

Patterns of thyroid cancer in Southwestern Saudi Arabia

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ABSTRACT

الأهداف: دراسة أنماط سرطان الغدة الدرقية، وتقييم حجم المشكلة، بالإضافة إلى تطوير الخطط الموضوعية لعلاج الأنماط الخبيثة من هذا المرض.

الطريقة: شملت هذه الدراسة الاسترجاعية جميع المرضى الذين يشكون من اضطرابات الغدة الدرقية والذين خضعوا لعمليات جراحية في مستشفى عسير المركزي، أبها، المملكة العربية السعودية وذلك خلال الفترة من يناير 1998م إلى ديسمبر 2007م. لقد قمنا بالرجوع إلى سجلات المرضى للبحث عن المعلومات التالية: المعلومات السريرية، وطرق العلاج، ونسبة عودة السرطان مرة أخرى.

النتائج: لقد خضع 516 مريضاً يعاني من اضطرابات الغدة الدرقية للعمليات الجراحية، حيث كان 92 مريضاً (17.8%) يعاني من الأورام الخبيثة (20 ذكراً و72 أنثى). وكان متوسط أعمار الذكور 41.35 ± 15.52 ، فيما كان متوسط أعمار الإناث 36.59 ± 13.28 . لقد شكل السرطان الحليمي 50% من الحالات الخبيثة، فيما وصلت نسبة الإصابة بالسرطان الجريبي إلى 4.3% فقط. احتل سرطان الغدة الدرقية الليمفاوي المرتبة الثالثة بما نسبته 1.1% فقط من جميع الأورام الخبيثة، ولم يُعثر على أي حالة من حالات سرطان النخاع (سرطان النقي). لقد تمت متابعة 75 حالة من أصل 92 حالة في العيادات الخارجية للمستشفى، ووصلت نسبة عودة السرطان مرة أخرى للمرضى الذين تم متابعتهم في العيادات إلى 31.5%.

خاتمة: أشارت الدراسة إلى أنه يجب عمل تخطيط صدق الرقبة العالي الوضوح، كما يجب فحص خلايا الخزعة التي تم ارتشافها وذلك من أجل فحص وتشخيص المرضى الذين يشكون من تورم في الغدة الدرقية. ويبدو أن الاستئصال الكامل للغدة الدرقية وإزالة جميع العقد الليمفاوية في الحيز المركزي من الرقبة هي الطريقة المثلى للعلاج، وبعد العملية الجراحية يجب اجتناب أنسجة الغدة الدرقية المتبقية باستخدام نظائر اليود المشع (I131).

Objectives: To examine the pattern of thyroid cancer, assess the magnitude of the problem, and evolve a management plan for such malignancies.

Methods: This is a retrospective cohort study of all thyroid cases operated at Aseer Central Hospital, Abha,

Kingdom of Saudi Arabia, between January 1998 and December 2007. Clinical presentations, management regimens, and recurrence were reviewed.

Results: Five hundred and sixteen patients were operated for different thyroid lesions. Ninety-two (17.8%) were malignant (20 males and 72 females). Mean age for males was 41.35 ± 15.52 years compared to 36.59 ± 13.28 years for females. Papillary carcinoma constituted 50%, while follicular carcinoma formed only 4.3% of malignant cases. Lymphoma ranked third with only 1.1% of all malignant thyroid lesions. No cases of medullary carcinoma were found. Of 92 patients, 75 reported for follow-up. The recurrence rate for follow-up patients was 29 (31.5%).

Conclusion: High resolution neck ultrasonography and image-guided fine needle aspiration cytology should be considered as routine investigative tools in patients with suspicious thyroid swelling. Total thyroidectomy and removal of all lymph nodes in the central compartment of the neck seem to be the ideal management plan, until such trials emerge. Residual thyroid tissues, following surgery, should be ablated using radioiodine (I131) isotope.

