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Incidence of Thyroid Malignancy in Thyroidectomies Done for Clinically Benign Thyroid Conditions

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Short title: *Incidence of thyroid malignancies*

Abstract: ***Aim*: The objective of the study was to determine the incidence of thyroid malignancy in thyroidectomies done for clinically benign thyroid conditions. *Materials and methods*: From January 2014 to June 2015, a total of 308 patients who underwent thyroidectomy for presumably benign thyroid disease were included in the study and evaluated for the presence of incidental malignancy. The distribution of malignancy in sex, age, place and clinical diagnosis were studied. Size of the tumour and its correlation with capsular invasion, vascular invasion and multifocality was also evaluated. *Results*: The incidence of malignancy was 16.9%. Papillary carcinoma was the commonest subtype. The mean age of occurrence of incidental malignancy was 41.9 years. Males showed an incidence of 17.9% and females showed 16.7%. Thrissur district had a higher incidence (20.2%). Mean tumour size was 1.7cm. Occurrence of capsular invasion, vascular invasion and multifocality increases as the mean size of the malignancy increases. *Conclusion*: The rate of incidental thyroid malignancies are increasing. Papilary carcinoma thyroid contributes to the main pathologic type. Due to the risk of occult malignancy, all the patients with multi-nodular goitre who have been treated conservatively need a close follow up for malignancy. Total/near-total thyroidectomy is the procedure of choice during the initial surgery for all presumably benign nodules.***

Keywords: incidence, incidental thyroid cancer, multinodular goitre, papillary carcinoma

1. Introduction

Thyroid carcinoma is a relatively rare tumour, but it represents the most frequent cancer of the endocrine glands. It represents 1% of all human neoplasias. The annual incidence of thyroid malignancy is estimated worldwide from 0.5 to 10:100000 subjects in the world population. Such incidence is increased if cases of occult carcinoma are taken into consideration.[1]

Surgery on the thyroid gland at present is most frequently carried out for nodules because of the possibility that they may be malignant. Although the nodule may seem to be a single nodule on palpation preoperatively, additional nodules are commonly found by the surgeon. Occasionally, one of these additional nodules is malignant.[2]

Most of the autopsy studies report a prevalence of thyroid nodules between 49.5-65%. Mortensen et al. reported a prevalence of 12.2% for single nodules and 37.3% for multiple nodules in postmortem examination of individuals without a prior history of thyroid disease. The major concern when faced with an incidentally detected thyroid nodule is the exclusion of thyroid cancer.[3]

Three to sixteen per cent of patients who undergo thyroidectomy for benign disease are found to have incidental malignancies.[4] But the incidence of thyroid cancer is relatively low compared with the high incidence of thyroid nodules. This suggest that most of these nodules are benign.[3] Autopsy and ultrasound data suggest that the prevalence of thyroid nodules in clinically normal individuals is around 50%.[4]

Incidental thyroid cancer is a malignancy undetected by preoperative imaging studies but identified by pathological examination of surgical specimens in patients treated for benign thyroid diseases. Thyroid incidentalomas are the most common form of endocrine incidentalomas encountered.[3] The incidence of incidental cancer ranges between 3 and 16%.[5]
The majority of cases of thyroid cancer depicted as thyroid incidentalomas are well-differentiated papillary carcinomas associated with a low cause-specific mortality.[3]

The likelihood of malignancy in Graves' disease, multinodular goiter and toxic multinodular goiter has historically been thought to be quite low (5% to 10%). Recent studies have suggested a much higher rate of malignancy within toxic and nontoxic multinodular goitre (10% to 22%). [6]

Therefore the incidence of malignancy is quite significant and it is not very low as was thought before. Due to risk of occult malignancy, all patients with benign thyroid conditions who are treated conservatively need a close follow up for malignancy.[7]

