

Incidence of differentiated cancer in nodular goiter

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ABSTRACT

Objective: The study aims to determine the incidence of differentiated thyroid cancer in surgically treated thyroid nodules and to study its clinical and pathological aspect. The objective was to formulate a uniform departmental policy for the most appropriate surgical management of this potentially curable disease.

Methods: This is a prospective clinicopathological study carried out at the Department of General Surgery, Riyadh Medical Complex, Riyadh, Kingdom of Saudi Arabia, from January 1996 through to December 2000. A total of 483 thyroidectomies were performed. Preoperative diagnosis of thyroid cancer was based on clinical and fine needle aspiration cytology (FNAC). The patients were identified as low risk and high risk groups for surgical treatment. The histopathological diagnosis of differentiated thyroid cancer was confirmed in 103 patients (21.3%). The medical records of all these patients were reviewed for age, sex, clinical presentation, investigations and outcome of surgery.

Results: A total of 103 patients (21.3%) with histopathologically confirmed differentiated thyroid cancer were studied. The female to male ratio was 4:1. The mean age was 36.7 years. Sixty-five percent of patients were

between 21-40 years. Nodular goiter was the most frequent presentation observed in 78.6% cases. Fine needle aspiration cytology was suggestive of malignancy in 86.4% cases. Most of the patients (84.5%) were identified as low-risk. Papillary carcinoma was the most common tumor (89%) followed by follicular cancer (8.7%). Eight percent of patients had cervical lymph node involvement at presentation. Total lobectomy was performed in 50.5% and total thyroidectomy in an additional 29% of patients. Overall operative morbidity was 6.8% with zero mortality. Two (1.9%) patients presented with ipsilateral lymph node recurrence with mean follow up of 26.5 months and underwent limited neck dissection.

Conclusion: The relatively high incidence of differentiated thyroid cancer in surgically treated nodular is attributed to increased confidence in FNAC and careful patient selection. Total lobectomy with isthmusectomy for low risk and total thyroidectomy for high risk patients may be recommended as the preferred treatment modalities.

Keywords: Nodular goiter, fine needle aspiration cytology, differentiated thyroid cancer.

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Thyroid cancer is the most frequent endocrine malignancy.¹ The disease is reported to be increasing worldwide and its characteristics are changing.^{2,3} In the United States of America (USA), approximately 10,000 new cases with 1000 deaths from this cancer are reported annually.⁴ The

assessment of thyroid nodules has also evolved, with percutaneous fine needle aspiration cytology (FNAC) becoming the pivotal element in the diagnostic armamentarium.⁵ In the Kingdom of Saudi Arabia (KSA), thyroid malignancies constituted 5% of all newly diagnosed cancers.⁶ Differentiated thyroid

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cancer is a slowly progressing disease and has an overall favorable outcome. However, the adequate management has been the subject of controversy for several decades.⁷ Riyadh Medical Complex is a tertiary hospital in the Central Riyadh region, KSA. Thyroid surgery is routinely performed here and shares a substantial operative share in the Department of General Surgery. This prospective study aimed at finding the incidence of thyroid cancer in the surgically treated nodular thyroid disease and to study its clinicopathological behavior. The objective was to formulate a consensus departmental policy for the most appropriate surgical treatment of operable differentiated thyroid cancers.

Methods. A total of 483 thyroidectomies were performed at the Department of Surgery, Riyadh Medical Complex, Riyadh, KSA from January 1996 through to December 2000. All patients presenting with nodular goiter were included in the study. The charts were reviewed for age at operation, sex, nationality, radiation history, family history of thyroid disease, clinical presentation, physical examination, investigations and type of surgery performed. Patients referred with a diagnosis of carcinoma of the thyroid following definitive surgery elsewhere were excluded from analysis, as were those undergoing re-operative thyroid or neck surgery. All patients underwent a detailed medical history, careful physical examination of the neck, indirect laryngoscopy, an analytic and hormone study, including determination of thyroid hormones and thyroglobulin levels, simple chest radiography, and fine needle aspiration of the thyroid nodule or any palpable cervical nodes at presentation, before surgery. Thyroid scan was routinely employed to confirm the solitary nature of the nodule or otherwise. An ultrasound of the neck was carried out where goiter was doubtful or cystic nature of the swelling needed confirmation. The cytodiagnosis on FNAC was divided into 4 categories: Benign (negative), suspicious (indeterminate), malignant (positive), and nondiagnostic (unsatisfactory).⁸ The results of FNAC were compared to the final histopathology. Each FNAC was then considered as true positive, true negative, false positive and false negative. If a "follicular neoplasm" was reported in FNAC and final histology was either follicular adenoma or follicular carcinoma, the FNAC was considered as true positive. All patients with follicular adenoma (benign) were later excluded from the study. Sensitivity and specificity for FNAC were then evaluated. Frozen sections were carried out in patients with inconclusive or unsatisfactory FNAC or where physical or operative findings were not considered in accordance with FNAC report. Various indications for thyroidectomy included FNAC positive for malignancy or suspicious of malignancy,