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Thyroid nodules are frequently seen in clinical practice. Most of them are benign lesions. Thyroid cancer is only found in 5-10% of hypo-functioning thyroid nodules.^{1,2} Approximately 18,000 new cases of thyroid malignancy were diagnosed in the United States of America in 1999.³ Hence, thyroid cancers account for only 0.17% of cancer deaths in men and 0.26% in women.¹ In Saudi Arabia, there were 415 cases of thyroid cancer, which is 6% of all newly diagnosed cases in the year 2004.⁴ This cancer ranked second among Saudi female population and fourteenth among males. It affected 87 (21%) males and 328 (79%) females with a male to female ratio of 100:266. The overall age-standardized rate (ASR) was 3.5/100,000. Age-standardized rate was 1.6/100,000 for males and 5.3/100,000 for females.⁴ Prognosis in thyroid cancer depends on the degree of differentiation. While anaplastic carcinoma is almost consistently fatal, while well-differentiated lesions have an excellent prognosis.⁵ The Aseer region (population of 1,200,000) is located in the southwest of Saudi Arabia covering an area of more than 80,000 km². The region extends from the high mountains of Sarawat (with an altitude of 3200m above the sea level) to the Red Sea, and lies few kilometers from the northern border of neighboring Republic of Yemen.⁶ Health services delivery in the southern region is provided by a network of 244 primary health care centers, 16 referral hospitals and one tertiary hospital, Aseer Central Hospital (ACH), Saudi Arabia. Aseer Central Hospital, with 500 beds, is run by the Ministry of Health and the College of Medicine of King Khalid University (KKU) Abha. The objective of this study is to report the patterns and prevalence of thyroid cancer among patients seen at ACH as well as discussing the management plans for the affected patients.

Methods. A retrospective cohort study of all patients who underwent thyroidectomy at ACH, which is also the main university teaching hospital in the region, was undertaken. Patients' database was reviewed using their hospital records after obtaining the Ethical Committee Approval. Medical records for 516 patients subjected to thyroidectomy between January 1998 and December 2007 were included. All cases with proven histopathological diagnosed thyroid malignancies during the study period were included, wherein cases with proven histopathological benign diagnosis during the study period were excluded.

Data collected included patients residence, nationality, age, gender, duration of symptoms, complete clinical examination, and laboratory investigation (thyroid-stimulating hormone, thyroxin and tri-iodothyronine levels). The findings of the ultra-sound of the neck, type of operation offered, post-operative complications,

histopathology report, and recurrences at follow-up were also included. Hemi-thyroidectomy was defined as removal of one of the lobes with the isthmus. Subtotal thyroidectomy entails removal of all the diseased side of the gland as well as the isthmus and majority of the opposite lobe. The removal of nearly all of each thyroid lobe and the isthmus leaving un-resected only a small portion of the gland adjacent to the entrance of the recurrent laryngeal nerve into the larynx was carried out in near-total thyroidectomy. A total thyroidectomy is the complete removal of the thyroid gland.

Data were coded and analyzed using SPSS version 13. Student t test, Chi-squared and analysis of variance, and F test were used as tests of significance at 5% level.

Results. A total of 516 benign and malignant thyroid neoplasms were operated upon over the 10-year study period (1998-2007), out of which 92 cases (17.8%) were malignant. The following are important features of the malignant thyroid neoplasm cases.

Twenty cases were males and 72 cases were females. The Saudi patients accounted for 83.7% (n=77). The mean age at diagnosis for males was 41.35 ± 15.52 years compared to 36.59±13.28 years for females, the difference is not statistically significant (t = 1.36, p=0.163).

Solitary nodules were found in 43 (46.7%) of cases followed by multi-nodular goiter 26 (28.3%) and diffuse thyroid enlargement 23 (25%). Solitary nodules were significantly ($\chi^2 = 4.85$, p=0.042) more common among females (52.8%) compared to males (25%). On the other hand, no gender predilection was found in multi-nodular goiter (MNG) and diffuse thyroid enlargement. The highest mean age was found for cases with MNG (44.65±12.23 years) followed by diffuse thyroid (35.68±12.68 years) and solitary nodules (34.48±14.28 years). The difference was statistically significant (F=5.02, p=0.009).

The histopathological diagnosis. Papillary carcinoma constituted the majority of cases (50%), followed by follicular carcinoma (4.3%). Lymphoma, on the other hand, ranked third with only 1.1% of all malignant lesions (Table 1).