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2. Methodology

The present study was conducted on 308 patients who presented with neck swelling to the Departments of Surgery and ENT. The study was conducted over a period of 18 months from January 2014 to June 2015.The initial evaluation of these patients included biodata, clinical details and relevant investigations and was recorded in the proforma. Type of benign thyroid disease and extent of surgery were also analysed. According to type of benign thyroid disease, the patients were classified into the following groups: patients with multinodular goitre (MNG), solitary nodule thyroid (SNT), Hashimoto thyroiditis, thyroiditis and controlled toxic goitre. The extent of surgery was classified into four groups: Near total thyroidectomy, Total thyroidectomy, Right hemithyroidectomy and Left hemithyroidectomy. The resected specimens were fixed in 10% formol saline overnight. The specimens were serially sectioned at 5mm intervals followed by detailed gross examination. All the gross findings were recorded. This included the size of the specimen and the gross appearance. Presence of any malignant lesions was looked for and if present was recorded. Bits were put from representative areas. All the malignant looking lesions were subjected for examination. The bits were then processed using an automated tissue processor followed by paraffin embedding. Sections were cut at five microns size and stained using a standard hematoxylin and eosin staining protocol for examining surgical specimens. The sections were studied under light microscopy.

Data analysis was done using SPSS (version 22.0.0.0).

3. Results

- Out of the 308 patients, 256 have benign thyroid conditions which comes to 83.1% and 52 have malignant thyroid carcinoma which comes to 16.9%.

Table 1: Incidence of benign conditions and malignancies in the study population

Benign/Malignant	No. of patients	Incidence
Benign	256	83.1%
Malignant	52	16.9%
Total	308	100.0%

- The most common benign condition in the study is nodular colloid goitre (75.4%) followed by follicular adenoma (14.4%) and Hashimoto thyroidits (4.3%).
- Among 52 malignant cases, 50 are papillary carcinoma (96.2%) with an incidence of 16.2%. one case each of Follicular carcinoma and Hurthle cell carcinoma is found with an incidence of 0.3% for each.

Table 2: Frequency and incidence of malignancies

Individual malignancies	Frequency	Incidence
Papillary carcinoma	50 (96.2%)	16.2%
Follicular carcinoma	1 (1.9%)	0.3%
Hurthle cell carcinoma	1 (1.9%)	0.3%

Classical papillary carcinoma is obtained in18 cases (34.6%) among 52 cases with an incidence of 5.8%. 15 cases of Follicular variant of papillary carcinoma and papillary microcarcinoma is present with an incidence of 4.8% for each. One case each of papillary carcinoma diffuse sclerosing variant and papillary carcinoma warthin like variant is present. Conditions associated with papillary carcinoma are nodular colloid goitre in 30 cases, lymphocytic thyroiditis in 4 cases, hashimoto thyroiditis in 3 cases and treated toxic goitre in 1 case.

