4 cm nodule in left thyroid lobe with deviation of trachea to right.



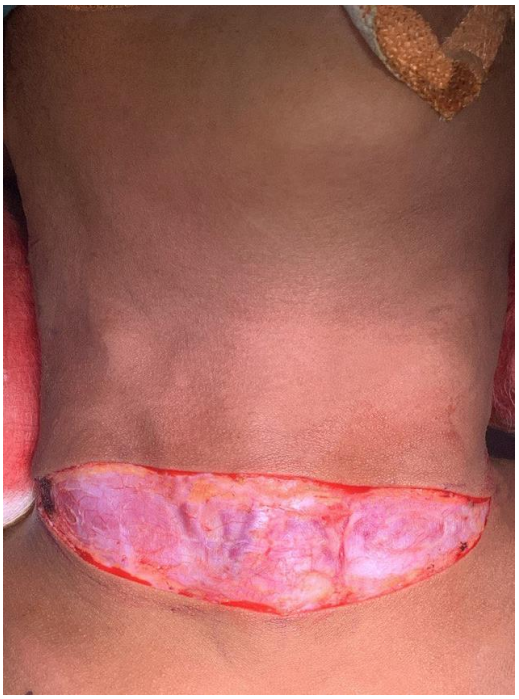
17.2- Left lobe TIRADS 4 nodule of size 2.4 X1.6 cms.



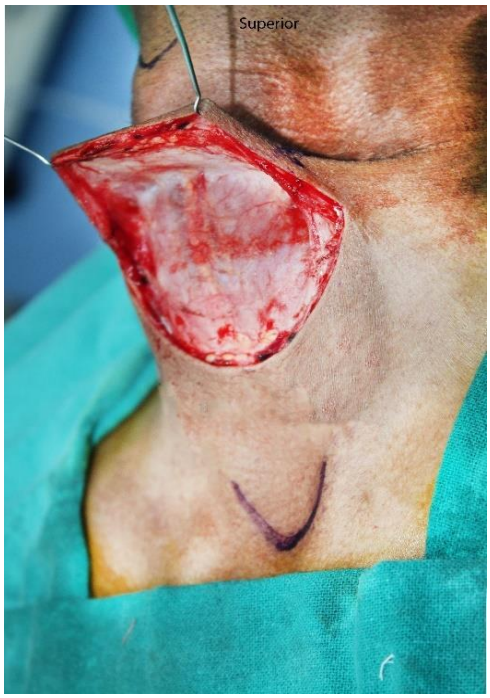
17.3- FNA of PTC, many papillae of tumour cells with enlarged nuclei, abundant cytoplasm and few multinucleated cells, (10X, H&E stain category VI)



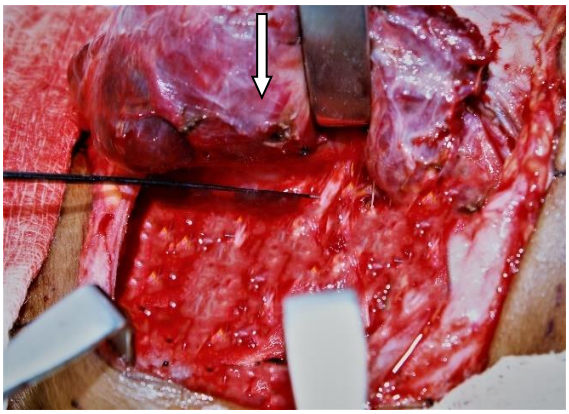
17.4- Incision marked for Total Thyroidectomy



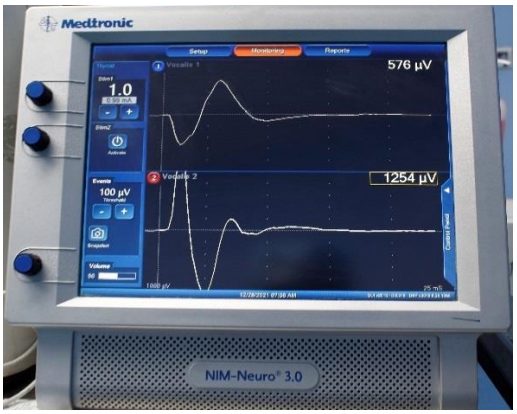
17.5- incision for total thyroidectomy



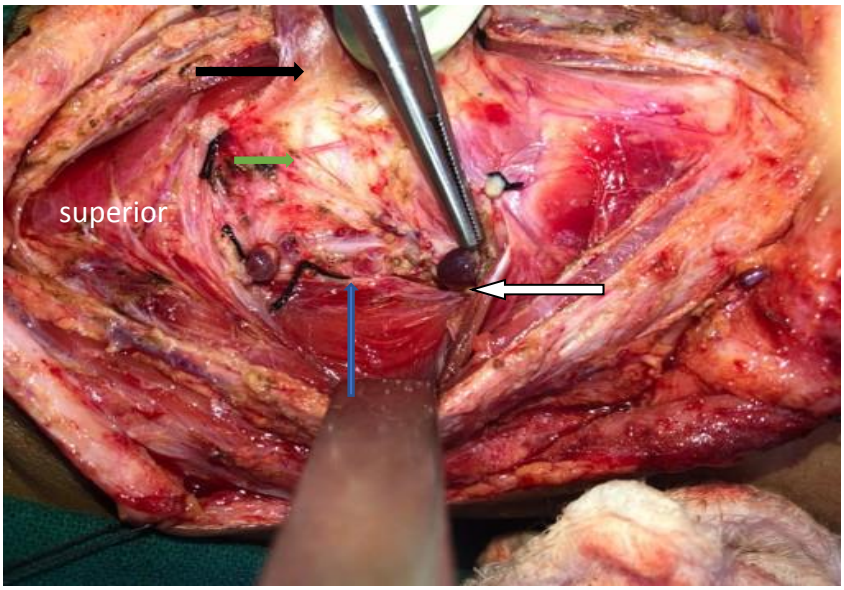
17.6- Raising subplatysmal flap



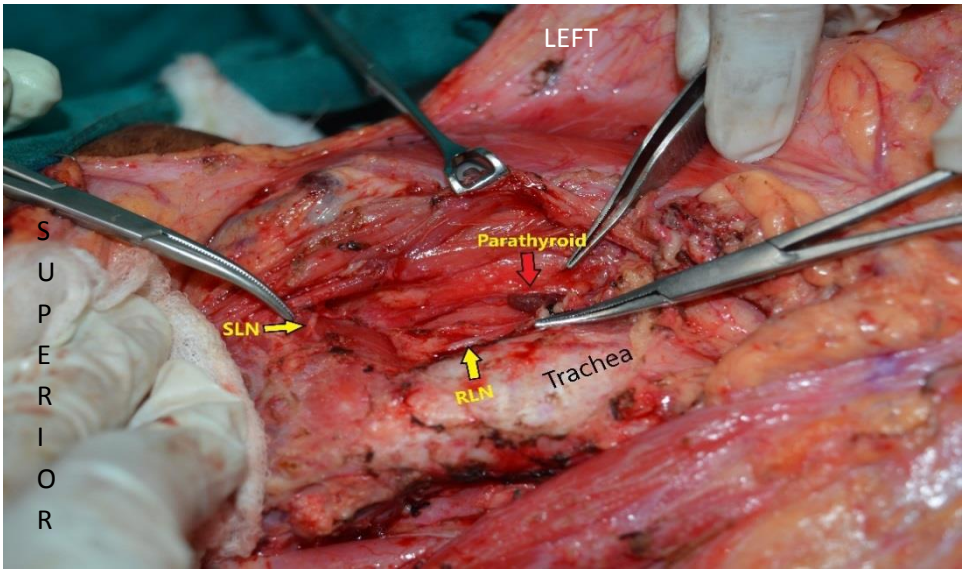
17.7- Identification of RLN and confirming using NIM neuro 3.0. White Arrow: Retracted Thyroid Gland.