presence of pressure symptoms and for cosmetic reasons. For the purpose of this study, the term "cancer incidence" was defined as the percentage of cancers found in thyroidectomies performed on patients with solitary, dominant or multinodular goiter disease to rule out cancer. The operative procedures were unilateral in form of total lobectomy (TL) or bilateral in form of total thyroidectomy (TT) or subtotal thyroidectomy (STT) selected on the basis of low or high risk groups. The definition of Low risk group in this study included young patients (men under 40 years old, women under 50 years old), no extra glandular involvement, no distant metastases, no residual tumor after surgery, papillary tumors of less than 4cm or follicular tumors less than 2cm with minor capsular invasion.¹

Statistical analysis was carried out employing exact Fisher test, the chi-square test, and analysis of variance for comparative analysis of the data using statistical package for social sciences-personal computer (SPSS-PC) statistical package for IBM PC.

Results. Out of total 483 thyroidectomies performed during the 5 years period under review, 380 patients (78.7%) had benign lesions on final histopathology whereas differentiated thyroid cancer was reported in another 103 cases (21.3%). The results were further analyzed and presented for these 103 patients. Seventy eight patients (75.7%) were Saudi whereas various other nationals comprised the rest 24.3% cases. Eighty three patients (83.6%) were female and 20 (19.4%) were male, with a female to male ratio of 4.15: 1. The mean age was 36.7 years (range 16-67 years). **Figure 1** shows the distribution of thyroid cancer among various age groups. Mean age for females was 35.2 years and for males was 46.4 years ($p < 0.05$). None of the patients in this study gave history of significant radiation exposure in the past. Family history of some form of thyroid enlargement was available in only 3 (2.9%) patients. Eighty-six patients (83.5%) presented with a clinically solitary nodule and 17 (16.5%) had multinodular disease. Pressure symptoms were observed in 23 cases (22.3%). Cervical lymphadenopathy was found in 4 patients (3.9%) at presentation, all confirmed as metastatic on FNAC. Eighty seven patients (84.5%) belonged to the low risk group and 16 (15.5%) were included in the high risk group. Thyroid scan employed in 91 cases (88.3%) confirmed the solitary nodule in 84 (92.3%) patients, whereas a dominant lobe was found in the rest 7 (7.7%) cases. Ultrasound neck carried in 43 cases (41.7%) was suggestive of solid solitary nodules in 41 patients and multinodular disease in 2 cases. Clinical diagnosis of thyroid cancer was made in 34 (33%) cases. Fine needle aspiration cytology, carried out in all cases, was conclusive of malignancy in 54 cases (52.4%) (true positive), suggestive of

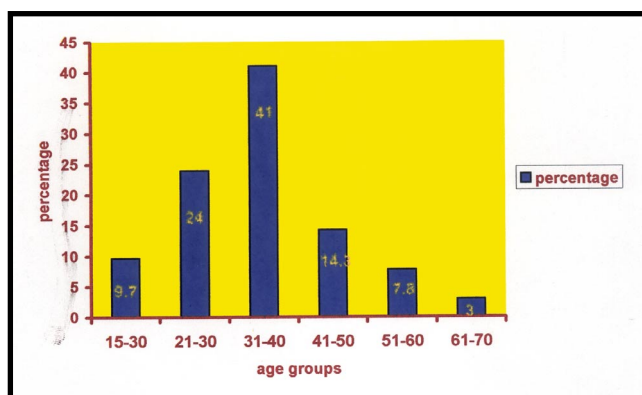


Figure 1 - Age distribution of patients with differentiated thyroid cancer n=103.