Figure 1: Papillary carcinoma with nodular goiter

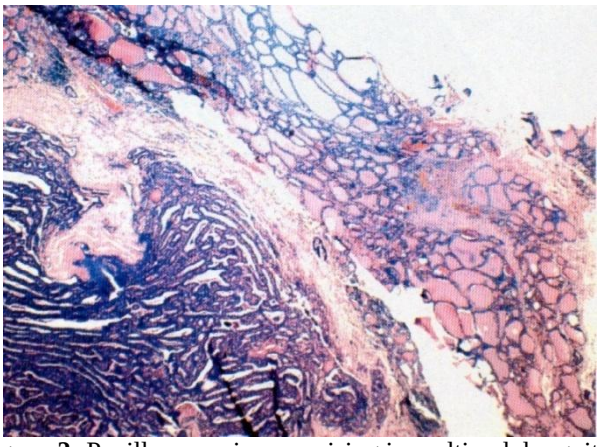

Figure 2: Papillary carcinoma arising in multinodular goiter

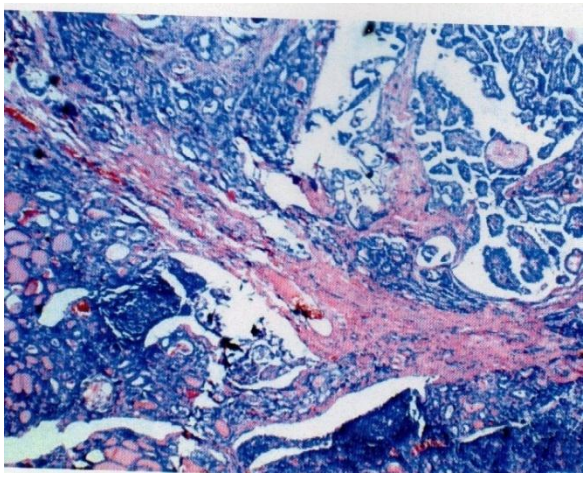

Figure 3: Papillary carcinoma with lymphocytic thyroiditis

- Age of the study population ranged from 16 years to 75 years with a mean age of 41.90 and standard deviation of 12.09. Maximum number of patients is found in the age group of 36- 45 years constituting 31.8%. Incidence of malignancy for this age group is 18.4%. Maximum number of patients with incidental thyroid malignancy is also found in the same age group with all of them being diagnosed with papillary carcinoma (100%). Highest incidence of malignancy is present in the age group of 15-

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25 years (27.3%). No significant association is found between age and occurrence of malignancies (p-value = 0.255).

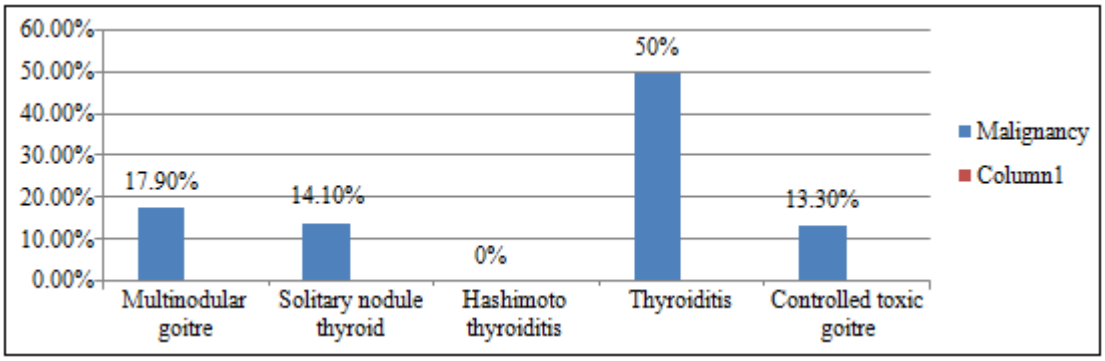
- Out of the 308 patients included in the study, 39(12.7%) are males and 269 (87.3%) are females. Male to female ratio is 1: 6.7. , males have an incidence of 17.9% whereas females have an incidence of 16.7%. Papillary carcinoma is the most common incidental thyroid malignancy in both sexes. There is no significant association between sex and malignancies (p-value = 0.849).
- Majority of the patients in the study are from Thrissur district (56.2%) followed by Palakkad (22.7%) and Malappuram (20.1%). Incidence of thyroid malignancy is found in 20.2% in patients from Thrissur which is the highest. The most common incidental malignancy in Thrissur, Palakkad and Malappuram is papillary carcinoma.. There is no significant association between place and malignancies (p-value = 0.445).

Table 3: Incidence of benign conditions and malignancies in each district

Place	Incidence	
	Benign Condition	Malignancy
Thrissur	79.8%	20.2%
Palakkad	88.6%	11.4%
Malappuram	85.5%	14.5%
Total	83.1%	16.9%

Incidence of malignancy in each clinical diagnosis

In my study population most of the patients are clinically diagnosed as having multinodular goitre. Among the 52 malignant cases, 39 patients are clinically diagnosed as multinodular goitre and 10 as solitary nodule thyroid. In both the groups, papillary carcinoma is found to be the commonest incidental malignancy. Incidence of malignancies in multinodular goitre and solitary nodule thyroid are 17.9% and 14.1% respectively. In my study, none of the patients with a clinical diagnosis of hashimoto thyroiditis has incidental malignancy. There is no significant association between clinical diagnosis and the malignancies (p-value = 0.617).