Recurrence. Seventy-five out of 92 patients reported for follow-up. The overall recurrence rate for follow-up patients was 29 (31.5%). The recurrence rate within papillary and follicular cancer was 38.6% and 50% respectively. The difference was not statistically significant ($\chi^2 = 0.207$, p=0.513). Most of cases of diffuse thyroid goiter were treated by total thyroidectomy (n=12, [54.4%]), followed by sub-total and near-total thyroidectomy (n=4 each [18.2%]). On the other hand, most of the solitary nodule cases were treated by hemi-thyroidectomy (n=31 [72.1%]) followed by

Table 1 - Histopathological diagnosis of thyroid cancer cases attending Aseer Central Hospital, Southwestern Saudi Arabia, 1998-2007.

Histopathological Diagnosis	N	(%)
Microscopic foci of papillary carcinoma	27	(29.3)
Papillary carcinoma	46	(50.0)
Follicular carcinoma	4	(4.3)
Recurrent papillary carcinoma	1	(1.1)
Hürthle cell carcinoma	3	(3.3)
Lymphocytic thyroiditis and papillary carcinoma	9	(9.8)
Papillary cancer and hashimoto disease	1	(1.1)
Lymphoma	1	(1.1)
Total	92	(100.0)

total thyroidectomy (n=6 [14%]). Management of multi-nodular goiter (MNG) cases were mostly through hemi-thyroidectomy (n=11 [42.3%]) followed by sub-total thyroidectomy (n=7, [26.9%]). The difference was statistically significant ($\chi^2=29.47$, $p=0.001$). Postoperatively, serum calcium was low in 7.6% of patients necessitating treatment with calcium.

Discussion. Thyroid tumors usually present as a one-sided painless thyroid nodule in a clinically euthyroid patient.³ This may have been noticed by the patient or found incidentally on performing ultrasound of the neck. In Saudi Arabia (SA) thyroid cancer is the second most common malignancy after breast cancer in female patients.⁴ Differentiated thyroid carcinoma (DTC) in SA accounted for 3.9-5% of all cancers and was observed as the most frequent endocrine malignancy. This figure was reported in 3 earlier series from Riyadh and Jeddah, SA.^{2,7,8} In this study, 91 out of 516 cases of thyroid patients (17.6%) had DTC. This figure is lower than that found in The Republic of Yemen (21%).⁹ We did not find proven risk factors for the development of DTC in our study. This was initially thought to be due to the study design. Our finding however coincides with the study carried out in Riyadh, SA.² Nonetheless, solitary nodule (SN) in young female patients and MNG in male patients should raise suspicion of malignancy. The mean age at diagnosis for males was 41.35 ± 15.52 years compared to 36.59 ± 13.28 years for females, which is similar to various other reports.^{6,10,11} Papillary variant of DTC is the most common type. In a study by Delides et al,¹² 11 papillary carcinomas were found in 611 resected thyroids. Six of these papillary carcinomas were associated with MNG, 3 with toxic adenoma and 2 with Hashimoto thyroiditis. Skorafas et al¹³ in their own study involving 27 papillary carcinoma patients, 21 were associated with MNG. In contrast, the present