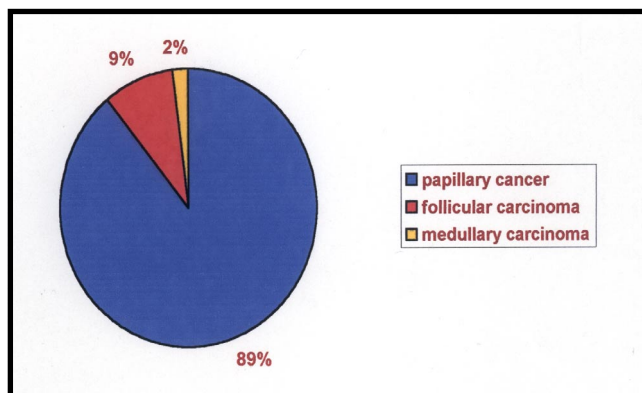


Figure 2 - Percentage distribution of different types of differentiated thyroid cancer n=103.

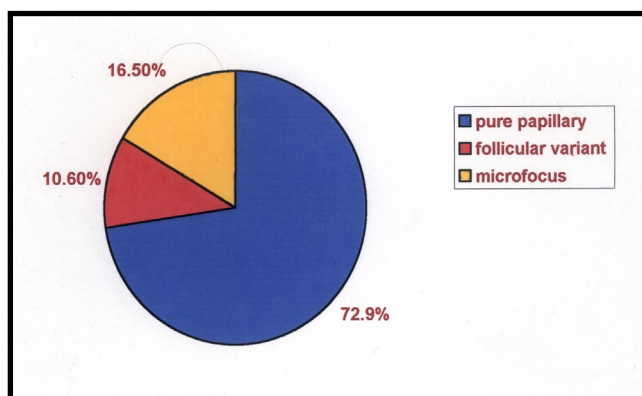


Figure 3 - Pathological varieties of papillary thyroid cancer n=92.

malignancy in 37 cases (35.9%) (true positive), benign in 3 cases (2.9%) (false negative), and an inadequate sample was reported on 9 occasions (8.7%). When considering all the patients n=486 who had FNAC, true positive, true negative, false positive and false negative yields were 18.7% (91 cases), 71.6% (348 cases), 1.4% (7 cases), 0.6% (3 cases), whereas 37 samples (7.6%) were reported as inadequate. Overall specificity of FNAC was 98% with sensitivity of 96.7%. The positive and negative predictive values were 92.6% and 99.1%. All 7 patients who underwent operation on account of false positive FNAC were later excluded from the final analysis of the data. The final histopathology in these patients revealed hyperactive follicular cells (3 cases), Hashimoto's thyroiditis (2 cases), and follicular adenoma (2 cases). Frozen section was performed in 97 cases and helped in changing the operative plan in 9 patients with thyroid carcinoma, reported either as negative (2 patients) or inadequate sample (7 patients) on FNAC. The majority of the patients (84.5%) were in the low risk group, only 16 (15.5%) patients belonged to the high risk group. Diagnosis of differentiated thyroid cancer was confirmed in 103 patients (21.2%) and accounted for a 21.2% of all surgically treated nodules. Differentiated thyroid cancer was associated with chronic thyroiditis in 12 cases (11.6%) and it occurred on background of multinodular goiter in 13 cases (12.6%). The overall incidence of differentiated cancer in true (histopathologically confirmed) solitary nodules was 21.8% (73 out of 334 cases) and 11.2% in multinodular goiter (17 out of 152 cases). Figure 2 depicts the incidence of various types of thyroid cancers among 103 cases of differentiated carcinoma. Papillary cancer was the most frequent differentiated cancer observed in 92 cases (89%), followed by follicular carcinoma found in 9 patients (8.7%), whereas the medullary carcinoma was found in another 2 cases (2%). Micro focus (<1.5 cm) of papillary carcinoma was observed in 17 (16.5%) cases whereas 75 (72.8%) patients were found to have clinically evident tumors (>1.5 cm). The follicular variant of papillary cancer was reported in another 11 (10.6%) patients (Figure 3). Hurthle cell variant of follicular carcinoma was observed in 2 (1.9%) cases. Fifty two patients (50.5%) underwent ipsilateral total lobectomy and isthmusectomy. Near-total thyroidectomy was performed in 21 (20.4%) cases whereas total thyroidectomy was undertaken in another 30 patients (29.1%). Eight (7.7%) patients underwent associated cervical lymph nodes dissection and 7 (6.7%) were found positive for metastasis from papillary carcinoma.