Association of duration of swelling and incidental malignancy:

- Duration of thyroid swelling in my study ranged from 1 month to 16 years. Incidence of malignancy is highest when duration of swelling is between 49-72 months (34.8%). No significant association was found between incidental malignancies and duration of swelling.
- Near total and total thyroidectomies detected more number of incidental malignancies than hemithyroidectomies.
- Greatest diameter of the thyroidectomy specimen ranges from 3cm to 15cm. Mean diameter is 7.2cm with a standard deviation of 2.02. Incidence of malignancy is seen increasing as the greatest diameter of the swelling increases. Mean microscopic size of the incidental malignancies is 1.7cm. But significant p-value was not obtained in this comparison. (p-value = 0.250).
- It was also found that as the mean size of the malignancy increases, occurrence of capsular invasion, vascular invasion and multifocality also increases.

Significant p value is obtained for capsular invasion (p-value = 0.019).

Table 4: Frequency of capsular invasion, vascular invasion and multifocality of malignancies

		N	Mean size	Std. Deviation	Std. Error Mean
Capsular Invasion	Present	9	2.633	1.576	0.525
	Absent	43	1.544	1.143	0.174
Vascular Invasion	Present	2	3.100	2.687	1.900
	Absent	50	1.678	1.216	0.172
Multifocality	Present	5	2.540	1.363	0.610
	Absent	47	1.647	1.256	0.183

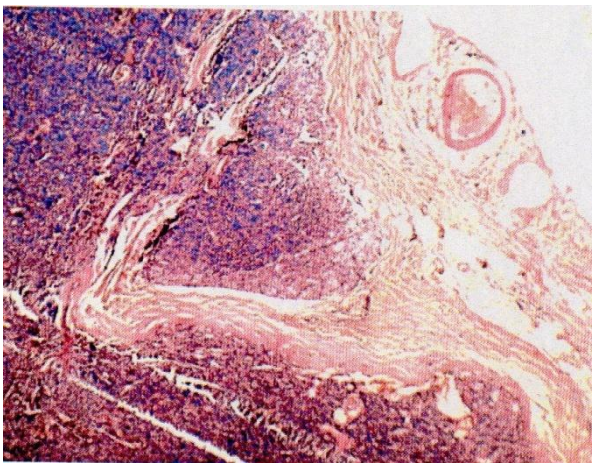


Figure 4: Papillary carcinoma with capsular invasion

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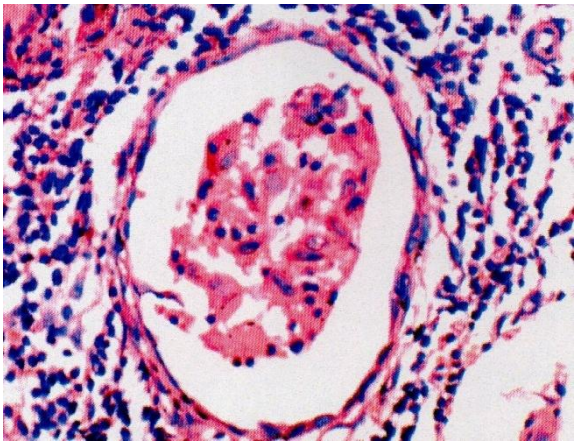

Figure 5: Vascular tumour emboli in papillary carcinoma

4. Discussion

Thyroid carcinoma is regarded as the most common endocrine malignancy with a variable geographic and ethnic distribution. The overall risk was reported to be increasing worldwide with changing characteristics. It accounts for 90% of all endocrine malignancies.[8] An unresolved issue is whether benign thyroid conditions are associated with carcinoma. So the present study was undertaken to evaluate the incidence of thyroid malignancies in clinically benign thyroid conditions.