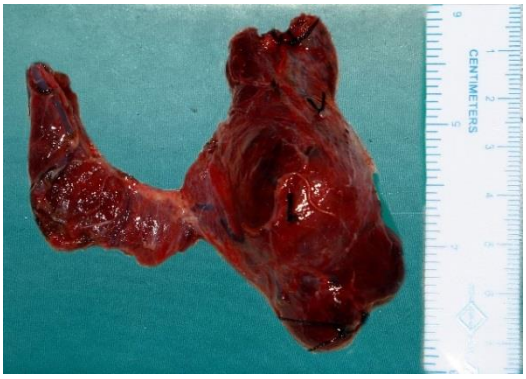
17.8- EMG of vocal cord (suggesting integrity of RLN) ON MEDTRONIC NIM-NEURO 3.0 AT CURRENT OF 1.0 mA and potential of 100 µV



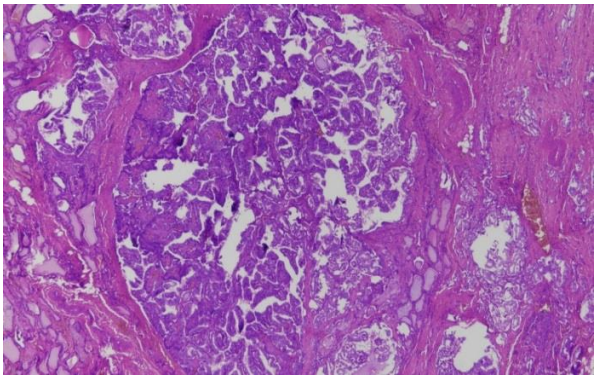
17.9- Delivery of Total thyroid specimen; Black Arrow –Retracted Thyroid Gland; White Arrow- Parathyroid Gland; Blue Arrow – RLN nerve; Green Arrow- Trachea



17.10- Preserved structures after removal Thyroidectomy specimen

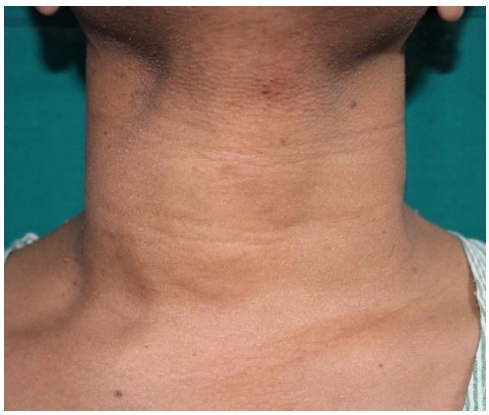


17.11- Total Thyroidectomy specimen

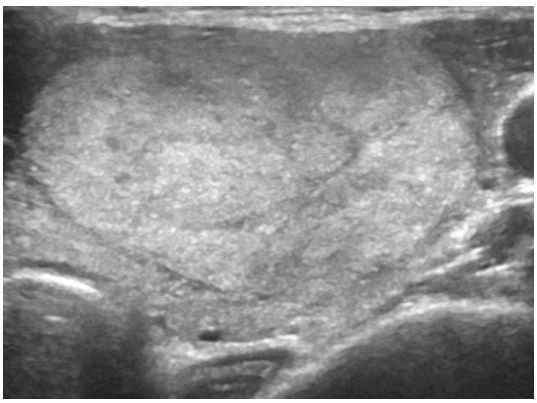


17.12- HPE image showing PTC (4x, H & E stain)

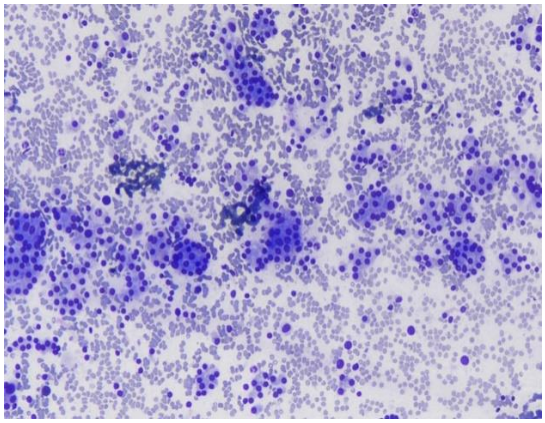
Fig: 18: Follicular neoplasm in a 30-year-old patient.



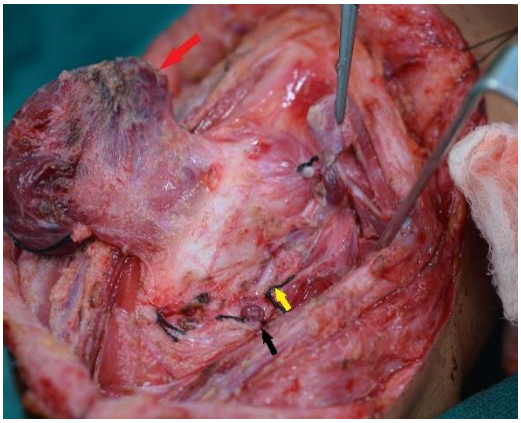
18.1- A 2x2 cm nodule in right lobe of thyroid



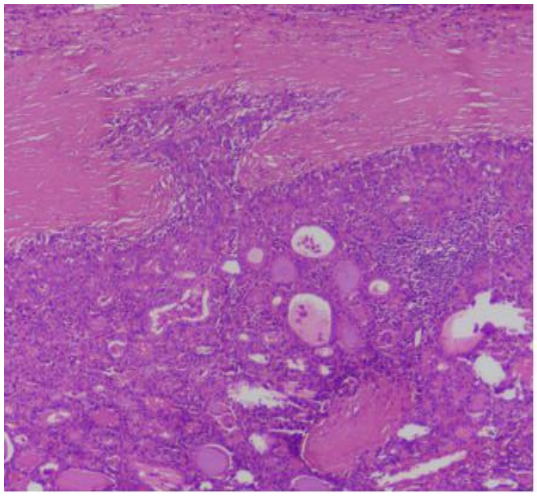
18.2- TIRADS 3 nodule of size 2x1.8 cm in right lobe of thyroid gland



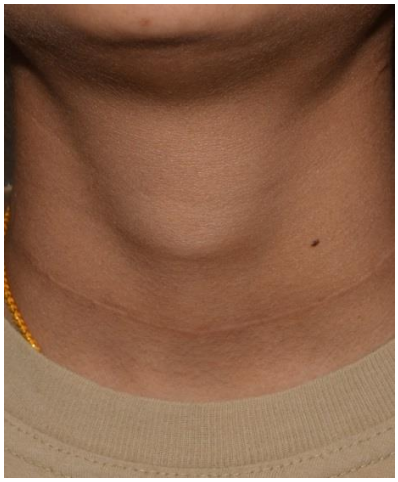
18.3- Follicular neoplasm, Bethesda Category IV



18.4- Intraoperative image of right hemithyroidectomy. (Red arrow- hemithyroidectomy specimen; yellow arrow- RLN; black arrow- Parathyroid Gland).



18.5- HPE image of Right Hemithyroidectomy showing minimally invasive Follicular Thyroid Carcinoma (4x, H&E Stain)



18.6- Postoperative Scar

Fig: 19– A young patient with small thyroid nodule with multiple neck nodes.

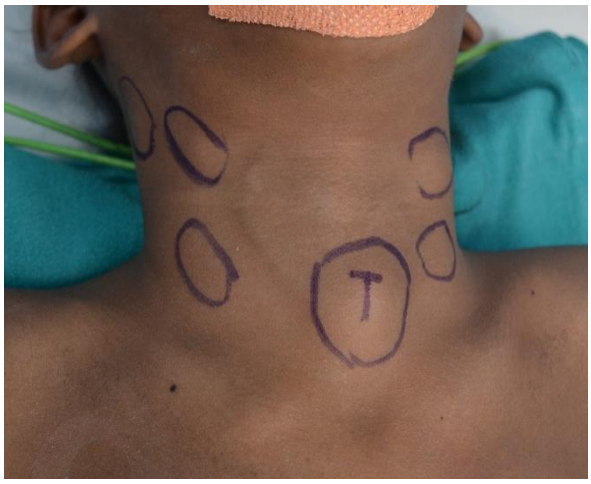
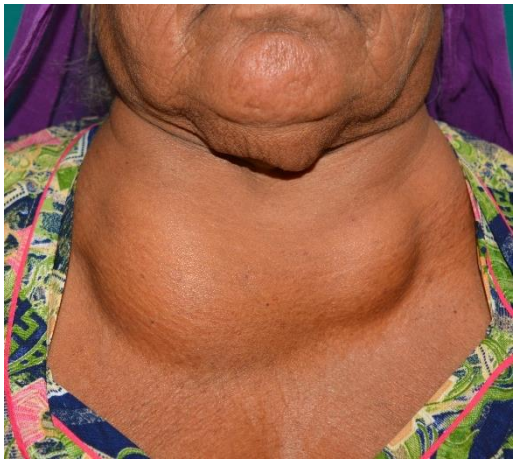
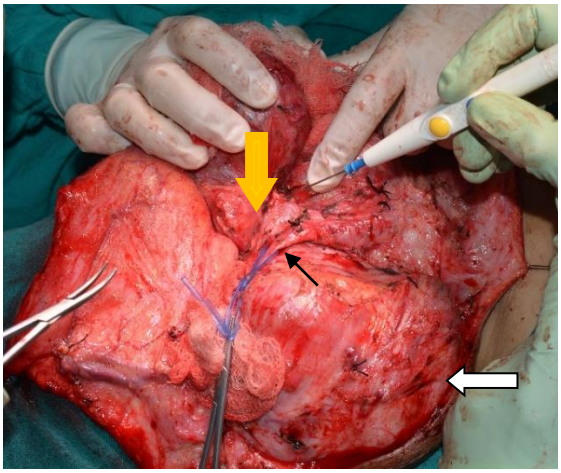