Discussion. Thyroid cancer is regarded as the most frequent endocrine malignancy with a variable geographic and ethnic incidence around the world.⁹

The overall incidence is reported to be increasing worldwide with changing characteristics.^{1,2,10} Papillary forms are on the rise, whereas follicular and anaplastic tumors are becoming less frequent.¹ Radiation exposure and endemic goiter have been suggested as strong etiological factors.^{9,11} The average age adjusted annual incidence for thyroid cancer in the USA is less than 40 cases per 1,000,000 populations and approximately 12,000 new cases are diagnosed annually with 1000 deaths each year from all types of thyroid cancer.¹² In KSA, thyroid carcinomas have been accounted for 5% of all newly diagnosed cancers and ranked 14th for males and 2nd for females.^{13,14} Riyadh Medical Complex is one of the largest tertiary referral hospitals in KSA and thyroid surgery is not infrequent in this center. This study is aimed at finding out the incidence and clinicopathological presentation of differentiated thyroid cancer among all the patients operated for nodular thyroid disease. During the 5 year period under review, a total of 2619 patients were operated for various malignancies in the Department of General Surgery, Riyadh Medical Complex, KSA. Differentiated thyroid carcinoma (103 cases) accounted for 3.9% of all cancers and was observed as the most frequent endocrine malignancy. This figure is lower than 4.4-5% reported in 2 earlier series from Riyadh and Jeddah, KSA.^{13,14} The lower figure (3.9%) may be explained by a higher number of cancer patients referred to those specialized cancer research centers. No known etiological factor (radiation exposure, endemic goiter) could be confirmed in any patient in this study. Marked female preponderance in this study is similar to various local and international reports.^{1,13-16} The mean age of 36.7 years is younger than 45-48 years quoted in various local and Western studies,^{1,14-16} but is similar to the studies by Al-Balawi et al¹³ and Al-Nuaim et al¹⁷ and

associates. The younger mean age at presentation may reflect a changing clinico epidemiological behavior of the disease needing further evaluation. The mean age for females is nearly 10 years younger than that for males and is similar to various other reports.^{1,14,17} The incidence of differentiated cancer in true solitary nodules (21.8%) and multinodular goiter (11.2%) is not significantly different from local and international figures of 15- 20% and 5-10%.¹ Clinical diagnosis of thyroid cancer in nodular goiter was possible in 33% cases, which is well within figures of 38% reported in the earlier studies.^{16,18} Cervical lymph nodes involvement was observed in 6.7% patients, which is similar to figure of less than 10% quoted in the Western studies.¹ Fine needle aspiration cytology of thyroid is now considered as an important diagnostic aid in the investigation of goiter. This is particularly useful in the screening and selection of patients presenting with solitary or dominant nodules. The positive diagnostic yield of FNAC for malignancy was 88.3% in this study. This is well within range of 70-97% described in the local and international literature.^{8,13,19-21} The sensitivity (96.7%), specificity (98%), positive predictive value (92.6%) and negative predictive value (99.1%) of FNAC in the diagnosis of thyroid lesions are well within the figures quoted in local and international studies.^{1,15,22-25} **Table 1** depicts a comparison of diagnostic yields (accuracy) of FNAC with local and international reports. The pivotal role of FNAC in the management of thyroid nodules cannot be overemphasized but requires adequate sampling, expert cytopathologist, and adequate correlations of results with the clinical presentation of the patient. Nearly 85% patients in this study were included in the low risk group, which is similar to the observation of Rossi et al¹ and colleagues. Papillary carcinoma was the most frequent differentiated

Table 1 - Comparison of diagnostic yield of fine needle aspiration cytology for nodular goiter.

