

New trends in the clinicopathological features of differentiated thyroid cancer in Central Jordan

Maha S. Shomaf, MD, Nidal A. Younes, MD, Nader M. Albsoul, MD, Ayman A. Musmar, MD, MSc, Mohammed M. Al-Zaheri, MD, Musleh S. Tarawneh, MD, Ahmad S. Sroujeh, MD, FRCS (UK).

ABSTRACT

Objectives: To investigate the current trends in presentation and distribution of differentiated thyroid cancer (DTC) at the largest referral hospital for endocrine cancers in Central Jordan.

Methods: We analyzed the clinical features, management and outcome of 110 patients diagnosed with thyroid carcinoma at Jordan University Hospital, Amman, between 1996 and 2001.

Results: Papillary carcinoma was diagnosed in 87 patients (80%), follicular carcinoma in 3 patients (2.7%), Hurthle cell carcinoma in 8 patients (7.3%), medullary carcinoma in 5 (4.5%), and anaplastic carcinoma in 4 patients (3.6%), metastatic cancer in 2 patients and lymphoma in one patient. Time course analysis showed an increasing trend in surgery for thyroid cancer from 28 cases in 1986-1991 to 48 in 1996-2001. As time advanced, the incidence of locally

invasive disease and lymph node involvement markedly increased over the last 5 years of the study (from 28-62%). All patients with follicular carcinoma were diagnosed in the period 1986-1994. After thyroidectomy and a follow up period of 2-15 years, 10 patients died of their disease, 4 of these died within one year from anaplastic thyroid carcinoma.

Conclusions: The dramatic decline in the incidence of follicular thyroid carcinoma combined with the increase in the advanced forms of thyroid cancer in Central Jordan may suggest a possible environmental factor in thyroid carcinogenesis in this region. We suggest a larger scale studies and steps to investigate the etiologic factors for thyroid carcinogenesis in Central Jordan.

Saudi Med J 2006; Vol. 27 (2): 185-190

Jordan is a developing country with a population of 5 millions; the majority of them are under the age of 30 years. The practice of iodine supplementation of table salt was started in 1993, yet the prevalence of goiter rate in Jordan is 32.1% in 2000 compared to 37.7% in 1993.¹ Thyroid gland is highly sensitive to irradiation exposure particularly during childhood period. Development of thyroid carcinomas has been

reported following all kinds of radiation exposure, therapeutic radiation, following atomic bomb explosions or as a result of fallout from thermonuclear explosions.²⁻⁴ The aim of the current study is to report on the spectrum of patients diagnosed with thyroid cancer at Jordan University Hospital over a period of 16 years with regard to the frequency, stage of cancer at the time of diagnosis, clinicopathologic characteristics and survival.

From the Department of Pathology (Shomaf, Tarawneh), Department of Surgery, (Younes, Albsoul, Musmar, Sroujeh), and the National Center for Diabetes, Endocrine and Inherited Diseases (Al-Zaheri), Faculty of Medicine, University of Jordan, Amman, *Jordan*.

Received 25th June 2005. Accepted for publication in final form 21st November 2005.

Address correspondence and reprint request to: Dr. Nidal Younes, Department of Surgery, Faculty of Medicine, University of Jordan, PO Box 13024, Amman 11942, *Jordan*. Fax. +9626 5353388. E-mail: niyounes@ju.edu.jo