This study included 308 patients who underwent thyroidectomy for various benign thyroid conditions. Benign conditions included multinodular goitre, solitary nodule thyroid, Hashimoto thyroiditis, other thyroiditis and treated toxic goitre. The patients underwent either total thyroidectomy, near total thyroidectomy or hemithyroidectomy.

In our study the incidence of thyroid malignancy in clinically benign thyroid conditions was found to be 16.9%. Incidental thyroid malignancy was found in 52 patients among the total of 308 subjects. This is comparable with the study by Pezzolla et al in 2010 in which 30 among 165 patients showed incidental malignancy with an incidence of 18.2%.[9] Studies by Nechaĭ OP et al in 2012[10] and Costamagna et al in2013[5] observed 9.2% and 9.3% of incidental thyroid malignancies respectively.

Table 5: Comparison of occurrence of incidental thyroid malignancy

S. No	Studies	Incidence
1	Pezzolla et al (2010)[9]	18.2%.
2	Nechaĭ OP et al (2012)[10]	9.2%
3	Costamagna et al (2013)[5]	9.3%
4	**Present study**	**16.9%**

Papillary thyroid carcinoma was found to be the most common incidental thyroid malignancy in our study. It accounted for 96.2% of the total incidental malignancies. Miccoli et al in 2006[11] found 95.2% of incidental papillary carcinomas which is similar to our study. 84.2% of incidental papillary carcinoma was reported by Pingitore et al in 1993.[12] More recently, Pezzolla et al in 2010[9] and Costamagna et al in 2013[5] found incidental papillary carcinomas in 76.7% and 83% respectively. Incidence of papillary carcinoma in our study is 16.2%.

Incidence in the above stated studies were between 7.5% and 20.1%. In a study by Gangadharan et al in 1999, the frequency distribution of papillary carcinoma thyroid in Kerala is 53.2%.[13]

Table 6: Comparison of occurrence of incidental papillary thyroid carcinoma

S. No	Studies	Incidence
1	Pingitore et al (1993)[12]	20.1%
2	Miccoli et al (2006)[11]	9.9%
3	Pezzolla et al (2010)[9]	7.5%
4	Costamagna et al (2013)[5]	7.7%
5	Present study	16.2%

Classical papillary carcinoma was present in 18 cases in our study which constitute 34.6% of incidental malignancies. Incidence of classical papillary carcinoma is 5.8%. Costamagna et al in 2013 observed an incidence of 3.5% for classical papillary carcinoma.[5]

Among the variants of papillary carcinoma, papillary microcarcinoma and follicular variant were found in equal proportions and constituted the maximum numbers. Each of these variants was present in 28.8% of incidental malignancies. Incidence of papillary microcarcinoma in our study was 4.9% and was comparable with many studies. Studies by Sakorafas et al in 2007[14] and Nechaĭ OP et al in 2012[10] stated an incidence of 7.1% for papillary microcarcinoma. Pezzolla et al in 2010[9] found 6.2% and Costamagna et al in 2013[5] found 5.9% of incidental papillary microcarcinoma. Costamagna et al in 2013 also reported that the incidence of follicular variant of papillary carcinoma as 4.2% which was lower than the percentage in our study.[5] In another study by Lam et al in 2005[15], incidence of follicular variant was 11.1% and in the study by Pezzolla et al in 2010[9], the incidence was 2.1%. One case each of diffuse sclerosing variant and warthin like variant was also present in our study.

Table 7: Comparison of incidence of papillary microcarcinoma

S. No	Studies	Incidence
1	Sakorafas et al (2007)[14]	7.1%
2	Pezzolla et al (2010)[9]	6.2%
3	Nechaĭ OP et al (2012)[10]	7.1%
4	Costamagna et al (2013)[5]	5.9%
5	Present study	4.9%

The various conditions found associated with papillary carcinoma in our study were nodular colloid goitre, Hashimoto thyroiditis, lymphocytic thyroiditis and treated toxic goitre. Maximum association was found with nodular colloid goitre which came around 60%.

