ORIGINAL ARTICLE

# Clinical assessment of the thyroid nodule: Factors that predict malignancy – A Prospective study

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## INTRODUCTION:

Thyroid nodules are found in around five percent of the adult population with an increase in incidence if ultrasonography is used as a screening tool; between 5%–15% of these nodules will be malignant depending upon age, gender, radiation exposure history, family history and other factors.(1)

Differentiated thyroid cancer (DTC), which includes papillary and follicular cancer, comprise the vast majority (90%) of all thyroid cancers. The increasing level of detection may be due to the increasing patient awareness, more frequent use of neck ultrasonography and incidental detection in other imaging modalities. The evaluation of a patient with a thyroid nodule consists of three arms; a good history and physical examination, ultrasonography of the gland and fine needle aspiration cytology of the nodule apart from biochemical assessment of function; yet 30-40% of nodules remain undiagnosed. Identifying the thyroid nodule that is malignant and requires surgical excision is a challenge to the surgeon.

Most of the literature and guidelines that are available have been based on studies that been conducted on western population. Does the same hold good for the Indian population?

## METHODS:

All patients presenting with newly diagnosed nodule/s of thyroid were included in this study. The clinical assessment was done by a two senior consultants. Most ultrasonograms were done before FNAC, by the designated radiologist. Ultra sound guided FNACs were done if the clinicians felt it was required.

The cytology was reported as per the Bethesda criteria. The gold standard for diagnosis in this study was taken as the histopathology result. The study was conducted in the time period between May 2011 and June 2012. There were 102 cases with malignant histopathology versus 93 cases of benign histopathology.

The following clinical criteria were used to indicate increased risk of malignancy:

- Age >40 YRS
- Male gender
- Family history of thyroid malignancy
- Persistent dysphonia, dysphagia or cough
- Consistency - hard
- Fixed swelling

### Statistics:

The information was entered into Epi Data and analysed using SPSS after conversion to an excel spreadsheet

### Literature review:

### CLINICAL EVALUATION OF THYROID NODULES:

### History and clinical examination:

There is no doubt that first and foremost, for an evaluation of a thyroid nodule, a detailed history and thorough clinical examination will lead the way to a sound diagnosis. Patients usually present with a large palpable nodule in the neck incidental nodule found on imaging studies . Some palpable nodules may not correspond to radiological abnormalities. Non palpable nodules that are detected on ultra sound or other anatomic imaging studies, usually as part of evaluation for other reasons are called incidentally discovered nodules or ''incidentalomas''. Non palpable nodules have a similar risk of malignancy as palpable nodules that are of the same size(2).

Generally, only the nodules that are >1 cm in size should be evaluated, as they have significantly higher risks of malignancy(2).

There are some nodules which are <1 cm in size that may require complete evaluation when suspicious ultra sound features, associated palpable lymphadenopathy or previous history of radiation to head or neck or history of thyroid malignancy in first-degree relatives(2).

However, in a recent study by Burch HB, Shrestha M, Crothers BA, they analysed Whether the size of the nodule plays a role in predicting malignancy.

During a ten year period (2001 to 2011), 3013 patients had fine needle aspirations of thyroid nodules at the Walter Reed Army Medical Center(3). The patients who underwent subsequent thyroid surgery were included in the analysis(3). The nodule size was assessed by ultrasound measurement of the largest diameter and cate¬gorized as 0.5 to 0.9 cm (group A), 1.0 to 3.9 cm (group B) and ≥4 cm (group C)(3). FNA cytology was categorized by the Bethesda System for Reporting Thyroid Cytopathology: benign, atypia (follicular lesion of undetermined significance), follicular neoplasm, suspicious for malignancy, or malignant. All categories except for benign were considered positive for calculation of the sensitivity and speci¬ficity of the FNA. There were 35 nodules in group A, 533 nodules in group B and 127 nodules in group C. The malignancy rate based on surgical pathology was 18.6% (129 of 695 nodules) and did not differ among the size categories. The malignancy rate was 23% in both men and women. (3) So this leads us back to the question of whether size matters? Traditionally, the teaching has been that, nodules greater than 4cm are at high risk for malignancy. However with the advent of imaging and detection of smaller cancers, size does not appear to be a risk factor.

