PROGNOSTIC FACTORS AND RISK GROUPS ANALYSIS IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

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ABSTRACT

OBJECTIVE : To analyse the initial manifestations, pathological findings, therapy, outcome and prognostic factors in patients with papillary and follicular carcinoma of the thyroid gland and also to evaluate DNA flowcytometry as a prognostic factor in diffrentiated thyroid carcinoma.

PATIENTS : Analysis of clinical and pathological records was conducted on 210 patients (48 male and 162 female) treated for well differentiated thyroid carcinoma refered to Clinical Oncology Department and Surgical Endocrinology Unit, Mansoura University Hospital in the period from Janury 1990 to December 1995.

RESULTS : The patients were 22.8% males and 77.2% females. 68.6% patients presented with papillary carcinom a. High incidence in fifth decade. 89.5% of cases the duration of symptoms was less than 6 months. 21% presented with neck node metastases, while distant metastases in 13% . Recurrences were recognised in 7% of patients. The two and five years disease free survival rates were 91% and 88% respectively. By univariate analysis, patientís age at the time of diagnosis, tumour size, extraglandular extension, nodal status, distant metastasis were found to be significant prognostic variables while the sex and histology were found to be non significant. DNA content was diploid in 57% of follicular carcinoma and 37% of papillary carcinoma. Aneuploid pattern was

found in 43% and 63% of follicular and papillary carcinoma respectively. DNA deploid pattern was associated with less mortality due to the cancer.

Introduction and Aim of the work :

Differentiated thyroid carcinoma is a relatively indolent disease. Despite the usually favorable prognosis, differentiated thyroid carcinoma is fatal in some patients (1) .

In the past, treatment strategies were often based upon incomplete knowledge of inaccurate assumptions regarding the significance of the presenting characteristics of the tumour and patient. More recently, several large retrospective reviews have identified those that have prognostic significance and those that do not. Using this knowledge, patients can be grouped into low, intermediate and high risk groups (l) .

Prognostic factors and risk group analysis have facilitated the development of more rational treatment algorithms and makes a selective approach to differentiated thyroid carcinoma possible (2)

Such an approach can spare many patients morbidity and aggressive expense of unnecessaril treatment without compromising outcome.

In a wide range of human cancers, tumour cell nuclear DNA content has been considered to represent one of the best prognostic indices of the malignant potential in thyroid carcinoma and the presence of an abnormal DNA. Stemline has been regarded as the single most reliable marker of neoplasia and has predictive power significantly greater than that of all other prognostic factors combined, (3) .

The purpose of this study is to review our experience with differentiated carcinoma of thyroid and studying different prognostic factors and its effect on survival in addition to evaluation of DNA ploidy as a significant prognostic variable .

PATIENTS AND METHODS

From January 1990 to December 1995, 210 patients diagnosed pathologically as differentiated thyroid carcinoma, refered to Clinical Oncology and Nuclear Medicine Department and Surgical Endocrinology unit, Mansoura University Hospital were enrolled in this study. From these patients 144 patients (68.6%) had

papillary thyroid carcinoma, 46 patients (21.9%) had follicular carcinoma and 20 patients (9.5%) had mixed papillary and follicular type.

Different parameters studied included age, gender, tumour size, extrathyroid extension, focality of primary tumour, presence or abscence of distant metastases, lymph nodes involvement, histological type, treatment and survival .

The primary treatment comprised of total thyroidectomy, TSH suppressive therapy with L-thyroxin and post operative radioiodine therapy in 173 patients. The radicallnes of previous thyroid surgery was assessed by neck ultrasound and I^{131} whole body scintigraphy performed after 4 weeks of L-thyroxin withdrawal .

Nuclear DNA content was analyzed in 40 patients by DNA flow cytometry post operatively. DNA histograms were scored as either diploid or aneuploid by single cell suspension preparation and the result was correlated with the survival and other prognostic factors.

Kaplan-meier survival analysis was used to calculate both cancer related mortality and disease free survival in the patients followed up. Cox's proportional hazard regression analysis for disease free survival was also used in this study .

RESULTS

This study evaluated the different prognostic factors in 210 patients with differentiated thyroid carcinoma attended Clinical Oncology and Nuclear Medicine Department and Surgical Endocrinology unit, Mansoura University from January 1990 to December 1995 .

They were 48 (22.8%) males and 162 (77.2%) females (Table I). Of this group 144 (68.6%) patients presented with papillary thyroid carcinoma 46 (21.9%) patients had follicular carcinoma of thyroid and 20 (9.5%) had mixed papillary and follicular carcinoma .