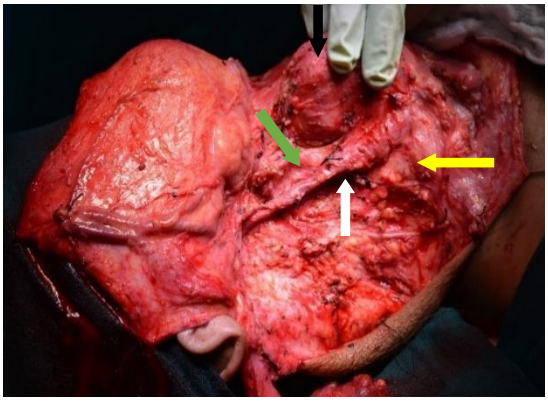
Fig: 20 – An elderly patient with massive Thyromegaly



20.1- Massive multifocal PTC; clinical image

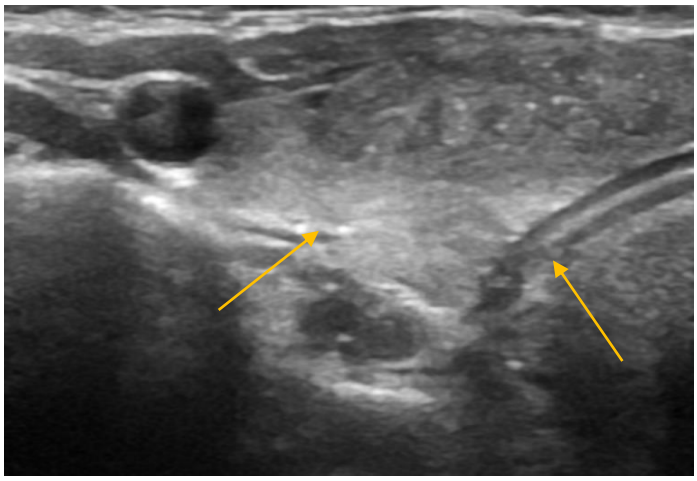


20.2- Intraoperative image showing large nodule with neck nodes. White Arrow: Enlarged thyroid nodule; Yellow Arrow: enlarged lymph node; Black Arrow: compressed IJV between nodule and lymph node.



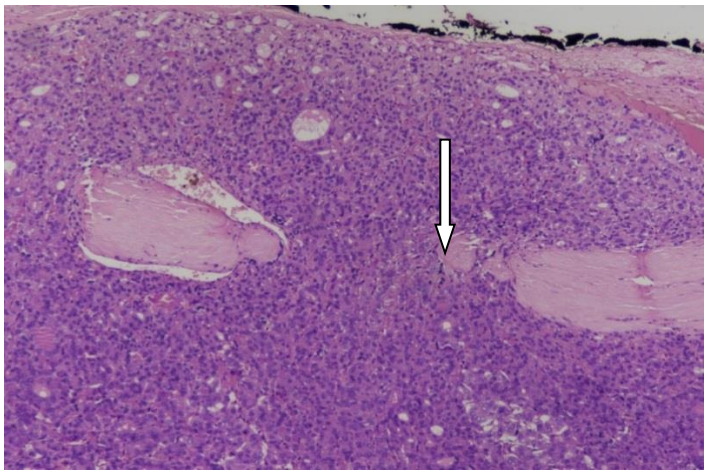
20.3- After removal of Total Thyroidectomy Specimen, status of IJV. White Arrow: IJV; Green Arrow: ICA; Yellow Arrow: Trachea; Black Arrow: Enlarged Lymph Node

Fig: 21- USG image showing capsular breach



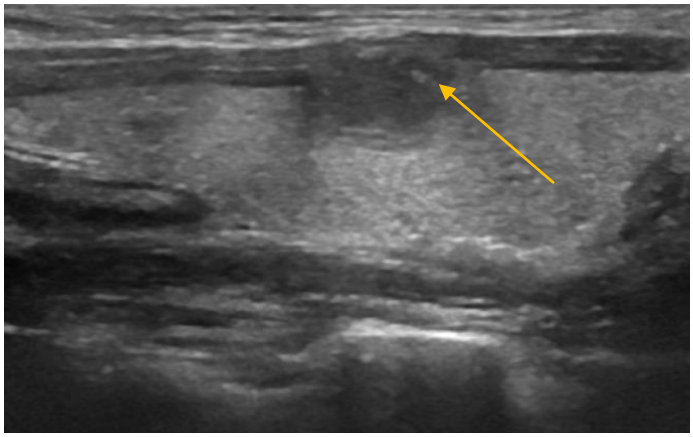
Arrow showing Capsular breach

Fig: 22 – Histopathological image showing capsular breach.



HPE showing capsular breach (H&E Stain, 4X)

Fig: 23- USG image showing Extra-thyroid Extension.



Arrow showing Strap Muscles involvement

Fig: 24 - Histopathological image showing lymph node metastasis of PTC.

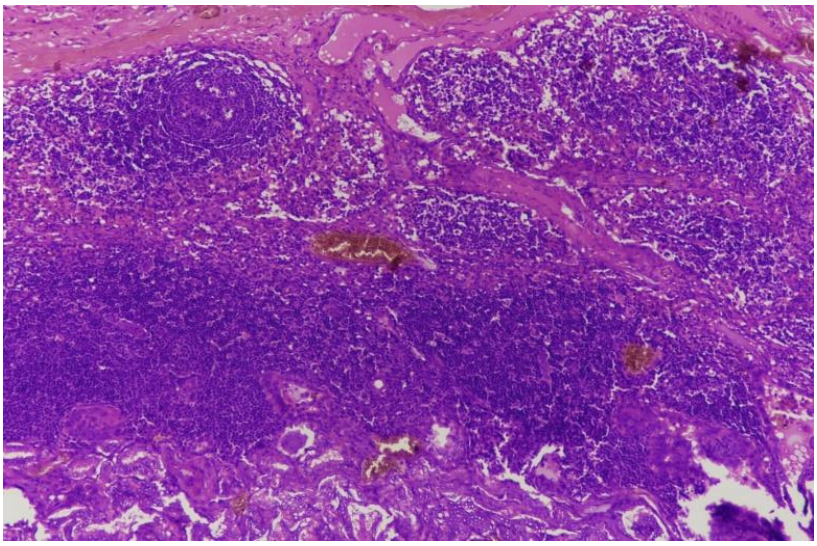


Fig. 24 HPE showing LNM (lower half of image) (H&E, 4X)

Thyroid cancer is one of the common malignancies and DTCs are the most common type of thyroid malignancy. Among DTCs, papillary Thyroid Cancer is most common accounting for about 90% of all DTCs. Size of nodule is considered as one of the most important independent prognostic factors of DTCs and size of nodule is incorporated in all prognostic classification system. Apart from nodule size there are multiple other prognostic indicators like age of patient, Gender, previous radiation exposure, ETE, Capsular invasion, LNM, and Distant Metastasis(12). But in our clinical experience we found that increasing nodule size in not necessarily indicative of poor prognosis and even smaller size nodule had poor prognosis. So, this study was aimed to determine the impact to nodule size on prognosis of DTCs. This study was a Cross- sectional study in which data was taken ambispectively in purposive type of sampling method and total of 57 patients were selected in the study. All the patients underwent USG neck then FNAC and underwent surgery. Their histopathology reports were assessed and poor prognostic indicators were compared with preoperative size of nodule.

In the present study, the mean age of participants was 35.91 ±1.82 and the median age is 35 years. The female to male ratio in the study is approximately 6:1, while in general female: male ratio for DTCs is about 3:1(82,83). The probable reason for this discrepancy is small sample size.

In this study, PTC was found in 66.7% of cases, FTC in 29.9% and Medullary Carcinoma in 3.5 % cases. According to recent studies, PTC account for about 90% of DTCs(9), the possible reason for this could be the small sample size. The prevalence of FTC is comparatively more in areas of iodine deficiency as compared to non-iodine deficient areas(84). Overall India is iodine deficient land but Rajasthan is one of the Indian state having iodine deficiency(85). This could be other possible reason of increased frequency of FTC in our study.