Hashimoto thyroiditis was found associated with papillary carcinoma in 5.8%, with lymphocytic thyroiditis in 7.7% and with treated toxic goitre in 1.9%. Girardi et al in 2015 found 35.4% association between papillary carcinoma and hashimoto thyroiditis.[16] Kim et al in 2009 found 14.9% association between papillary carcinoma and lymphocytic

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thyroiditis.[17] Jeong et al in 2012[18] observed 26.5% and Kebebew et al in 2001[19] reported 30% association.

Follicular carcinoma and hurthle cell carcinoma were equally distributed in our study with each constituting 1.9%. Incidence of follicular carcinoma and Hurthle cell carcinoma was 0.3% in my study. Incidence of follicular carcinoma was 2.1% in the study by Pingitore et al in 1993,[12] 2.5% in the study by Pezzolla et al in 2010[9] and 0.7% in the study by Costamagna et al in 2013.[5] Occurence of Hurtle cell carcinoma as incidental malignancy was reported by Pezzolla et al in 2010 which showed 0.4% incidence.[9]

Age of our study population ranged from 16 years to 75 years. Mean age was 41.90. Maximum number of patients with incidental malignancy was found in the age group of 36- 45 years which constituted 31.8%. Study by Sakorafas et al in 2007 observed the mean age to be 45.2 years which is comparable with our study.[14] Vaiana et al in 1999 found the mean age to be 52.2 year[20] and Bombil et al in 2014 found it to be 46 years.[21] National cancer intelligence network stated that the incidence of thyroid malignancies is highest in the age group 40-44 years in females and in males the incidence rates increased steadily with age. Maximum number of cases in males was noted in the age group 60-64 years.[22] Similar findings were noted by the Cancer Research UK.[23] Incidence was highest in the age group 15-25 years followed by 36-45 years in our study. Maximum number of cases in males was seen in 36-45 years and in 66-75 years. Maximum number of cases in females was present in 36-45 years.

In our study incidental thyroid malignancy was present in 7 males and 45 females. Incidence in males was 17.9% and in females was 16.7%. Incidence in males and females did not show marked variation. Study by Cerci et al in 2007 reported an incidence of 12.2% in males and 10% in females.[24] In another study by Ahsan et al in 2013, incidence was 11.1% in males and 7.3% in females.[25]

Majority of the patients in our study was from Thrissur district (56.2%). Being a tertiary referral centre, we have patients from the nearby districts also. 22.7% of patients were from Palakkad and 20.1% were from Malappuram. Incidenctal malignancies were found to be high in Thrissur (20.2%). The figures were higher than the incidence obtained in the whole study and also higher than the values obtained in various other studies.[5,9,10] This shows that the number of undetected malignancies are higher in Thrissur district compared to other places. According to the National Cancer Registry Programme, Thiruvananthapuram had the highest relative frequency of thyroid cancer among all the cases enrolled in the registry with 1.99% in males and 5.71% in females.[26] Relative proportion of thyroid cancer among females is 6.6% in Thrissur and 4.1% in Palakkad according to NCRP.[27]

The most common clinical diagnosis in our study was multinodular goitre. Among the 218 patients clinically diagnosed with multinodular goitre, 39 (17.9%) had incidental thyroid malignancy. Pascual et al in 2012[28] observed 22.2% of incidental thyroid malignancy in multinodular goitre whereas Cerci et al in 2007[24] had 10.6%. Other studies by Hanumanthappe et al in 2012[7], Pang et al in 2007,[29] Prades et al in 2002[30] and Memon et al in 2010[31] reported incidences of 10%, 21.2%, 12.2% and 8 to 10% respectively.