Methods. One hundred and ten diagnosed with thyroid cancer at Jordan University Hospital (JUH) were included in this study. Jordan University Hospital is the largest referral hospital for endocrine cancers in Jordan. It is a 500-bed referral hospital serving all sectors of health care system in central Jordan. The records were studied to collect data with regard to the age, gender, signs, symptoms and preoperative evaluation. Histopathology was evaluated through the original pathology reports and clinical descriptions. The details of histopathology diagnosis included histopathological subtypes, size of the tumor, presence of capsular invasion or extrathyroidal extension, or both. All patients who had curative thyroid surgery were followed 4-8 weeks later by diagnostic whole body scan. Thereafter, radioiodine 131 therapeutic dose was given to ablate a residual tumor, lymph nodes metastases or distant metastases. All patients were put on a suppressive dose of L-thyroxine and kept under regular follow up. Six to twelve months after radioiodine therapy, a follow-up radioiodine whole body scans, and serum thyroglobulin were performed whenever indicated. Total thyroidectomy was performed for all patients with preoperative diagnosis of thyroid cancer except for 3 patients with a clinical picture suggestive of anaplastic carcinoma, excisional biopsy was carried out. If the dissection around the recurrent laryngeal nerve was difficult, near total (minimal thyroid tissue around the nerve) or subtotal thyroidectomy (2-3 grams of thyroid tissue) was performed to avoid injury. All specimens were evaluated using light microscope of hematoxylin and eosin stained slides and immunohistochemical stains including thyroglobulin, calcitonin, carcinoembryonic antigen (CEA) cytokeratin (CK) and leukocyte common antigen (LCA) are included as indicated. Histopathological diagnosis of papillary carcinoma was based on strict criteria of cytologic features and is defined according to WHO classification as a malignant epithelial tumor showing evidence of follicular cell differentiation typically with papillary and follicular structures as well as characteristic nuclear changes (ground glass, large size, pale irregular outline with deep grooves and intranuclear pseudo inclusions).⁵ When the cytological features of papillary carcinoma were lacking the diagnosis of other carcinomas was made and confirmed by immunohistochemical staining as appropriate.

Statistical analyses were performed with ANOVA and a *p*-value less than 0.05 was considered to be significant. The software used in this study was Microsoft window XP2000.

Results. The results are based on the analysis of 110 cases of thyroid cancer diagnosed between January 1986 and January 2001. Lost of follow-up was the exclusion criteria. Seventy-one were females and 39 were males, the female to male ratio was 1.8:1. The age of patients ranged between 4-95 years with a mean age of 40 years. Cervical lymph node involvement was detected in 39 patients unilateral involvement in 32 patients (29%) and bilateral in 7 patients (6.4%). Metastases in neck nodes were detected by clinical examination, or by neck computed tomography scan. Obvious distant metastasis was found on clinical and radiological assessment performed at presentation in 2 patients. In 21 patients (19%), fine needle aspiration (FNA) confirmed the diagnosis of cancer before surgery. In 8 patients (7.2%) FNA was suspicious and diagnostic hemithyroidectomy was carried out and revealed the presence of cancer. In 8 patients, thyroidectomy was carried out for indications other than cancer, yet the final pathology revealed cancer in spite of benign preoperative FNA. In 18 patients, the diagnosis of thyroid cancer was based on the results of cervical lymph node biopsy. Twenty-eight patients were referred for completion thyroidectomy after being diagnosed with thyroid cancer elsewhere. Total thyroidectomy was performed for 89 patients (80%), subtotal thyroidectomy for 6 patients (5.4%), near-total thyroidectomy for 8 patients (7%). Incisional biopsy was performed in 3 (3%) patients and hemithyroidectomy in 4 (3%) patients. Papillary carcinoma (PTC) was encountered in 87 patients (79%), follicular carcinoma (FTC) in 3 patients (2.7%), medullary carcinoma (MTC) in 5 patients (4.5%), Hurthle cell cancer (HCC) in 8 patients (7.3%) and anaplastic thyroid carcinoma (ATC) in 4 patients (3.6%), metastatic cancer in 2 patients and lymphoma in one patient. The primary tumor was larger than 3 cm in 60 (54.5%) patients, 1-3 cm in 25 patients (44.6%) and occult (<1 cm) in 14 patients (26.8%). During surgery, extrathyroidal extension was seen in 6 patients and 2 postoperative gross residual tumor. Microscopic extrathyroidal extension was also confirmed histopathologically in 6 more patients (**Figure 1**).

Stage of the tumor (DeGroot's clinical staging), intrathyroidal disease was encountered in 54 patients (49%), metastasis to cervical lymph nodes in 47 patients (42%), extrathyroidal extension to the adjacent structures (starp muscles or trachea) in 6 patients (5.5%), and systemic dissemination of cancer in 2 patients (1.8%). Neck dissection (modified/radical), was performed in 69 patients; cervical lymph node involvement was found in 45 cases (64%). Six patients were diagnosed with thyroid cancer above the age