In this study correlation between TIRADS and Bethesda staging of disease and reliability of TIRADS grading was also conducted. We found that there is statistically significant positive correlation, with 75% of tumours with TIRADS 3 grade were Bethesda III and IV (P-value <0.05); whereas 81.2% and 82.3% respectively of TIRADS 4 and 5 lesion were Bethesda V and VI (P -value > 0.05). Biswas et al have done a study to see the correlation and stated that out of 37 patients who had TIRADS 2 lesion, 32 of them have Bethesda II lesion. Whereas only 4 patients with TIRADS 2 nodule turned out to be PTC on FNAC (i.e., Bethesda IV or V). In our study we had not taken patients with Bethesda II, so, this correlation cannot be done. They also stated that among TIRADS 3 nodule 70.5% of them were Bethesda II and III. In our study we have also got similar result(74). Periakaruppan et al had done similar study and stated that 90.2% patients with TIRADS 2 nodule on FNAC were having Bethesda II grading. In patients with TIRADS 3 nodule 93% were diagnosed as Bethesda II on FNAC. Our study result was not in concordance with this possibly because of small sample size. Whereas, only 38.5% of TIRADS 4 nodule came out be Bethesda V and VI. This is in striking difference with our study. Similarly, we found difference between TIRADS 5 nodule diagnosed as Bethesda 5 and 6 as compared to other studies(73).

In this study number of patients in size group < 2 cm, 2-4 cm and >4 cm was 18, 28 and 11 respectively. In our study we have found that prevalence of capsular invasion was low for nodule size >4 cm [36.4% (P- value > 0.05)] as compared to smaller nodule size [< 2cm- 50%; 2-4 cm 57.1% (P -value > 0.05)], suggesting that capsular

invasion is not necessarily related to increased nodule size. Araz et al, had done a study in September 2021 and stated that capsular invasion is associated with larger nodule size and in cases of multifocal nodule the sum of diameter of all nodules is associated with capsular invasion(86). Luo et al, had done study in September 2020 to look for the impact of size on capsular invasion and found statistically significant correlation between increasing size and capsular invasion with a size cut- off of 1.1 cm. with sensitivity and specificity of 80.6% and 56.3% respectively(87). But in our study, we found no statistically correlation between size and capsular invasion. The probable reason for this could be small sample size and this needs to be further investigated with a larger prospective study. However prognostic significance of capsular invasion is questionable. Furlan et al, had done a study to look for prognostic implication of capsular invasion in 350 cases and stated that 53.1% cases had capsular invasion but, there was no significant difference in short term or long-term prognosis of patients(88).

Similar results were found on correlation of nodule size and ETE, with 38.9%, 42.9% and 27.3% incidence of ETE in nodule size group <2 cm, 2-4 cm and >4 cm respectively. This indicates ETE is not related with nodule size however this data is statistically insignificant. However, it is proven that ETE is a poor prognostic factor(14) and it is also included in TNM classification and ATA guidelines of DTCs. Kuo et al had done a study in September 2020 and stated that 33% patients of DTC had ETE and size of nodule is an independent factor for ETE with an odd ratio of 1.915(89). Shaha et al and Wang et al independently studied the effect nodule size on ETE and found a statistically significant difference in nodules <4 cm and ≥ 4 cm and concluded that size is an independent indicator of ETE(27,38). In our study, we found there is no correlation between nodule size and ETE, the likely reason this could be small sample size but this an important finding, so this needs to further investigated with larger study.

On comparing the impact of size on LNM, the results were almost equal in all three size groups with a frequency of 44.4%, 50% and 45.5% respectively with P-value > 0.005, suggesting that nodule size is not associated with LNM. Tam et al, found a statistically significant difference in LNM and locoregional metastasis in patients with nodule size <4 cm and > 4 cm and stated that larger nodule size is associated with a greater risk of LNM. They also stated that presence of micro ETE was also associated

with increased chances of LNM. They found 1% patients with nodule size < 4cm with no micro ETE had LNM while in 2% with nodule size < 4 cm with micro ETE. However, in patients with nodule size > 4 cm with micro ETE, 15% had LNM(36). Similarly, various studies found statistically significant increase in LNM and distant metastasis in patients with nodule size > 2 cm. Reddy et al, studied the incidence of LNM in nodules < 2 cm and found prevalence of LNM is 45%(35), in our study we have also got similar results. Valderrabano et al in their study of 652 patients stated that there is no correlation of size and prevalence of LNM and there is no change in prognosis with increasing nodule size(90). In our study, we found no statistically significant correlation between tumor size and LNM. This is probably due to small sample size and this needs to be further investigated with larger study to confirm if tumor size is independent indicator of LNM.

On evaluating effect of nodule size on vascular invasion, we found that frequency of vascular invasion has increasing relation to increase in nodule size (P- value > 0.05), with frequency of 22.2%, 17.9% and 36.4% respectively for nodule size <2 cm, 2-4 cm and > 4cm. Reddy et al, in their study of 551 patients stated that there is a statistically significant correlation between increase in nodule size and vascular invasion(35). Tam et al, in their study, stated that the presence of vascular invasion was significantly higher in nodule larger than 4 cm as compared to nodule< 4 cm They also stated that presence of micro ETE was also associated with increased chances of vascular invasion. They found 10% patients with nodule size < 4cm with no micro ETE had vascular invasion while in 33% with nodule size < 4 cm with micro ETE. However, in patients with nodule size > 4 cm with micro ETE, 69% had vascular invasion(36). Valderrabano et al in their study of 652 patients stated that there is no correlation of size and prevalence of Lympho-vascular invasion(90). In our study, we had also found similar result but this needs to be further investigated with larger study to well establish the fact.

In the present study impact of nodule size on incidence of RLN involvement or preoperative VC palsy was evaluated and we found that total of 5 patients had VC palsy with 2 patients with nodule size < 2 cm, 2 patients with nodule size >4 cm and 1 patient with nodule size 2-4 cm. In their study, Rivest et al stated that the incidence of vocal cord palsy in patients with thyroid nodules was 1.3% (25/1923). Within the category of VC palsy, 76% (19/25) was due to malignant pathology. They stated that

the reason for this are i) direct involvement of RLN by disease, ii) compression of RLN(91). In their study, Chen et al stated that out of 3236 patients 105 patients had RLN palsy. They found a positive correlation between size and RLN involvement with a cut-off size of 1 cm. However, they stated that apart from size there are multiple other important factors like ETE, oesophageal involvement, tracheal extension and LNM which can lead to RLN involvement(92). In our study, we found almost equal incidence of RLN in tumors <2 cm and >4 cm suggesting that even small nodules can have RLN palsy. It is likely that small nodule will not cause compression over RLN that lead to palsy. This indirectly suggest that small tumours can have extracapsular involvement and RLN involvement leading to palsy. But, the sample size of the study is small so, this need to be further confirmed with a larger study.

Although size of nodule in DTCs is considered to be an independent prognostic indicator and size of nodule is incorporated in all prognostic classification of DTCs, including TNM classification and ATA guidelines. Also, there are multiple publication and authors who consider size as an independent prognostic indicator. There are evidences that prove size is an independent marker for short term prognostic indicators like, LNM, Capsular Invasion, ETE, Nuclear atypia, Tumoral necrosis, Vascular Invasion and RLN involvement(27,36,86,87,89,92). However, there are multiple authors who got the results otherwise and stated that prognosis of DTCs does not depend on size of nodule(20,35,90,93). In our clinical practice we have also observed that even small nodule can have worse outcome. In our study also, we found no correlation between size of nodule and short-term prognostic indicator (**Table 15**). Even though, we could not establish a statistically significant correlation between nodule size and poor prognostic indicators due to small sample size, we found that prevalence of some prognostic indicators like Capsular Invasion, ETE and Tumoural necrosis were higher in nodules < 2 cm in size as compared to that of > 4 cm in size. So, we recommend that results of this study need to be further investigated. Also, our study is single centre study. To extrapolate the results multicentric study with large sample size to cover a diverse population may be done to establish more robust evidence.

STRENGTHS AND LIMITATIONS

STRENGTHS AND LIMITATION

STRENGTHS:

1. All the patients were enrolled after complete evaluation.
2. Short term prognostic indicators (e.g., Capsular Invasion, Vascular Invasion, LNM, ETE, tumoural necrosis etc) were assessed. No other study has been done only on short term prognostic indicators.
3. There was no loss to follow up.

LIMITATIONS:

1. No long term follow up was done
2. Single centre study
3. Disease specific survival, recurrence, mortality was not assessed.
4. No blinding was done.

RECOMMENDATIONS

RECOMMENDATIONS

The incidence of thyroid cancer has been increasing worldwide and in India in the last three decades. However much of this increase is attributed to extensive use of screening USG. As per the results of this study we recommend that each palpable thyroid nodule must be screened by USG and a suspicious nodule on USG (TIRADS 3 and above), should be further evaluated with FNAC. We also recommend that decisions about the management of thyroid nodules should not be based on the size of the nodule because even small tumours can have poor outcomes. However, this needs to be further evaluated by a prospective, multicentre study with larger sample size.