Table 8: Comparison of incidental thyroid malignancy in multinodular goitre

SL NO	Studies	Incidence
1	Prades et al (2002)[30]	12.2%
2	Cerci et al (2007)[24]	10.6%
3	Pang et al (2007)[29]	21.2%
4	Memon et al (2010)[31]	8 to 10%
5	Hanumanthappe et al (2012)[7]	10%
6	Pascual et al (2012)[28]	22.2%
7	Present study	17.9%

The second most common clinical diagnosis in our study was solitary nodule thyroid with a total of 71 cases.14.1% of them turned out to be malignant. In contrary to the belief that carcinomas are more common in solitary nodules of thyroid than in multinodular goitre, our study showed no significance in the occurrence of incidental malignancy in both these benign conditions. This was in agreement with the study by McCall in 1986.[32] McCall and Cutfield in 1981[33] both reported 17% incidence of malignancy in solitary thyroid nodules.

In our study majority of the incidental malignancies have duration of swelling of less than two years (51.9%). Highest incidence is obtained when the duration is between 49-72 months (34.8%). No significant association was found between incidental malignancies and duration of swelling.

In the current study, the most common surgical procedure resorted to was total thyroidectomy (42.9%). Detection of incidental malignancy is more in near total thyroidectomy (48.1%) and total thyroidectomy (40.4%) than in hemithyroidectomy (11.5%). Considering this, a total or near total thyroidectomy should be performed in all presumably benign thyroid disesases. The same was suggested by Sakorafas et al in 2007.[14]

In the present study, greatest diameter of the specimen ranges from 3cm to 15cm. The incidence is highest when the diameter of the swelling is >10cm (23.1%). It is also seen that as the diameter of the swelling increases, the incidence also increases. So it can be inferred that more the size of thyroid swelling, more is the chance for having a malignancy. Also the chance for missing a clinical diagnosis of malignancy is more as the size of the thyroid swelling increases.

In our study, the size of tumour varies from 0.1cm to 5cm. The mean size of the tumour is 1.7cm. Majority of the incidental malignancies were < 2cm in size (57.7%). The smaller size of the tumour may be the cause for under diagnosis of malignancy clinically. In the study by Cerci et al in 2007, the average tumour size was 24.76mm which is comparable with our study.[24] Other studies by Costamagna et al in 2013[5], Miccoli et al in 2006[11] the mean diameter of incidental malignancy was 1.14cm and 1.4cm respectively. Pascual et al in 2012[28] reported the mean tumour size as 6.9mm.

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Table 9: Comparison of mean diameter of tumours

S. No	Studies	Mean diameter of tumour (in cm)
1	Miccoli et al (2006)[11]	1.4
2	Cerci et al (2007)[24]	2.47
3	Pascual et al (2012)[28]	0.69
4	Costamagna et al (2013)[5]	1.14
5	Present study	1.7

Capsular invasion is present in 17.3% of incidental malignancies in our study. This differed from the study by Cerci et al in 2007[24] where 33.3% showed capsular invasion. 14% of papillary carcinoma showed capsular invasion in our study. One case of follicular carcinoma and Hurthle cell carcinoma are present in our study and both showed capsular invasion. Present study showed 3.8% of vascular invasion in incidental malignancies. The percentage obtained by Cerci et al in 2007 was 22.2% which is higher than our study.[24] Follicular and Hurthle cell carcinoma showed vascular invasion. None of the papillary carcinomas showed vascular invasion. 5 cases in our study showed multifocality (9.6%). Studies by Pingitore et al,[12] Miccoli et al,[11] Costamagna et al,[5] Cerci et al[24] and Bombil et al[21] reported 18.4%, 19.8%, 26.4%,22.2% and 25% respectively. It was inferred that as the mean size of the malignancy increases, occurrence of capsular invasion, vascular invasion and multifocality also increases.

5. Conclusion

The rate of incidental thyroid malignancies is increasing. Papillary carcinoma contributes to the main pathologic type in both males and females. Due to the risk of occult malignancy, all the patients with multinodular goitre who have been treated conservatively need a close follow up for malignancy. Total/near-total thyroidectomy is the procedure of choice during the initial surgery for all presumably benign thyroid conditions. This avoids the need for reoperation for patients with incidental malignancies.

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