| Authors | Year | Total n of cases | Malignant cases n (%) | Benign FNAC | | Suspicious FNAC | | Malignant FNAC | |
|-------------------------------|------|------------------|-----------------------|------------------|-----------------------|------------------|-----------------------|------------------|-----------------------|
| | | | | Total n of cases | Malignant cases n (%) | Total n of cases | Malignant cases n (%) | Total n of cases | Malignant cases n (%) |
| Lowhagen et al ²⁴ | 1979 | 412 | 96 (23.3) | 226 | 9 (4) | 123 | 24 (19.5) | 63 | 63 (100) |
| Abu-Nema et al ²² | 1987 | 124 | 8 (6.5) | 89 | 1 (1.1) | 28 | 0 (0) | 7 | 7 (100) |
| Altavilla et al ²³ | 1990 | 233 | 46 (19.7) | 160 | 8 (5) | 53 | 18 (33.9) | 20 | 20 (100) |
| Mandreker et al ²⁵ | 1993 | 213 | 30 (14.1) | 163 | 9 (5.5) | 38 | 10 (26.3) | 12 | 11 (91.7) |
| Al-Rikabi et al ¹⁵ | 1996 | 125 | 32 (25.6) | 76 | 0 (0) | 24 | 7 (29.2) | 25 | 25 (100) |
| Present study | 2002 | 486 | 103 (21.2) | 351 | 3 (0.9) | 37 | 32 (86.5) | 54 | 52 (96.3) |

FNAC - fine needle aspiration cytology, n - number

thyroid cancer found in 89.3% of cases, followed by follicular (8.7%) and medullary carcinoma (2%). The incidence (89.3%) of papillary carcinoma is higher than 70-80% reported in the Western experience.²⁶⁻²⁸ Similarly the incidence (8.7%) of follicular cancer is much less than 15-20% described in the international literature.^{29,30} Same is true for the low incidence (2%) of medullary carcinoma in this study. This is much lower than the figures of up to 5-10% in Western experience.^{31,32} A relative high incidence of papillary carcinoma and lower incidence of follicular and medullary carcinoma in this study is similar to the observation of Ahmad et al¹⁴ and associates from King Faisal Specialist Hospital and Research Center (KFSH&RC), and further supports a changing pattern of thyroid cancer in the Kingdom as opposed to European and American experience. Associated chronic thyroiditis was found in 11.8% of cases of differentiated cancer (all papillary). This is well within figures of 5%-22.5% association with various thyroidities reported in the literature.³³ Microfocus (<1.5 cm) of papillary carcinoma was observed in 16.5% patients in this study. This figure is higher than 7% reported in an earlier study from the Central Riyadh region in 1996,¹⁷ but is well within 29.5% reported in the Western literature.^{1,34} These high figures clearly demonstrate the impact of FNAC on the early diagnosis of thyroid cancer. Fine needle aspiration cytology is recommended as the investigation of choice in the management of nodular goiter. The incidence of follicular variant of papillary carcinoma (10.6%) and that of Hurthle cell variant of follicular cancer (1.2%) is in accordance with the reported range of 14% and 2-10% in the local and international literature.^{13,15,35} As 83.5% of patients presented in the low risk group, an ipsilateral lobectomy with isthmusectomy (50.5%) and near-total thyroidectomy (20.4%) can be justified as the surgical treatment of choice in this study. Eight percent of patients underwent functional neck nodes dissection with 6.7% incidence of nodal metastases. These figures are in accordance with the local and international reports.^{1,13,20} Although a number of studies have evaluated the extent of thyroidectomy for differentiated thyroid cancer on ultimate patient outcome, as a whole the findings have been described as equivocal.³⁶⁻³⁸ The relatively high incidence of differentiated thyroid cancer in surgically treated nodules in the present study is attributed to increased confidence in FNAC and careful patient selection. Total lobectomy with isthmusectomy for low risk and total thyroidectomy for high risk patients can be recommended as the treatment modalities of choice. The authors recommend that the optimal extent of thyroid surgery should be based on patient selection and subsequent categorization in low and high risk groups, institution specific outcome figures for differentiated thyroid cancer recurrence or mortality (institutional policy), and the surgeon specific complication rate.

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