(Table 1) shows the high incidence (58.0%) among the age of 40 : 49 years . Neck tumours was the commonest symptom, 80%. Duration of symptoms was less than 6 months in 89.5% of cases . Extra thyroid invasion was found only in 16 cases and neck node metastases was present in 44 patients (21 %). Distant metastas-

es was present in 27 (13%) cases while the number of lesion was multiple in 44 cases. Recurrences were recognized in 15 (7%) patients, six in thyroid bed, three in neck lymph nodes only and six in both sites (Table 1) .

During whole period of observation 27(13%) patients suffered from distant metastases. 10 in lungs, 14 in bones, 2 in liver and one in brain (Table 2).

Regarding the results of DNA flowcytometric analysis and its relation to histopathological analysis. Twelve cases out of 21with follicular carcinoma showed diploid pattern (57%) and 9 cases were of aneuploid pattern (43%), of the 19 cases with papillary carcinoma, 12 were of aneuploid pattern (60.3%) and 7 were diploid (39.7%) (Table 3) .

The univariate analysis identified age at time of diagnosis, glandular extrathyroid extension, tumor size and distant metastases as significant prognostic factors with major effect on survival. Other factors such as gender, multifocality or regional lymph node metastases had no effect on survival (Table 4).

Important prognostic factors identified on multivariate analysis were age older than 45 years ($P<0.001$), extrathyroid extension, tumor size exceeding 5 cm, and the presence or absence of distant metastases ($P<0.001$).

The 2 and 5 years survival for the entire series of patients with papillary carcinoma was 92% and 91% and of folliculer carcinoma it was 91% and 88% respectively while for patients with mixed carcinoma it was 90% and 88% respectively (Table 5).

In studying response to treatment and disease free survival for these group of patients, it was found that complete response to treatment and disease free period were higher in cases showed diploid pattern whether the pathological type was follicular or papillary , it was 90% and 96% respectively in comparison to 86% and 90% respectively in cases showed aneuploid pattern, (Table 6).

Table " 1 " *Clinical Investigational Characteristics of 210 Cases with differentiated Thyroid Carcinoma*

Characteristics	Number	Percent
• **Age (years)**		
40 - 49	122	58.0
50 - 59	65	31.0
60 - 69	10	4.8
70 - 79	8	3.8
80 - 89	5	2.4
• **Gender**		
Male	48	22.8
Female	162	77.2
• **Symptoms**		
Neck tumour	168	80.0
Hoarsness	40	19.0
Neck Pain	5	2.4
Dyspnea	2	0.9
Dysphagia	2	0.9
• **Duration of symptoms in months**		
≤ 6	188	89.5
> 6	22	10.5
• **Maximum diameter of the tumour**		
≤ 5 cm	158	75
> 5 cm	52	25
• **Number of lesions**		
Solitary	166	79
Multiple	44	21
• **Extrathyroid invasion**		
Absent	194	92
Present	16	8
• **Nodal metastases**		
Absent	166	79
Present	44	21
• **Local recurrence**		
In Thyroid bed	6	2.8
In Neck Lymph Nodes	3	1.4
In Both	6	2.8
• **Distant metastases**		
Absent	183	87
Present	27	13

Table " 2 " ***Initial Presentation & Outcome of Distant Metastases***

Site	*No of Patients*		
	Total	**At initial diagnosis**	**In follow up period**
Bones	14	2	12
Lungs	10	7	3
Liver	2	1	1
Brain	1	0	1
Total	27	10	17

Table " 3 " ***DNA Pattern Among the Studied patients and its Relation to Histopathological Examination***

Ploidy Pattern	*Histopathological Types*		
	Follicular	**Papillary**	**Total**
Diploid	12	7	19
Aneuploid	9	12	21
Total	21	19	40

Table " 4 " ***Analysis of Prognostic Factors in Patients with Differentiated Thyroid Carcinoma***

Factor	NO	%	P.value
Age < 49 Ys	122	58	< 0.001
Male	48	22.9	N.S
Size > 5cm	52	24.8	< 0.001
Solitary	166	79	N.S
Extra Capsular Extension	16	7.6	< 0.001
Nodal Metastases	34	16.2	N.S
Distant Metastases	27	12.9	< 0.001

N.S : Not Significant

Table " 5 " ***Two and Five Years Survival for Differentiated Thyroid Carcinoma***

Type	No. of cases	2 years survival %	5 years survival %
Papillary	144	92	91
Follicular	46	91	88
Mixed	20	90	88

Table " 6 " ***DNA Pattern and its Relation to Survival in 40 Patients***

Histopathology	Number	Disease Free Survival %	P. value
(I) Follicular :-			
a- Diploid	12	90%	N.S.
b- Aneuploid	9	86%	N.S.
(II) Papillary			
a- Diploid	7	96%	N.S.
b- Aneuploid	12	90%	N.S.