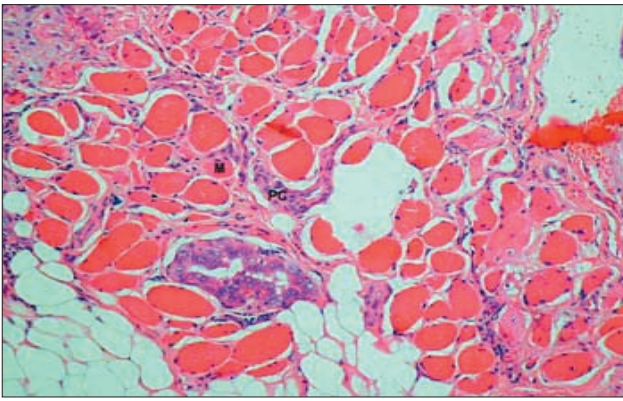


Figure 1 - Papillary thyroid carcinoma (PC) infiltrating the muscle fibers (M), hematoxylin and eosin 10 x 20.

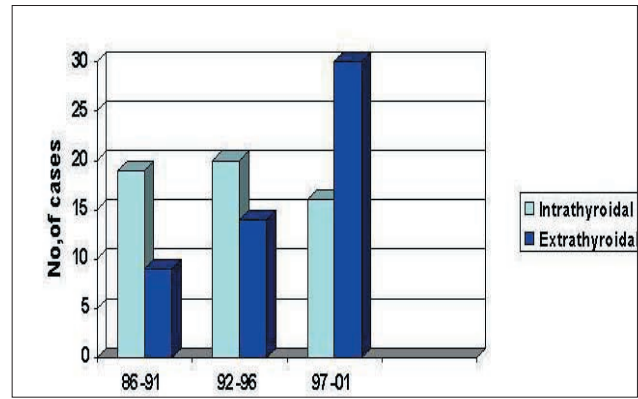


Figure 2 - The distribution of thyroid cancer (intrathyroidal versus extrathyroidal) disease at the time of presentation among the 3 study groups.

Table 1 - Clinicopathological characteristics of patients died of thyroid cancer (n=10).

Patients no.	Age (years)	Clinical presentation	Extent of 1st operation	Adjuvant Rx
1	70	Anaplastic cancer	Thyroid biopsy	None
2	64	Anaplastic + CLN	Thyroid biopsy	EBR
3	70	Anaplastic + CLN	Thyroid biopsy	None
4	64	Anaplastic cancer	Thyroid biopsy	RAI
5	77	PTC + ETD + CLN	Total thyroidectomy +	RAI+EBR
6	75	PTC + CLN	MND	None
7	20	Lymphoma	Total thyroidectomy	EBR
8	53	Mets SCC	Total thyroidectomy	None
9	60	PTC + lung mets	Near total thyroidectomy	None
10	59	PTC + lung mets	Total thyroidectomy	None

PTC - papillary thyroid carcinoma, ETD - extrathyroidal disease, Mets SCC - metastatic squamous cell carcinoma, CLN - cervical lymph node involvement, TTX - total thyroidectomy, nTTX - near total thyroidectomy, MND - modified neck dissection, Thy Bx - thyroid biopsy, RAI - radioactive iodine ablation, EBR - external beam radiation.

Table 2 - Frequency of different types of thyroid cancer in this study and other series.

Studies	Year	n	Country	Papillary thyroid cancer %	Follicular thyroid cancer %	Extrathyroidal extension %
Sroujeh et al ²⁰	1990	100	Jordan	62	22	35
Larijani et al ²¹	2004	1177	Iran	79.7	8.8	28.6
Hod et al ²⁹	2004	45	Saudi Arabia	82.2	4.4	Not mentioned
Zidan et al ³⁰	2004	97	Yemen	93.8	4.3	Not mentioned
Parking et al ³¹	2001	129	Israel	100	-	25.6
Goretzki ³²	1997	53	Israel	66	34	Not mentioned
Shomaf et al	Present study	110	Jordan	80	2.7	62

of 70 years, 4 of them had an advanced presentation (66%) whereas 9 patients diagnosed with thyroid cancer below the age of 20 years, 4 (44%) of them had advanced presentation. In an attempt to identify the correlation of the stage of thyroid cancer and the year of presentation, the study group was divided in 3 groups. Group A included 28 patients (mean age of 39.2 years) diagnosed with thyroid cancer between 1986 and 1991, group B included 34 patients (mean age 39.6 years) diagnosed between 1992 and 1996, and group C included 48 patients (mean age of 41 years) diagnosed between 1997 and 2001. Analysis of the clinicopathologic characteristics showed statistically significant difference between patients in the 3 groups. Whereas 9 patients (28%) presented with advanced thyroid cancer in group A, 14 patients (41%) were advanced cancers at the time of presentation in group B, and 30 patients (62%) in group C ($p < 0.0129$ ANOVA test) (**Figure 2**).