study found that thyroid cancer with SN in 46.7%¹⁴ of cases followed by MNG (n=26, (28.3%) and diffuse thyroid enlargement (n=23, (25%). It was observed also in this study that papillary carcinoma was diagnosed in 16.9% (87 of 516) of patients who were treated surgically for presumably benign thyroid disease and 94.6% (87 of 92) of malignant ones, while follicular carcinoma formed only 4.3% of these cases. This finding matches other reported studies.^{14,15} Lymphoma, on the other hand, ranked the third with only 1.1% of all malignant lesions. No cases of medullary or anaplastic carcinoma was seen in our study. The wide range of prevalence of thyroid papillary cancer in published studies (3-36%) may represent differing meticulousness of thyroid gland sectioning, completeness of thyroidectomy, the histologic criteria for diagnosing papillary thyroid cancer as well as possible population/geographic differences.¹³ The highest prevalence (35.6%) was seen by looking at the whole gland in 2-3 mm slices with 4 μ m slices of each block. Seventy-seven percent of tumor foci were found <1 mm in diameter.¹⁶ The high incidence of papillary thyroid micro carcinoma (PTMC) in autopsy studies suggests that most of them have a relatively "benign" biological behavior. These studies showed that a significant percentage of patients (up to 36%) who died of diseases other than thyroid cancer had PTMC that remained asymptomatic throughout their lives.¹⁶⁻¹⁷ Papillary thyroid micro carcinoma is often undetectable (clinically) because of its small size and usually remains clinically silent.¹⁷ It is often discovered as incidental finding at autopsy or in specimens of thyroid removed for other reasons. However, with the advent of improved methods of diagnostic evaluation, including high resolution neck ultrasonography and image-guided fine needle aspiration cytology (FNAC), the diagnosis can now be made preoperatively. Tumors as small as 1 and 2 mm in diameter can be detected with the use of high-resolution transducers.¹⁷ In a good center with expert cytologists, FANC is currently considered the most effective, accurate, safe, and cost-effective for preoperative differentiation between benign and malignant thyroid nodule.^{16,19-21} Although the primary treatment of DTC is thyroidectomy, there is still uncertainty regarding the extent of surgery. This is due mainly to lack of prospective randomized controlled studies comparing the extent of thyroidectomy and the use of postoperative treatments such as radioactive iodine.^{3,17} Total thyroidectomy is considered to be the operation of choice for all thyroid cancers which are not small and non-aggressive in young patients. The survival in DTC is strongly determined by TNM stage, sub-classification of histopathological finding and completeness of surgery. The performance of less extensive surgery in patients with TNM stage III disease significantly increased the mortality risk.²¹

Even though, the incidence of nodal metastasis in DTC ranges between 40-75%, elective neck dissection is generally not recommended for patients with DTC. However, if clinically apparent nodal disease is noted in the tracheoesophageal groove during surgery, central compartment clearance is advised.²¹⁻²⁴ In the lateral compartment of the neck, modified neck dissection preserving the sternomastoid, accessory nerve, and jugular vein is also advised. Appropriate consideration should be given for parathyroidal transplantation if the blood supply to the parathyroids is damaged. If patients present with bulky nodal disease, the use of postoperative radioactive iodine dosimetry and ablation should be considered. Differentiated thyroid carcinoma represents a distinctive disease in the human body, where lymph node metastasis has no prognostic implication. Aggressive surgical clearance is advised in patients with medullary thyroid cancer in the central compartment and the jugular chain lymph nodes.²⁵ The overall recurrence rate for follow-up patients in this study was 31.5%.²⁵ The recurrence rates within papillary was 38.6% and follicular cancer was 50%. The difference was not statistically significant ($\chi^2=0.207$, $p=0.513$).

Limitation is mainly due to the fact that it is a retrospective cohort study based on the quality of records keeping in the hospital.

We conclude that high resolution neck ultrasonography and image-guided FNAC should be considered as routine investigative tools in patients with suspicious thyroid swelling. There are no published randomized controlled trials, at hand, for the management of DTC. Total thyroidectomy and removal of all lymph nodes in the central compartment of the neck seem to be the ideal management plan, until such trials emerge. Residual thyroid tissues, following surgery, should be ablated using radioiodine (I131) isotope.

References

1. Dean DS, Hay ID. Prognostic Indicators in Differentiated Thyroid Carcinoma. *Cancer Control* 2000; 7: 229-239.
2. Al-Salamah SM, Khalid K, Bismar HA. Incidence of differentiated cancer in nodular goiter. *Saudi Med J* 2002; 23: 947-952.
3. Nix P, Nicolaides A, Coatesworth AP. Thyroid cancer review 1: presentation and investigation of thyroid cancer. *Int J Clin Pract* 2005; 59: 1340-1344.
4. Bazarbashi S. Saudi Cancer Registry. Cancer Incidence Report 2004. Riyadh (KSA): Saudi Cancer Registry; 2008. p. 1-98.
5. Alvarado R, Sywak MS, Delbridge L, Sidhu SB. Central lymph node dissection as a secondary procedure for papillary thyroid cancer: Is there added morbidity? *Surgery* 2009; 145: 514-518.
6. Preliminary results of 2004 census. Central Department of Statistics. Riyadh (KSA): Ministry of Economy and Planning; 2005.