The most pronounced environmental risk factor for thyroid cancer is exposure to ionizing radiation. Ionizing radiation is either due to medical treatment (childhood radiation therapy for benign or malignant disease, adult treatment of malignancies) or nuclear fallout (atomic bomb / testing survivors, nuclear energy accidents ).

Ionizing radiation may exert this effect through several changes to the cell, including Genomic instability. The effects of ionizing radiation are most pronounced in children,

Especially those younger than 10 years old at the time of exposure. The latency Period of developing cancer from this exposure is approximately 10 years for patients Having external beam radiation exposure to less than 5 years for victims of the Chernobyl accident and the increased risk persists for 30 to40 years. Exposure to Ionizing radiation has been shown to increase the risk of malignancy for a thyroid Nodule to 30% to 40%. Furthermore, this risk of malignancy is increased regardless of nodule number and size and multifocal malignancy is found more than half of the time. A history of prior radiation exposure mandates initial total thyroidectomy. The gender-specific distribution is equal in those older than 65 and given that overall two- thirds of cancer cases are women, there would seem to be a link between reproductive hormones and the development of thyroid cancer. Estrogen has been linked as a stimulus for genomic instability and this may be how it exerts its mutagenic effects on the thyroid. Studies have yet to conclusively link traditional carcinogens such as alcohol and tobacco to the development of well differentiated thyroid cancers. Data are conflicting as to what role iodine - rich versus iodine - deficient diets play in the development of thyroid cancer.

Countries with iodine-rich diets such as the United States and Sweden have slightly increased incidence of papillary cancer and countries with iodine-deficient diets such as Switzerland and Australia have slightly increased incidence of follicular thyroid cancer. (4) A dominant or solitary nodule is more likely to represent carcinoma than a Multi nodular gland with an incidence of malignancy from 2.7 to 30% and 1.4 to 10% respectively(1). Yet, the overall risk of malignancy within a gland with a solitary nodule is approximately equal to that of a multi nodular gland due to the additive risk of each nodule. Important elements in the patient's history which increase the likelihood of malignancy include reports of rapid growth, dysphagia, dysphonia, male gender, presentation at extremes of age (less than 20 years or more than 70 years) and a family history of medullary thyroid carcinoma or multiple endocrine neoplasia(1). Patients must be asked for any family history of either benign or malignant thyroid diseases. Although not well defined, there most certainly exists a genetic component to thyroid cancers. In fact a family history of thyroid carcinoma may increase an individual's risk 3-fold when a parent has the disease and up to 6-fold if a sibling has the disease.(4)

The familial medullary thyroid cancers, multiple endocrine neoplasia 2, The familial papillary thyroid

tumours, familial polyposis coli, Cowden disease, Gardner's syndrome even though they are not common, must be considered.(5). Papillary thyroid cancers and follicular thyroid cancers have distinct genomic and proteomic signatures. Pathways are now emerging that demonstrate how these differences play a role in governing tumor biology. Mutations that involve RET, NTRK1, BRAF, PPARγ, or Ras can be detected in almost 70% of cases. There are at least 12 different RET mutations, known as PTC/Ret chimeric onco proteins, which seem to be an early event in thyroid tumorigenesis, with series showing a high prevalence in papillary micro carcinomas and also a high proportion of the post-Chernobyl childhood-induced papillary thyroid carcinomas.