Out of the 110 patients included in the current study, the data of 95 patients were available for evaluation. There is a median follow-up of 6 years (range 2-15 years); 10 patients died of cancer. The clinicopathologic characteristics of these patients are illustrated in (**Table 1**).

Discussion. Thyroid cancer accounts for 1% of all new malignant diseases. The vast majority of carcinoma is epithelial in origin. The median age at diagnosis is 45-50 years and thyroid carcinomas are 2-4 times as frequent in women as in men.⁶⁻⁸ The mean age of our patients was 40 years, which is similar to the findings from Saudi Arabia (36 years)⁹ and other reports from Iran (42.8 ± 0.9 years).¹⁰ Five to 20% of patients have local or regional recurrences and around 10% have distant metastasis at the time of diagnosis.¹¹⁻¹² In this study, 35.4% of the tumors had metastasized to cervical lymph nodes at the time of presentation. Introduction of FNA cytology has increased the accuracy of diagnosing thyroid and neck masses. Routine use of FNA biopsy has significantly increased the incidence of thyroid cancer in surgical specimens from 14-29% and the cost of care has decreased by approximately 25%.¹³⁻¹⁵ Fine needle aspiration confirmed the diagnosis of thyroid carcinoma in 19% of our patients, so that they were subjected directly to a total or near-total thyroidectomy. Cervical lymph node biopsy revealed the presence of thyroid cancer in 16% and the diagnosis of cancer was established on final pathology in 25% of patients subjected to hemithyroidectomy for benign thyroid problems. Total or near total thyroidectomy was the recommended treatment for all patients with preoperative diagnosis of thyroid

cancer as it eradicates multicentric disease, facilitates postoperative radioiodine ablation and allows thyroglobulin levels to be used as a tumor marker for follow-up. The 7 patients who were subjected to conservative surgery were either patients discovered to have occult thyroid cancer postoperatively (4 patients) or had a clinical picture suggestively of anaplastic carcinoma (3 patients). In the current study, 69 patients were subjected to neck-node dissection. Studies showed that the various tumors distribution in iodine age standardized incidence rates per 100000 population in different parts of the world vary from 0.8-5.0 for males and 1.9-9.4 for females.¹⁶ Several studies have shown that thyroid cancer is rising worldwide despite the decline in mortality especially in countries exposed to nuclear fall out.¹⁷⁻¹⁸ The type of thyroid cancer varies greatly in different populations, and the evidence suggests that this variation is mainly a consequence of living in an iodine rich or iodine poor environment, some deficient areas are similar to that in iodine rich areas.¹⁹ It has been suggested that excess iodine intake increases the incidence of PTC whereas low iodine intake increases the incidence of FTC. In Jordan and in spite of the iodination program, iodine intake is still low in various parts of the country.¹ In a previous report of 100 cases of thyroid carcinoma by Sroujeh et al²⁰ from JUH, PTC was observed in 62%, FTC in 22%, MTC in 8%, and anaplastic carcinoma in 7%. In that report, 24% of patients were found to have cervical lymph node metastasis and 11% had distant metastasis at the time of diagnosis. The incidence of PTC in this report is 80% significantly higher than what is reported previously but similar to those reported in Iran (79.7%).²¹ In addition, there is a dramatic drop in the incidence of FTC (from 22 to 2.7%) and dramatic rise in extrathyroidal disease at the time of presentation (35-62%) (**Table 2**). The development of thyroid carcinoma is influenced by environmental, genetic and hormonal factors. The environmental factors include genotoxic and non-genotoxic effects. Because of the fact that thyroid depends on obtaining iodine from the environment, which is vulnerable to genotoxic effects (DNA damage) of radioactive iodine and also to the non-genotoxic effects (TSH stimulation) resulting from iodine deficiency. Papillary carcinoma is the most closely linked to radiation either external²²⁻²³ or internal irradiation from radioactive iodine. Young children are particularly susceptible since thyroid growth occurs primarily in childhood period. A marked increase in thyroid cancer in children has been reported in Belarus following the Chernobyl crisis in 1986. In the decade following the Chernobyl crisis, the incidence of thyroid cancer increased at least 30