CONCLUSION

CONCLUSION

As per this study, we conclude that there is no relationship between preoperative nodule size and poor prognostic indicators in patients with DTCs and each patient with thyroid nodule should be screened by USG neck and/ or FNAC/ USG guided FNAC and further management should be planned accordingly. In this study even small sized nodules had RLN involvement, suggesting that even small sized tumour can have extensive ETE. So, even small size nodules should be dealt by high volume surgeons. In this study, we have studied only short-term prognostic indicators and no patient was followed up to look for DSS, mortality or morbidity. However, this study is ambispective and the sample size is small and the results needs to be further investigated with a prospective, multicentre study with a larger sample size to confirm the finding and to establish robust evidence.

REFERENCES

REFERENCES

1. Marketos S, Eftychiadis A, Koutras DA. Thyroid Diseases in the Byzantine Era. J R Soc Med. 1990 Feb;83(2):111–3.
2. DuBose J, Barnett R, Ragsdale T. Honest and sensible surgeons: the history of thyroid surgery. Curr Surg. 2004 Mar;61(2):213–9.
3. 0354-950X0303009I.pdf [Internet]. [cited 2021 Oct 10]. Available from: http://www.doiserbia.nb.rs/img/doi/0354-950X/2003/0354-950X0303009I.pdf
4. operatie story of goitre, halsted.pdf.
5. Becker WF. Pioneers in Thyroid Surgery: Ann Surg. 1977 May;185(5):493–504.
6. 30984.pdf.
7. Cancer of the Thyroid - Cancer Stat Facts [Internet]. SEER. [cited 2021 Dec 24]. Available from: https://seer.cancer.gov/statfacts/html/thyro.html
8. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. JAMA. 2017 Apr 4;317(13):1338.
9. Nilubol N, Kebebew E. Should small papillary thyroid cancer be observed? A population-based study: Mortality intSmall Thyroid Cancer. Cancer. 2015 Apr 1;121(7):1017–24.
10. Panato C, Vaccarella S, Dal Maso L, Basu P, Franceschi S, Serraino D, et al. Thyroid Cancer Incidence in India Between 2006 and 2014 and Impact of Overdiagnosis. J Clin Endocrinol Metab. 2020 Aug 1;105(8):2507–14.
11. Deng Y, Li H, Wang M, Li N, Tian T, Wu Y, et al. Global Burden of Thyroid Cancer From 1990 to 2017. JAMA Netw Open. 2020 Jun 26;3(6):e208759.
12. Shah JP. Thyroid Carcinoma: Epidemiology, Histology, and Diagnosis. Clin Adv Hematol Oncol HO. 2015 Apr;13(4 Suppl 4):3–6.
13. Zhang D, Tang J, Kong D, Cui Q, Wang K, Gong Y, et al. Impact of Gender and Age on the Prognosis of Differentiated Thyroid Carcinoma: a Retrospective Analysis Based on SEER. Horm Cancer. 2018 Oct;9(5):361–70.
14. AJCC Cancer Staging Form Supplement to the AJCC Cancer Staging Manual, Eighth Edition.pdf.
15. Kazaure HS, Roman SA, Sosa JA. The impact of age on thyroid cancer staging: Curr Opin Endocrinol Diabetes Obes. 2018 Oct;25(5):330–4.
16. Zhao L, Wang L, Jia X, Hu X, Pang P, Zhao S, et al. The Coexistence of Genetic Mutations in Thyroid Carcinoma Predicts Histopathological Factors Associated With a Poor Prognosis: A Systematic Review and Network Meta-Analysis. Front Oncol. 2020 Nov 3;10:540238.

17. Zhang G-Q, Shen C-T, Song H-J, Qiu Z-L, Luo Q-Y. High Expression of Interleukin-12A and Its Association with the Clinicopathology and Prognosis of Differentiated Thyroid Cancer. Eur Thyroid J. 2020;9(3):139–47.

18. Figlioli G, Chen B, Elisei R, Romei C, Campo C, Cipollini M, et al. Novel genetic variants in differentiated thyroid cancer and assessment of the cumulative risk. Sci Rep. 2015 Mar 10;5(1):8922.

19. Ganly I, Ibrahimpasic T, Rivera M, Nixon I, Palmer F, Patel SG, et al. Prognostic Implications of Papillary Thyroid Carcinoma with Tall-Cell Features. Thyroid. 2014 Apr;24(4):662–70.

20. Sobin LH, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours. :332.

21. Chen D, Huang L, Chen S, Huang Y, Hu D, Zeng W, et al. Innovative analysis of distant metastasis in differentiated thyroid cancer. Oncol Lett. 2020 Mar;19(3):1985–92.

22. Zhao Y, Zhang Y, Liu X-J, Shi B-Y. Prognostic Factors for Differentiated Thyroid Carcinoma and Review of the Literature. Tumori J. 2012 Mar;98(2):233–7.

23. Song E, Jeon MJ, Oh H-S, Han M, Lee Y-M, Kim TY, et al. Do aggressive variants of papillary thyroid carcinoma have worse clinical outcome than classic papillary thyroid carcinoma? Eur J Endocrinol. 2018 Sep;179(3):135–42.

24. Byar DP, Green SB, Dor P, Williams ED, Colon J, van Gilse HA, et al. A prognostic index for thyroid carcinoma. A study of the E.O.R.T.C. thyroid cancer cooperative group. Eur J Cancer 1965. 1979 Aug;15(8):1033–41.

25. Lang BH-H, Lo C-Y, Chan W-F, Lam K-Y, Wan K-Y. Staging Systems for Papillary Thyroid Carcinoma: A Review and Comparison. Ann Surg. 2007 Mar;245(3):366–78.

26. Teo K, Yuan N, Tan W, Parameswaran R. Comparison of prognostic scoring systems in follicular thyroid cancer. Ann R Coll Surg Engl. 2017 Jul;99(6):479–84.

27. Shaha AR. Implications of Prognostic Factors and Risk Groups in the Management of Differentiated Thyroid Cancer: The Laryngoscope. 2004 Mar;114(3):393–402.

28. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery. 1993 Dec;114(6):1050–7; discussion 1057-1058.

29. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The

American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016 Jan;26(1):1–133.

30. Cramer JD, Fu P, Harth KC, Margevicius S, Wilhelm SM. Analysis of the rising incidence of thyroid cancer using the Surveillance, Epidemiology and End Results national cancer data registry. Surgery. 2010 Dec;148(6):1147–53.

31. Lortet-Tieulent J, Franceschi S, Dal Maso L, Vaccarella S. Thyroid cancer "epidemic" also occurs in low- and middle-income countries: Thyroid Cancer "Epidemic" in developing countries. Int J Cancer. 2019 May 1;144(9):2082–7.

32. Glikson E, Alon E, Bedrin L, Talmi YP. Prognostic Factors in Differentiated Thyroid Cancer Revisited. 2017;19:5.

33. Tuttle RM, Alzahrani AS. Risk Stratification in Differentiated Thyroid Cancer: From Detection to Final Follow-Up. J Clin Endocrinol Metab. 2019 Sep 1;104(9):4087–100.

34. Krämer JA, Schmid KW, Dralle H, Dietlein M, Schicha H, Lerch H, et al. Primary tumour size is a prognostic parameter in patients suffering from differentiated thyroid carcinoma with extrathyroidal growth: results of the MSDS trial. Eur J Endocrinol. 2010 Oct;163(4):637–44.

35. Reddy RM, Grigsby PW, Moley JF, Hall BL. Lymph node metastases in differentiated thyroid cancer under 2 cm. Surgery. 2006 Dec;140(6):1050–5.

36. Tam S, Amit M, Boonsripitayanon M, Busaidy NL, Cabanillas ME, Waguespack SG, et al. Effect of Tumor Size and Minimal Extrathyroidal Extension in Patients with Differentiated Thyroid Cancer. Thyroid. 2018 Aug;28(8):982–90.

37. Tam S, Boonsripitayanon M, Amit M, Fellman BM, Li Y, Busaidy NL, et al. Survival in Differentiated Thyroid Cancer: Comparing the AJCC Cancer Staging Seventh and Eighth Editions. Thyroid. 2018 Oct;28(10):1301–10.

38. Wang Z, Zhang Q, Ye H, Jia C, Lv Z, Liu J, et al. Tumor Size is an Independent Predictor of Mortality Risk in Differentiated Thyroid Cancer Patients with T4 Disease. Endocr Pract. 2020 May;26(5):499–507.

39. Tran B, Roshan D, Abraham E, Wang L, Garibotto N, Wykes J, et al. The Prognostic Impact of Tumor Size in Papillary Thyroid Carcinoma is Modified by Age. :6.

40. Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS, et al. Extent of Surgery Affects Survival for Papillary Thyroid Cancer. Ann Surg. 2007 Sep;246(3):375–84.