BRAF mutations are seldom found in radiation-induced cancer. These mutations are postulated to produce a more aggressive phenotype of papillary cancers as they are found in many of the more poorly differentiated subtypes. Follicular carcinomas have mutations in PPARγ (rarely found in papillary cancers), AKT pathways, and Ras. Symptoms like difficulty in breathing, neck tenderness, pain, difficulty in swallowing or even change in voice can be attributed to thyroid problems, but in many patients, these symptoms are due to non thyroid diseases. In those patients that are symptomatic, evaluation must start with getting a proper history, doing a full physical examination, reassuring the patient and for choosing the correct laboratory tests. Acute pain is most often because of hemorrhage in to a nodule that is cystic in nature. However, patients that present with rapid increase in size of the thyroid nodule, lymphoma or anaplastic carcinoma of thyroid must be considered.

The beginning and slow progress of neck symptoms and signs are usually because of compression of the structures in the neck and upper chest cavity (oesophagus and trachea), which happens in those thyroid nodules that are found in large goiters.

The features of compression are not so common and are found in the elderly or middle-aged having a long - standing multi nodular goitre. The goiter that is growing downwards into the superior mediastinum can result in partial or complete obstruction of the chest inlet, causing venous obstruction. When the patient is made to raise his or her arms above the head ; i.e. Pemberton's sign, more narrowing of the chest inlet is produced which is followed by over filling of the external jugular veins and facial congestion.

If this is seen when there is a smaller goiter, the features of tracheal compression may suggest an underlying cancer. Differentiated thyroid cancers will usually not cause airway obstruction or vocal cord palsy or oesophageal problems but even if there are no symptoms, it does not rule out malignancy.(5)

**Physical examination:**

Physical exam findings that increase the concern for malignancy include:

- Nodules that are larger than 4 cm in size (19.3% risk of malignancy)
- Firmness to palpation
- Fixation of the nodule to adjacent tissues
- Cervical lymphadenopathy

However, these findings are very often limited by certain factors such as the patient's body habitus, as well as an inherent variation between physicians and their assessment of nodules so much so that precise measurement using imaging is a must of evaluation of a thyroid nodule.(1)

A hard nodule is suspicious as traditionally goitre has always been described as firm. However a benign multi nodular goitre may turn hard because of calcifications or hemorrhage.

Fixity of a nodule is because of its infiltration into surrounding structures. This feature is seen in malignant thyroid nodules and fixed swelling almost always require excision.

Cervical lymphadenopathy in the Ipsilateral level 3 or 4 is the most specific pointer to malignancy in a thyroid nodule; rarely this may prove to be red herring as in a patient with a thyroid swelling, they may have associated reactive hyperplasia of a the corresponding draining lymph nodes especially in the presence of autoimmune thyroiditis. However, it is essential to assess these lymph nodes with an ultra sound of the neck and plan the surgery with an option of doing a neck dissection with a frozen section of the lymph node if necessary.

**RESULTS:**

| Table 1 : Age distribution of cases | | | | | |
|---|---|---|---|---|---|
| | | | Cases | | |
| | | | Malignant | benign | Total |
| Page | 15 - 40 | No. | 64 | 35 | 99 |
| | | % within age | 64.6% | 35.4% | 100.0% |
| | 41-50 | No. | 22 | 33 | 55 |
| | | % within age | 40.0% | 60.0% | 100.0% |
| | >51 | No. | 16 | 25 | 41 |
| | | % within age | 39.0% | 61.0% | 100.0% |
| Total | | No. | 102 | 93 | 195 |
| | | % within age | 52.3% | 47.7% | 100.0% |

**P value = 0.002**

| Table 2: Sex distribution | | | | | |
|---|---|---|---|---|---|
| | | | Cases | | |
| | | | malignant | benign | Total |
| Sex | female | No. | 69 | 64 | 133 |
| | | % | 51.9% | 48.1% | 100.0% |
| | male | No. | 33 | 29 | 62 |
| | | % | 53.2% | 46.8% | 100.0% |
| Total | | No. | 102 | 93 | 195 |
| | | % | 52.3% | 47.7% | 100.0% |