fold in Belarus while in Gomel (the region closest to Chernobyl) the incidence reached about 100 fold higher than estimated worldwide incidence of thyroid cancer in children (one per million children per year). This is primarily been due to exposure to radioactive I^{131} and I^{132} which are concentrated by thyroid about 1000 times greater than the rest of the body. The relative risk for the development of thyroid cancer in children in Belarus under the age of one year at exposure reached 237 while those age 10 at exposure reached a relative risk of 6, this difference is due to the fact that young children have higher uptake of radioactive iodine than adults and are more likely to consume radioactive iodine in milk than older children and adults.²⁴ Increased incidence of papillary thyroid cancer was also reported from Poland¹⁸ and Austria after Chernobyl crisis.²⁵ Radiation induced papillary thyroid carcinoma is more aggressive than the usual slowly growing PTC.^{24,26} The frequency of follicular carcinoma in this study is 2.7% which is far less than Japan (17%) and the United States (16%) which are considered as countries of high iodine intake (>240 mg/day) and theoretically should have low frequency of FTC.²² The increasing trends of PTC histology and the decline in follicular histology in this study and other regional studies (Table 2)^{20,21,27-30} may not be explained solely of increase iodine intake because Jordan for example still have a high goiter rate (32.1%) 7 years after the start of implementation of iodine to table salt launched in the early 1990s. One explanation for this change might be related to changing pattern of interpretation among pathologists over the past 20-30 years because currently, most pathologists would consider follicular variant of papillary thyroid cancer as papillary carcinoma, which might be true in few cases only, but not to this dramatic level as seen in this study. The question of background radiation exposure and the increased rate of thyroid, breast & lung carcinomas between 1996 and 2002 in central Jordan (Jordan national cancer registry) is far from being completely answered. Similarly, Parkin³¹ suggested that environmental exposures are the major causative factors for thyroid, ovarian, cervical & colorectal cancers. However, the finding of a high prevalence of P53 and retPTC3 mutation in these cases would legally be an accepted molecular genetic confirmation of suspected radiation induced thyroid cancer.³² The data presented here reflect the current epidemiological features of thyroid cancer in central Jordan. It is still too premature to draw any firm conclusion from these results. The authors however feel that there is a great need for population-based large collaborative studies, to investigate the time trends and true epidemiology of thyroid cancer in Jordan.

Acknowledgments. This work was supported by the Faculty of Medicine, University of Jordan. We thank Mr Saleh Massad for his help with the graphs.

References

1. Kharabsheh S, Belbesi A, Qarqash W, Azizi F. Goiter prevalence and urinary iodine excretion in schoolchildren of Jordan. *Int J Vitam Nutr Res* 2004; 74: 301-304.
2. Younes N, Robinson B, Delbridge L. The etiology, investigation and management of surgical disorders of the thyroid gland. *Aust N Z J Surg* 1996; 66: 481-490.
3. Vanov VK, Gorski AI, Maksoutov MA, Vlasov OK, Godko AM, Tsyb AF, et al. Thyroid cancer incidence among adolescents and adults in the Bryansk region of Russia following the Chernobyl accident. *Health Phys* 2003; 84: 46-60.
4. Pasiaka JL. Anaplastic thyroid cancer. *Curr Opin Oncol* 2003; 15: 78-83.
5. Russell CF, Edis AJ, Scholz DA, Sheedy PF, van Heerden JA. Mediastinal parathyroid tumors, experience with 38 tumors requiring mediastinotomy for removal. *Ann Surg* 1981; 193: 805-809.
6. Schlumberger MJ. Papillary and follicular thyroid carcinoma. *N Engl J Med* 1998; 338: 297-306.
7. Kinder BK. Well differentiated thyroid cancer. *Curr Opin Oncol* 2003; 15: 71-77.
8. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics 1999. *CA Cancer J Clin* 1999; 49: 8.
9. 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.
10. Larijani B, Aghakhani S, Khajeh-Dini H, Baradar-Jalili R. Clinicopathological features of thyroid cancer as observed in five referral hospitals in Iran--a review of 1177 cases. *Acta Oncol* 2003; 42: 334-337.
11. 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.
12. Samaan NA, Schultz PN, Hickey RC, Ordenez NG. The results of various modalities of treatment of well differentiated thyroid carcinoma: a retrospective review of 1599 patients. *J Clin Endocrinol Metab* 1992; 75: 714-720.
13. Arda IS, Yildirim S, Demirhan B, Firat S. Fine needle aspiration biopsy of thyroid nodules. *Arch Dis Child* 2001; 85: 313-317.
14. Asp AA, Georgitis W, Waldron EJ, Sims JE, Kidd GS 2nd. Fine needle aspiration of the thyroid. Use in an average health care facility. *Am J Med* 1987; 83: 489-493.
15. Saha AR. Controversies in the management of thyroid nodule. *Laryngoscope* 2000; 110 (2 Pt 1): 183-193.
16. Tai P, Mould RF, Pryszyzhnyuk AY, Gristchenko VG, Obodovsky IA. Descriptive epidemiology of thyroid carcinoma. *Current Oncology* 2003; 10: 54-65.
17. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* 1995; 141: 259-277.
18. Niedziela M, Korman E, Breborowicz D, Trejster E, Harasymczuk J, Warzywoda M, et al. A prospective study of thyroid nodular disease in children and adolescents in western Poland from 1996 to 2000 and the incidence of thyroid carcinoma relative to iodine deficiency and the Chernobyl disaster. *Pediatr Blood Cancer* 2004; 42: 84-92.