DISCUSSION

Well differentiated thyroid carcinomas are usually slow-growing neoplasm with an indolent Clinical course.

Assessment of treatment modalities for them requires a long-term follow-up in a large population (4).

Our understanding of the natural history of differentiated thyroid carcinomas has improved with the definition of prognostic factors. These prognostic factors have helped us to identify patients in various risk groups (5).

The concept of prognostic factors in thyroid cancer was first described more than 20 years ago by wollier (1968) (6)

In our study, univariate analysis identified age, glandular extrathyroid extension, tumour size and distant metastases as significant prognostic factors with major effect on survival. The same prognostic factors were identified by different studies 4, 5, 6, 7 and 8. In study done by Tsuchiy (1995) (9) , he found that lymph nodes metastases and operative procedure also have a significant prognostic factors.

Five years survival in our study was 91% in cases with papillary carcinoma and 88% in cases with follicular carcinoma. It was 92% and 88% respectively (8) .

Multivariate analysis was conducted on survival data of 187 patients who underwent curative resection for differentiated thyroid cancers.

The important prognostic factors identified were age older than 45 years, extrathyroid extension, tumour size exceeding 5 cm and presence or absence of distant metastases. These results were in agreement with many studies 7, 9, 10 .

Based on data derived from our study in DNA pattern done for forty patients (21 of follicular and 19 of papillary subtypes) , 5 years survival rates was noticed to be higher in the groups which showed diploid DNA patterns (90% vs 86%) in cases with aneuploid pattern in follicular carcinoma and 96% vs 90% in papillary carcinoma and this reflected that the finding of non-diploid DNA appears to be associated with higher cancer mortality, these results were in occordance with results re-

ported by Many outhors, 3, 11, 12) .

CONCLUSIONS : We concluded that there ia a high prevalence of papillary carcinoma in our country. Age at time of diagnosis, glandular extra thyroid extension, tumor size and distant metastases were significant prognostic factors by univariante analysis with major effect on survival. Other factors such as gender, multi focality or regional lymph node metastases had no effect on survival.In studing response to treatment and disease free survival for comparison with the result of DNA flow cytometry . It was found that complete response to treatment and disease free period were higher in cases showed diploid pattern whether the pathological type was follicular or papillary .

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دراسة فى العوامل التكهنية والكامنة الخطورة فى مرضى أورام الغدة الدرقية السرطانية المميزة

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*قسم علاج الأورام والطب النووى - وحدة جراحة الغدد الصماء**

تمت دراسة هذا البحث على ٢١٠ مريضاً بأورام سرطان الغدة الدرقية المميزة. يمثل الذكور ٤٨ حالة والاناث ١٦٢ حالة أى بنسبة ٢٢.٨٪- ٧٧.٢٪ وعولج هؤلاء المرضى بقسم علاج الأورام والطب النووى ووحدة جراحة الغدد الصماء بمستشفى المنصورة الجامعى فى الفترة من يناير عام ١٩٩٠ حتى ديسمبر عام ١٩٩٥. وكان الغرض من الدراسة هو تقييم العوامل التكنية لهؤلاء المرضى. ومن البحث وجد أن الفترة الحياتية للمرضى لمدة عامين ولمدة خمسة أعوام هى ٩١٪ و ٨٨٪ بالترتيب وبعمل التحليل Univariate وجد أن عمر المريض وقت تشخيص المرض وحجم الورم والامتداد خارج الغدة وحالة الغدد الليمفاوية والثانويات المنتشرة هى العوامل ذات التأثير الهام على الفترة الحياتية للمرضى بينما نوع الجنس والحالة الباثولوجية ليست ذات أهمية وبدراسة محتوى الحمض الامينى النووى د.ن.أ وجد أنه مضاعف النموذج فى ٥٧٪ من حالات الأورام الجرابية وفى ٣٧٪ من حالات الأورام الحليمية وغير مضاعف فى ٤٣٪ و ٦٣٪ بالترتيب ووجد أن الفترة الحياتية المتوقعة للمرضى أطول حالات الأورام التى تحتوى على النموذج المضاعف للحمض الأمينى النووى د.ن.أ.