**P=0.861**

| Table 3 : Features of compression or nerve involvement | | | | | |
|---|---|---|---|---|---|
| | | | Cases | | |
| | | | malignant | benign | Total |
| | | Asymptomatic | 85 | 76 | 161 |
| | | % | 52.8% | 47.2% | 100.0% |
| | | Symptomatic | 17 | 17 | 34 |
| | | % | 50.0% | 50.0% | 100.0% |
| Total | | Count | 102 | 93 | 195 |
| | | % | 52.3% | 47.7% | 100.0% |

P=0.767

| Table 4: Dominant consistency | | | | | |
|---|---|---|---|---|---|
| Dominant consistency | | | cases | | Total |
| | | | malignant | benign | |
| | | Hard | 11 | 1 | 12 |
| | | % | 91.7% | 8.3% | 100.0% |
| | | Soft | 2 | 1 | 3 |
| | | % | 66.7% | 33.3% | 100.0% |
| | | Cystic | 0 | 3 | 3 |
| | | % | .0% | 100.0% | 100.0% |
| | | Firm | 89 | 88 | 177 |
| | | % | 50.3% | 49.7% | 100.0% |
| Total | | | 102 | 93 | 195 |
| | | % | 52.3% | 47.7% | 100.0% |

**P=0.01**

| Table 5: Fixity to surrounding structures | | | | | |
|---|---|---|---|---|---|
| | | | cases | | Total |
| | | | malignant | benign | |
| fixity | | No | 98 | 93 | 191 |
| | | % | 51.3% | 48.7% | 100.0% |
| | | Yes | 4 | 0 | 4 |
| | | % | 100.0% | .0% | 100.0% |
| Total | | Count | 102 | 93 | 195 |
| | | % | 52.3% | 47.7% | 100.0% |

**P=0.054**

| Table 6: Clinical size | | | | | |
|---|---|---|---|---|---|
| Size in cms | | | Cases | | Total |
| | | | malignant | benign | |
| size | 0-3 | | 46 | 33 | 79 |
| | | % | 58.2% | 41.8% | 100.0% |
| | 3-6 | | 41 | 37 | 78 |
| | | % | 52.6% | 47.4% | 100.0% |
| | >6 | Count | 15 | 23 | 38 |
| | | % | 39.5% | 60.5% | 100.0% |
| Total | | Count | 102 | 93 | 195 |
| | | % | 52.3% | 47.7% | 100.0% |

**P = 0.164**

From Table 1, it is clear that most of our patients were in the age group 15 – 40 yrs. There were more number of benign thyroid swellings than malignant, which was statistically significant(P=0.002). However, literature tells us that malignant swellings are common in the younger and older extremes of age(9). This is not reflected here in this study. It could be because, there were lesser number of patients in the >50yrs age groups.

Table 2 shows us that there were more number of females enrolled into the study than males. But the number of benign and malignant thyroid swellings were almost equally distributed in the male group.

This is contrary to literature that tells us that being of male sex is a risk factor for malignancy(9).

Table 3 tells us that even though traditionally features of compression or nerve involvement have been considered as features of malignancy, it may not be the case.

Table 4,5 show us that hard consistency, fixity are definite risk factors for malignancy with a significant P values. Table 6 reveals that larger size was not a risk factor for malignancy.

## DISCUSSION:

This study was conducted on a small sample size in a single centre with its own bias of patient profile; therefore extrapolation to a general population is limited. Previous similar studies have had a larger ample size. Most have been retrospective studies making it much easier to acquire a large sample size. However, this was a prospective study, over a period of one and a half years, therefore the data may be more reliable.

## CONCLUSIONS:

This small prospective clinical study revealed some interesting clinical pointers to malignancy.

1) Older age and male gender were not risk factors for malignancy.

2) Features of compression was not a risk factor for malignancy.

3) Hard consistency, fixity were definite risk factors for malignancy.

4) Size was not seen to be a risk factor for malignancy in this study

The need for a larger community based study or a multicentre study of pooled data in further clarifying these clinical points of diagnosis in the Indian context is apparent.