41. Chereau N, Trésallet C, Noullet S, Godiris-Petit G, Tissier F, Leenhardt L, et al. Does the T1 subdivision correlate with the risk of recurrence of papillary thyroid cancer? Langenbecks Arch Surg. 2016 Mar;401(2):223–30.

42. Shah S, Boucai L. Effect of Age on Response to Therapy and Mortality in Patients With Thyroid Cancer at High Risk of Recurrence. J Clin Endocrinol Metab. 2018 Feb 1;103(2):689–97.

43. Shen X, Zhu G, Liu R, Viola D, Elisei R, Puxeddu E, et al. Patient Age–Associated Mortality Risk Is Differentiated by *BRAF* V600E Status in Papillary Thyroid Cancer. J Clin Oncol. 2018 Feb 10;36(5):438–45.

44. Yan H, Winchester DJ, Prinz RA, Wang C-H, Nakazato Y, Moo-Young TA. Differences in the Impact of Age on Mortality in Well-Differentiated Thyroid Cancer. Ann Surg Oncol. 2018 Oct;25(11):3193–9.

45. Kim S, Myong JP, Suh H, Lee KE, Youn Y-K. Optimal Cutoff Age for Predicting Mortality Associated with Differentiated Thyroid Cancer. Soares P, editor. PLOS ONE. 2015 Jun 23;10(6):e0130848.

46. Lorenz K, Schneider R, Elwerr M. Thyroid Carcinoma: Do We Need to Treat Men and Women Differently? Visc Med. 2020;36(1):10–4.

47. Lee YH, Lee YM, Sung TY, Yoon JH, Song DE, Kim TY, et al. Is Male Gender a Prognostic Factor for Papillary Thyroid Microcarcinoma? Ann Surg Oncol. 2017 Jul;24(7):1958–64.

48. Liu C, Chen T, Zeng W, Wang S, Xiong Y, Liu Z, et al. Reevaluating the prognostic significance of male gender for papillary thyroid carcinoma and microcarcinoma: a SEER database analysis. Sci Rep. 2017 Dec;7(1):11412.

49. Maino F, Forleo R, Pacini F. Prognostic indicators for papillary thyroid carcinoma. Expert Rev Endocrinol Metab. 2017 Mar 4;12(2):101–8.

50. Ito Y, Hirokawa M, Masuoka H, Yabuta T, Kihara M, Higashiyama T, et al. Prognostic factors of minimally invasive follicular thyroid carcinoma: Extensive vascular invasion significantly affects patient prognosis. Endocr J. 2013;60(5):637–42.

51. Subash A, Sinha P, Singh A. BRAF mutation and age in differentiated thyroid cancer risk stratification: Two sides of the same coin. Oral Oncol. 2020 Jul;106:104732.

52. Kim TY, Kim WB, Rhee YS, Song JY, Kim JM, Gong G, et al. The BRAF mutation is useful for prediction of clinical recurrence in low-risk patients with conventional papillary thyroid carcinoma. Clin Endocrinol (Oxf). 2006 Sep;65(3):364–8.

53. Lee J-H, Lee E-S, Kim Y-S. Clinicopathologic significance ofBRAF V600E mutation in papillary carcinomas of the thyroid: A meta-analysis. Cancer. 2007 Jul 1;110(1):38–46.

54. Daliri M, Abbaszadegan MR, Mehrabi Bahar M, Arabi A, Yadollahi M, Ghafari A, et al. The role of BRAF V600E mutation as a potential marker for prognostic

stratification of papillary thyroid carcinoma: a long-term follow-up study. Endocr Res. 2014 Nov;39(4):189–93.

55. Gillanders SL, O'Neill JP. Prognostic markers in well differentiated papillary and follicular thyroid cancer (WDTC). Eur J Surg Oncol. 2018 Mar;44(3):286–96.

56. Brauckhoff M. Classification of aerodigestive tract invasion from thyroid cancer. Langenbecks Arch Surg. 2014 Feb;399(2):209–16.

57. McCaffrey JC. Aerodigestive Tract Invasion by Well-Differentiated Thyroid Carcinoma: Diagnosis, Management, Prognosis, and Biology: The Laryngoscope. 2006 Jan;116(1):1–11.

58. Du B, Wang F, Wu L, Wang Z, Zhang D, Huang Z, et al. Cause-specific mortality after diagnosis of thyroid cancer: a large population-based study. Endocrine. 2021 Apr;72(1):179–89.

59. McLeod DSA, Cooper DS, Ladenson PW, Ain KB, Brierley JD, Fein HG, et al. Prognosis of Differentiated Thyroid Cancer in Relation to Serum Thyrotropin and Thyroglobulin Antibody Status at Time of Diagnosis. Thyroid. 2014 Jan;24(1):35–42.

60. Mussazhanova Z, Rogounovitch TI, Saenko VA, Krykpayeva A, Espenbetova M, Azizov B, et al. The Contribution of Genetic Variants to the Risk of Papillary Thyroid Carcinoma in the Kazakh Population: Study of Common Single Nucleotide Polymorphisms and Their Clinicopathological Correlations. Front Endocrinol. 2021 Jan 22;11:543500.

61. Nguyen QT, Lee EJ, Huang MG, Park YI, Khullar A, Plodkowski RA. Diagnosis and Treatment of Patients with Thyroid Cancer. Am Health Drug Benefits. 2015 Feb;8(1):30–40.

62. Traylor KS. Computed Tomography and MR Imaging of Thyroid Disease. Radiol Clin North Am. 2020 Nov;58(6):1059–70.

63. Horvath E, Majlis S, Rossi R, Franco C, Niedmann JP, Castro A, et al. An Ultrasonogram Reporting System for Thyroid Nodules Stratifying Cancer Risk for Clinical Management. J Clin Endocrinol Metab. 2009 May 1;94(5):1748–51.

64. Zhuang Y, Li C, Hua Z, Chen K, Lin JL. A novel TIRADS of US classification. Biomed Eng OnLine. 2018 Dec;17(1):82.

65. Floridi C, Cellina M, Buccimazza G, Arrichiello A, Sacrini A, Arrigoni F, et al. Ultrasound imaging classifications of thyroid nodules for malignancy risk stratification and clinical management: state of the art. Gland Surg. 2019 Sep;8(Suppl 3):S233–44.

66. Russ G, Bigorgne C, Royer B, Rouxel A, Bienvenu-Perrard M. Le système TIRADS en échographie thyroïdienne. J Radiol. 2011 Jul;92(7–8):701–13.

67. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults: The EU-TIRADS. Eur Thyroid J. 2017 Sep;6(5):225–37.

68. Shin JH, Baek JH, Chung J, Ha EJ, Kim J, Lee YH, et al. Ultrasonography Diagnosis and Imaging-Based Management of Thyroid Nodules: Revised Korean Society of Thyroid Radiology Consensus Statement and Recommendations. Korean J Radiol. 2016;17(3):370.

69. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Am J Clin Pathol. 2009 Nov;132(5):658–65.

70. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. J Am Soc Cytopathol. 2017 Nov;6(6):217–22.

71. Lechner MG, Hershman JM. Thyroid Nodules and Cancer in the Elderly. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2022 Jan 21]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK278969/

72. Alshaikh S, Harb Z, Aljufairi E, Almahari SA. Classification of thyroid fine-needle aspiration cytology into Bethesda categories: An institutional experience and review of the literature. CytoJournal. 2018 Feb 16;15:4.

73. Periakaruppan G, Seshadri KG, Vignesh Krishna GM, Mandava R, Sai VPM, Rajendiran S. Correlation between Ultrasound-based TIRADS and Bethesda System for Reporting Thyroid-cytopathology: 2-year Experience at a Tertiary Care Center in India. Indian J Endocrinol Metab. 2018;22(5):651–5.

74. Biswas A, Basu K, De S, Karmakar S, De D, Sengupta M, et al. Correlation between Thyroid Imaging Reporting and Data System and Bethesda System of Reporting of Thyroid Cytopathology of Thyroid Nodule: A Single Center Experience. J Cytol. 2020;37(4):193–9.

75. Vargas-Uricoechea H, Meza-Cabrera I, Herrera-Chaparro J. Concordance between the TIRADS ultrasound criteria and the BETHESDA cytology criteria on the nontoxic thyroid nodule. Thyroid Res. 2017 Dec;10(1):1.

76. Singaporewalla RM, Hwee J, Lang TU, Desai V. Clinico-pathological Correlation of Thyroid Nodule Ultrasound and Cytology Using the TIRADS and Bethesda Classifications. World J Surg. 2017 Jul;41(7):1807–11.

77. Hay ID, Grant CS, Taylor WF, McConahey WM. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery. 1987 Dec;102(6):1088–95.

78. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery. 1988 Dec;104(6):947–53.