19. Larijani B, Shirzad MA, Haghpanah V, Mosavi-Jarrahi AR et al. Epidemiologic analysis of the Tehran cancer institute data system registry (TCIDSR). *Asian Pac J Cancer Prev* 2004; 5: 36-39.
20. Sroujeh AS, Abu-kalaf M, Swaiss A, Farah GR, El-Muhtaseb H, Ajlouni K, et al. Carcinoma of the thyroid gland: report of 100 cases from Jordan university hospital. *Jordan Med J* 1990; 24: 134-144.
21. Larijani B, Aghakhani S, Khajeh-Dini H, Baradar-Jalili R. Clinico-pathological features of thyroid cancer as observed in five referral hospitals in Iran- a review of 1177 cases. *Acta Oncol* 2003; 42: 334-337.
22. Mayr B, Potter E, Goretzki P, Ruschoff J, Dietmaier W, Hoang-Vu C, et al. Expression of Ret/PTC1, -2, -3, -delta3 and -4 in German papillary thyroid carcinoma. *Br J Cancer* 1998; 77: 903-906.
23. Bounacer A, Wicker R, Caillou B, Cailleux AF, Sarasin A, Schlumberger M, et al. High prevalence of activating proto-oncogene rearrangements, in thyroid tumors from patients who had received external radiation. *Oncogene* 1997; 15: 1263-1273.
24. Nikiforov Y, Gnepp DR, Fagin JA. Thyroid lesions in children and adolescents after the Chernobyl disaster: implications for the study of radiation tumorigenesis. *J Clin Endocrinol Metab* 1996; 81: 9-14.
25. Gomez Segovia I, Gallowitsch HJ, Kresnik E, Kumnig G, Igerc I, Matschnig S, et al. Descriptive epidemiology of thyroid cancer in Carinthia, Austria. 1984-2001. *Thyroid* 2004; 14: 277-286.
26. Maxon HR. Radiation-induced thyroid disease. *Med Clin North Am* 1985; 69: 1049-1061.
27. Qari FA. Pattern of thyroid malignancy at a university hospital in western Saudi Arabia. *Saudi Med J* 2004; 7: 866-870.
28. Abdulmughni 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.
29. Hod N, Hagag P, Sandbank J, Horne T. Epidemiological characteristics and I¹³¹ scintigraphic of patients with papillary thyroid carcinoma with distant metastases. *Harefuah* 2001; 140: 1134-1138.
30. Zidan J, Kassam S, Karen D, Kuten A, Robinson E. Differentiated thyroid cancer in Arabs in northern Israel. *Harefuah* 1997; 132: 6-9, 72.
31. Parkin DM, Iscovich J. Risk of cancer in migrants and their descendants in Israel: Carcinoma and germ- cell tumours. *Int J Cancer* 1997; 70: 654-660.
32. Goretzki PE, Dotzenrath C, Simon D, Roher HD. Studies of oncogenes and tumor-suppressor genes in human thyroid carcinomas, and their clinical implications. *Langenbecks Arch Surg* 1999; 384: 1-8.