7. Ahmed M, Al-Saihati B, Greer W, Al-Nuaim A, Bakheet S, Abdulkareem AM, et al. A study of 875 cases of thyroid cancer observed over a fifteen-year period (1975-1989) at the King Faisal Specialist Hospital and Research Centre. *Ann Saudi Med* 1995; 15: 579-584.
8. Al-Balawi IA, Meir HM, Yousef MK, Nayel HA, Al-Mobarak MF. Differentiated thyroid carcinoma referred for radioiodine therapy. *Saudi Med J* 2001; 22: 497-503.
9. Al-Jaradi M, Sallam A, Jabr H, Borda A, Decaussin-Petrucci M, Berger N. Prevalence of differentiated thyroid cancer in 810 cases of surgically treated goiter in Yemen. *Ann Saudi Med* 2005; 25: 394-397.
10. Rossi RL, Majlis S, Rossi RM. Thyroid Cancer. *Surg Clin North Am* 2000; 80: 571-579.
11. al-Nuaim AR, Ahmed M, Bakheet S, Abdul Kareem AM, Ingmenson S, al-Ahmari S, et al. Papillary thyroid cancer in Saudi Arabia. Clinical, pathologic, and management characteristics. *Clin Nucl Med* 1996; 21: 307-311.
12. Delides GS, Elemenoglou J, Lekkas J, Kittas C, Evthimiou C. Occult thyroid carcinoma in a Greek population. *Neoplasma* 1987; 34: 119-125.
13. Sakorafas GH, Giotakis J, Stafyla V. Papillary thyroid microcarcinoma: a surgical perspective. *Cancer Treat Rev* 2005; 31: 423-438.
14. Abdumughni YA, Al-Hureibi MA, Al-Hureibi KA, Ghafoor MA, Al-Wadan AH, Al-Hureibi YA. Thyroid cancer in Yemen. *Saudi Med J* 2004; 25: 55-59.
15. Peix IL, Lifante JC. Differentiated thyroid cancer: initial surgical treatment. *Nuclear Medicine Imaging-Metabolic and Function* 2003; 27: 135-141. French
16. Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer* 1985; 56: 531-538.
17. Sakorafas GH, Stafyla V, Kolettis T, Tolumis G, Kassaras G, Peros G. Microscopic papillary thyroid cancer as an incidental finding in patients treated surgically for presumably benign thyroid disease. *J Postgrad Med* 2007; 53: 23-26.
18. Hay ID, Grant CS, van Heerden JA, Goellner JR, Ebersold JR, Bergstralh EJ. Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. *Surgery* 1992; 112: 1139-1146.
19. Senchenkov A, Staren ED. Ultrasound in head and neck surgery: thyroid, parathyroid, and cervical lymph nodes. *Surg Clin North Am* 2004; 84: 973-1000.
20. Sakorafas GH, Peros G, Farley DR. Thyroid nodules: does the suspicion for malignancy really justify the increased thyroidectomy rates? *Surg Oncol* 2006; 15: 43-55.
21. Carpi A, Mechanick JL, Nicolini A, Rubello D, Iervasi G, Bonazzi V, et al. Thyroid nodule evaluation: what have we really learned from recent clinical guidelines? *Biomed Pharmacother* 2006; 60: 393-395.
22. Lundgren CI, Hall P, Dickman PW, Zedenius J. Influence of surgical and postoperative treatment on survival in differentiated thyroid cancer. *Br J Surg* 2007; 94: 571-577.
23. Bonnet S, Hartl D, Leboulleux S, Baudin E, Lumbroso JD, Al Ghuzlan A, et al. Prophylactic lymph node dissection for papillary thyroid cancer less than 2 cm: implications for radioiodine treatment. *J Clin Endocrinol Metab* 2009; 94: 1162-1167.
24. Lee SH, Lee SS, Jin SM, Kim JH, Rho YS. Predictive factors for central compartment lymph node metastasis in thyroid papillary microcarcinoma. *Laryngoscope* 2008; 118: 659-662.
25. Shaha AR. Management of the neck in thyroid cancer. *Otolaryngol Clin North Am* 1998; 31: 823-831.