79. Tang J, Kong D, Cui Q, Wang K, Zhang D, Liao X, et al. The role of radioactive iodine therapy in papillary thyroid cancer: an observational study based on SEER. OncoTargets Ther. 2018 Jun 19;11:3551–60.

80. Luster M, Clarke SE, Dietlein M, Lassmann M, Lind P, Oyen WJG, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. Eur J Nucl Med Mol Imaging. 2008 Oct;35(10):1941–59.

81. Giannoula E, Melidis C, Papadopoulos N, Bamidis P, Raftopoulos V, Iakovou I. Dynamic Risk Stratification for Predicting Treatment Response in Differentiated Thyroid Cancer. J Clin Med. 2020 Aug 21;9(9):2708.

82. Nagarkar R, Roy S, Akheel M, Palwe V, Kulkarni N, Pandit P. Incidence of Thyroid Disorders in India: An Institutional Retrospective Analysis. Int J Dent Med Spec. 2015;2(2):19.

83. Thyroid Cancer - Statistics [Internet]. Cancer.Net. 2012 [cited 2021 Dec 26]. Available from: https://www.cancer.net/cancer-types/thyroid-cancer/statistics

84. Der EM. Follicular Thyroid Carcinoma in a Country of Endemic Iodine Deficiency (1994–2013). J Thyroid Res. 2018 Feb 25;2018:e6516035.

85. Pandav CS, Yadav K, Srivastava R, Pandav R, Karmarkar MG. Iodine deficiency disorders (IDD) control in India. Indian J Med Res. 2013 Sep;138(3):418–33.

86. Araz M, Özkan E, Gunduz P, Soydal C, Küçük NÖ, Kır KM. Negative Histopathological Prognostic Factors Affecting Morbidity in T1 Differentiated Thyroid Carcinoma. Cancer Biother Radiopharm. 2021 Sep 15;

87. Luo H, Yan F, Lan L, Ma B, Zhao H, He Y, et al. Ultrasonographic Features, Nodule Size, Capsular Invasion, and Lymph Node Metastasis of Solitary Papillary Carcinoma of Thyroid Isthmus. Front Oncol [Internet]. 2020 [cited 2022 Feb 6];10. Available from: https://www.frontiersin.org/article/10.3389/fonc.2020.558363

88. Furlan JC, Bedard YC, Rosen IB. Significance of tumor capsular invasion in well-differentiated thyroid carcinomas. Am Surg. 2007 May;73(5):484–91.

89. Kuo C-Y, Yang P-S, Chien M-N, Cheng S-P. Preoperative Factors Associated with Extrathyroidal Extension in Papillary Thyroid Cancer. Eur Thyroid J. 2020 Sep;9(5):256–62.

90. Valderrabano P, Khazai L, Thompson ZJ, Otto KJ, Hallanger-Johnson JE, Chung CH, et al. Association of Tumor Size With Histologic and Clinical Outcomes Among Patients With Cytologically Indeterminate Thyroid Nodules. JAMA Otolaryngol Neck Surg. 2018 Sep 1;144(9):788–95.

91. Kay-Rivest E, Mitmaker E, Payne RJ, Hier MP, Mlynarek AM, Young J, et al. Preoperative vocal cord paralysis and its association with malignant thyroid disease and other pathological features. J Otolaryngol - Head Neck Surg. 2015 Dec;44(1):35.

92. Chen W, Lei J, You J, Lei Y, Li Z, Gong R, et al. Predictive factors and prognosis for recurrent laryngeal nerve invasion in papillary thyroid carcinoma. OncoTargets Ther. 2017 Sep 11;10:4485–91.

93. Zhang T, Li C, Wen S, Huang D, Sun G, Zhu Y, et al. Effects of tumor size on prognosis in differentiated thyroid carcinoma smaller than 2 cm. Oncol Lett [Internet]. 2019 Feb 28 [cited 2021 Nov 19]; Available from: http://www.spandidos-publications.com/10.3892/ol.2019.10088

ANNEXURES

ANNEXURE- A: INFORMED CONSENT FORM (ENGLISH)

Serial no._____

INFORMED CONSENT FORM
All India Institute of Medical Sciences Jodhpur

Subject: - Consent for taking information about my disease in patients of differentiated thyroid carcinoma and to use their information for research purpose.

Participant's registration number: _____.

I declare that on date ..... all the details of this information sheet given to me has been explained to me in my language. I am told that in this process, information about my disease will be taken and will be used for research purpose. This research is being done for studies and treatment. I have been explained that no active intervention will be done by the researcher and my treatment will continue as same decided by my doctors. I understand that all information related to me in this research will be kept by the responsible person of AIIMS Jodhpur. I allow them to see all the information related to me. I have been told that all the information related to me will be kept confidential. I have also been told that the results of this research can be published in any book or journal and can be displayed in any conference. I have also been told that my name or any other identity will not be used without my consent. I know that I am participating in this research with my consent and I can refuse to participate in this research at any time without any reason.

I agree to participate in this research.

(Signature) Date:

Place:

Name of the Participant: _____

Son / Daughter / Spouse of: _____

Complete postal address: _____

This is to certify that the above consent has been obtained in my presence.

1) Witness – 1 2) Witness – 2

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Name: Name:

Address: Address:

Signatures of the principal investigator: Dr. Pankaj Kumar

Place: Date:

ANNEXURE- B: INFORMED CONSENT FORM (HINDI)

क्रम संख्या---

सूचित सहमति पत्र का दस्तावेज:

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर

विषय- डिफ्रेंटिएटेड थाइरोइड कैंसर के मरीजों के बीमारी के बारे में जानकारी लेने और रिसर्च में उस जानकारी का उपयोग करने की सहमति |

मैं यह घोषणा करता/करती हूँ कि दिनाक ..... को मुझे दिए गये इस सूचना पत्र के समस्त विवरण के बारे में मुझे मेरी भाषा में समझा दिया गया है | मुझे यह बताया गया है कि इस शोध कार्य में मेरे बीमारी के बारे में जानकारी ली जा रही है और इसका इस्तेमाल इस शोधकार्य के लिए किया जायेगा| शोधकर्ता के द्वारा मेरे बीमारी की इलाज़ में कोई परिवर्तन नहीं किया जायेगा| यह कार्य शोध अध्ययन एवं इलाज के लिए के लिए किया जा रहा है| मैं यह समझता हू कि इस शोध में मेरे/मुझसे सम्बंधित समस्त जानकारी एम्स जोधपुर के जिम्मेदार व्यक्ति के द्वारा रखी जायेगी | मैं उन्हें मुझसे सम्बन्धित समस्त जानकारी देखने की अनुमति देता हूँ | मुझे यह बताया गया हें कि मुझसे संबंधित समस्त जानकारी को गोपनीय रखा जायेगा | मुझे यह भी बताया गया है कि इस शोध के परिणामों को किसी भी पुस्तक या जर्नल में प्रकाशित किया जा सकता है एवम् किसी भी कांफ्रेंस में प्रदर्शित किया जा सकता है | मुझे यह भी बताया गया है कि मेरा नाम या अन्य कोई भी पहचान मेरी सहमति के बिना काम में नहीं ली जयेगी | मुझे पता है की मैं इस शोध में अपनी सहमति से भाग ले रहा हूँ तथा मैं किसी भी समय बिना किसी कारण बताए इस शोध में भाग लेने से इंकार कर सकता हूँ |

मैं इस शोध में भाग लेने के लिए सहमति देता हू |

हस्ताक्षर.. दिनांक..

भागीदार का नाम.. पिता /पति/ पत्नी का नाम..

पुरा स्थायी पता..

यह प्रमाणित किआ जाता है कि उपरोक्त सहमति मेरी उपस्थति में ली गयी है |

1. गवाह-1 2. गवाह-2

नाम व पता नाम व पता

शोधकर्ता के हस्ताक्षर (डॉ पंकज कुमार)

ANNEXURE- C: PATIENT INFORMATION SHEET (ENGLISH)

Department of Otorhinolaryngology

All India Institute of Medical Sciences, Jodhpur

PATIENT INFORMATION SHEET

TITLE: Correlation of preoperative tumor size with post-operative histopathological prognostic indicators in patients with differentiated thyroid carcinoma.

This study requires your detailed information and recall of previous treatment seeked elsewhere for the assessment to be done to proceed in this study. You will be subjected to detailed clinical assessment and routine workup and will be followed up till the histopathological report after surgery is known. This study would require the details of preoperative size of tumor measured by ultrasound neck and postoperative histopathological prognostic indicators. You are expected to attend to all the questions put in front of you in depending on the mutual comfort of you and the investigator. There are no obvious, expected or known adverse effects on the patient due to this study. You have been invited to take part in a study, which will help us in better understanding of the disease. You are free to withdraw from the study at any time and this will not have any negative implication on you/your ward's future treatment in the hospital.

Contact Persons for further queries.

Dr. Pankaj Kumar

ANNEXURE- D: PATIENT INFORMATION SHEET (HINDI)

ऑटोराइनोलैरीनगोलोजी विभाग

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर

सूचनापत्र

टाइटल**:** विभेदित थायरॉयड कार्सिनोमा के साथ रोगियों में पोस्ट ऑपरेटिव हिस्टोपैथोलॉजिकल रोगसूचक संकेतकों के साथ प्रीऑपरेटिव ट्यूमर के आकार का सहसंबंध।

इस अध्ययन में आगे बढ़ने के लिए मूल्यांकन के लिए इस अध्ययन के लिए आपकी विस्तृत जानकारी की आवश्यकता है। आपको विस्तृत नैदानिक मूल्यांकन और रूटीन वर्कअप के अधीन किया जाएगा और सर्जरी के बाद हिस्टोपैथोलॉजिकल रिपोर्ट तक इसका पालन किया जाएगा। । इस अध्ययन के लिए अल्ट्रासाउंड गर्दन और पोस्टऑपरेटिव हिस्टोपैथोलॉजिकल रोगसूचक संकेतकों द्वारा मापा जाने वाले ट्यूमर के पूर्ववर्ती आकार के विवरण की आवश्यकता होगी। आपको और जांचकर्ता के आपसी आराम के आधार पर आप के सामने रखे गए सभी प्रश्नों में भाग लेने की उम्मीद है। इस अध्ययन के कारण रोगी पर कोई स्पष्ट, अपेक्षित या ज्ञात प्रतिकूल प्रभाव नहीं हैं। आपको एक अध्ययन में भाग लेने के लिए आमंत्रित किया गया है, जो हमें आपकी बीमारी को बेहतर समझने में मदद करेगा। आप किसी भी समय अध्ययन से वापस लेने के लिए स्वतंत्र हैं और अस्पताल में आपके / आपके वार्ड के भविष्य के उपचार पर इसका कोई नकारात्मक प्रभाव नहीं होगा।

अधिक प्रश्नों के लिए संपर्क करें

डॉ पंकज कुमार

ANNEXURE- E: CASE RECORD FORM

CASE RECORD FORM

A. BIODATA **C.R.NO.:**

1. Name
2. Age/Sex
3. Address
4. Rural/ urban
5. Phone/mob. No.
6. Date of Examination

B. HISTORY

Swelling of neck:

- Duration

- Site

- Progression

Compressive features

Any history of dysphagia, hoarseness or dyspnea

Any history suggestive of hyper/hypothyroidism

PAST MEDICAL HISTORY

Any significant history

FAMILY HISTORY

History of thyroid disease in family (first degree relative)

SOCIAL AND PERSONAL HISTORY

Smoking, alcohol consumption

C. CLINICAL EXAMINATION:

I. General Examination

II. Systemic Examination:

III ENT EXAMINATION:

Local Examination

INSPECTION:

PALPATION:

Retrosternal extension

Carotid Pulsations:

Cervical Lymphadenopathy

AUSCULTATION

Signs of hypo/hyperthyroidism

Vocal cord status

D. LABORATORY INVESTIGATIONS:

1. Thyroid function tests (T3, T4, TSH)

E. RADIOLOGICAL INVESTIGATIONS

1. Ultrasonography neck and thyroid

F. FNAC (Fine Needle Aspiration Cytology)/ USG guided FNAC (Bethesda classification).

G. OPERATIVE DETAILS

1. Difficult intubation
2. Type of Surgery
3. Infiltration

4. Tumour dimensions (volume and weight)

5. Size of lymph nodes (if present)

H. COMPLICATIONS

- Vocal cord palsy/ RLN palsy
- Hypocalcemia
- Bleeding/hematoma
- Chyle leak
- Need for tracheostomy
- Others

K. HISTOPATHOLOGICAL FINDINGS

1. Tumor size
2. Tumor weight
3. Nuclear atypia
4. Tumoral necrosis
5. Mitotic frequency
6. Vascular invasion
7. Capsular invasion
8. Extra thyroid extension
9. Histological degree
10. Lymph node metastasis)

Others:

ANNEXURE- F: THYROID SURGERY PERFORMA

PERFORMA FOR THYROID SURGERIES

1. **Name of Patient:** **CR. No.**
2. **Name of Surgeon:**
3. **TYPE OF SURGERY DONE:**

   Lobectomy **hemithyroidectomy**

   Total thyroidectomy **total thyroidectomy + neck dissection**

   Completion thyroidectomy
4. **TYPE OF INCISION MADE:**

   Transcervical **hockey stick**

   Others specify
5. **PLATYSMA INFILTRATED:** **yes/no**
6. **STRAP MUSCLE INFILTRATED: yes/no** **split** **+/- infiltration +/-**
7. **SUPERIOR THYROID PEDICLE right harmonic/ligated** **left harmonic/ligate**
8. **MIDDLE THYROID PERDICLE (PRESENT/ ABSENT)**
9. **INFERIOR THYROID PEDICLE**
10. **SIZE OF THYROID LOBE: right lobe** **left lobe** **Isthmus**
11. **NODES:**

    level VI size and number **level VII size and number**

    other if any

12. PARATHYROID PRESERVED: yes/ no

13. SUPERION LARYNGEAL NERVE PRESERVED: yes/ no

14. RELATION OF RLN TO INFERIOR THYROID ARTERY:

15. APPROACH FOR IDENTIFICATION OF RLN:

16. RETROSTERNAL EXTENSION: present /absent

17. ANY INFILTRATON: trachea/ esophagus/ RLN/great vessels/any other structure, specify

18. WEIGHT OF THE SPECIMEN:

19. CLOSURE TECHNIQUE:

Staplers Ethilon

subcuticular

ANNEXURE- G: IEC CERTIFICATE

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2020/2039 **Date: 01/01/2020**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2019-20/981**

Project title: **"Correlation of preoperative tumor size with post-operative histopathological prognostic indicators in patients with differentiated thyroid carcinoma"**

Nature of Project:	**Research Project**
Submitted as:	**M.S. Dissertation**
Student Name:	**Dr.Pankaj Kumar**
Guide:	**Dr. Darwin Kaushal**
Co-Guide:	**Dr.Amit Goyal, Dr.Bikram Choudhury, Dr.Kapil Soni, Dr.Poonam Elhence, Dr.Pushpindra Khera & Dr.Binit Sureka**

This is to inform that members of Institutional Ethics Committee (Annexure attached) met on **23-12-2019** and after through consideration accorded its approval on above project. Further, should any other methodology be used, would require separate authorization.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Enclose:
1. Annexure 1

Page 1 of 2

Basni Phase-2, Jodhpur, Rajasthan-342005, **Website:** www.aiimsjodhpur.edu.in, **Phone:** 0291-2740741 Extn. 3109
Email: ethicscommittee@aiimsjodhpur.edu.in

Annexure 1

Institutional Ethics Committee
All India Institution of Medical Sciences, Jodhpur

Meeting of Institutional Ethics committee held on **23-12-2019 at 10:00** AM at Committee Room, Admin Block AIIMS Jodhpur.

Following members were participated in the meeting:-

S/No.	Name of Member	Qualification	Role/Designation in Ethics Committee
1.	Dr. F.S.K Barar	MBBS, MD (Pharmacology)	**Chairman**
2.	Justice N.N Mathur	LLB	Legal Expert
3.	Dr. Varsha Sharma	M.A (Sociology)	Social Scientist
4.	Mr. B.S.Yadav	B.Sc., M.Sc. (Physics), B.Ed.	Lay Person
5.	Dr. K.R.Haldiya	MD (General Medicine)	Clinician
6.	Dr. Arvind Mathur	MBBS, MS (General Medicine)	Clinician
7.	Dr. Surajit Ghatak	MBBS, MS (Anatomy)	Basic Medical Scientist
8.	Dr. Vijaya Lakshmi Nag	MBBS, MD (Microbiology)	Basic Medical Scientist
9.	Dr. Sneha Ambwani	MBBS, MD (Pharmacology)	Basic Medical Scientist
10.	Dr. Kuldeep Singh	MBBS, MD (Paediatric), DM (General Medicine)	Clinician
11.	Dr. Abhinav Dixit	MBBS, MD (Physiology), DNB (Physiology)	Basic Medical Scientist
12.	Dr. Pradeep Kumar Bhatia	MBBS, MD (Anaesthesiology)	Clinician
13.	Dr. Tanuj Kanchan	MBBS, MD (Forensic Medicine)	Basic Medical Scientist
14.	Dr. Pankaj Bhardwaj	MBBS, MD (CM&FM)	Clinician
15.	Dr. Praveen Sharma	M.Sc., Ph.D. (Biochemistry)	Member Secretary

Dr. Praveen Sharma
Member Secretary
Institutional Ethics Committee
AIIMS,Jodhpur