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RESEARCH

Thyroid Cancer in Egypt: Histopathological Criteria, Correlation With Survival and Oestrogen Receptor Protein Expression

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Abstract Thyroid cancer represents approximately 1% of new cancer and oestrogen may play a role in the pathogenesis of thyroid neoplasm. We aimed to study the clinicopathological criteria and ER expression of thyroid cancer in Mansoura University (*Egypt*), and to correlate the survival to these clinicopathological data and ER expression. This retrospective study reviewed 644 patients with histologically proven thyroid carcinoma during the period from 2003 to 2011. 152 cases during the period between 2008 and 2011 were retrieved from the archive and examined by immunohistochemistry for oestrogen receptor-α (*ER*) expression. ER-α expression is significantly associated with the female sex, lymph node metastasis, TNM stage, extrathyroid extension, multifocality disease and recurrence and in the whole series ($p<0.5$). The same was noticed in papillary carcinoma (PTC) except the gender of the patient. Tumour type, extrathyroid extension and ER expression were the independent prognostic factors of DFS, while in PTC, only ER expression was the independent one. The histological type was the only independent prognostic factor for OAS in the series were studied for ER expression, while extrathyroid extension was the only one that affected OAS of PTC. There was significant positive correlation with lymph node metastasis and ER expression in whole patient and PTC cases. No difference in survival between the low and high ranges of positive oestrogen expression. The prognosis of thyroid carcinoma in Egypt is similar to that occurs worldwide. ER-α expression was a significant prognostic marker for DFS in thyroid cancer and can be used as a predictive factor of lymph node metastasis.

Keywords Thyroid cancer · Immunohistochemistry · Papillary carcinoma · Oestrogen receptor · Egypt

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Introduction

Thyroid cancer accounts for approximately 1% of new cancer diagnosed each year. The incidence of thyroid cancer has increased over the last thirty years worldwide except in Africa, which is most likely due to insufficient screening [1]. The increased incidence is noted for small-sized tumors and the mortality rate for patients with thyroid cancer during the same time period remained constant [2, 3]. In Egypt, thyroid cancer represents about 1.5% of all cancers and constitutes about 30% of endocrine malignancies. The rate among Egyptian females is 0.0027% with female to male ratio is less than 3 [4].

Differentiated Thyroid carcinoma (*DTC*) which is derived from follicular cells includes PTC and FTC. PTC represents about 80–85% of thyroid cancers, while FTC is the second most frequent subtype representing approximately 10–15% of all thyroid cancers [5]. Other types of thyroid cancer exist, including; medullary thyroid carcinomas (*MTCs*) which are derived from parafollicular cells and account for about 3–4% of all cases of thyroid cancer [6], and anaplastic carcinoma (*ATC*) is derived from thyroid epithelial cells and accounts for about 1–2% of all thyroid malignancy [7]. Other cancer including primary lymphomas and sarcomas are very rare [8].

Thyroid diseases are more prevalent in women between puberty and menopause. These epidemiological data suggest a

role of oestrogen in the pathogenesis of thyroid diseases [9]. Recent reports show that oestrogen receptors (*ERs*) are present in thyroid tissue and suggest that oestrogen may play a role in the pathogenesis of thyroid neoplasm. Few researchers have examined the correlation between receptor content and clinical behavior of the thyroid lesions in detail. The significance of these receptors is still unclear [10–12]. In the study by Kishino et al., the antitumor effect of tamoxifen in high doses for multidrug resistant anaplastic thyroid carcinoma was considered beneficial [13].

The aim of the present study was to study the incidence and outcome of thyroid cancer in Mansoura university hospital (*Egypt*), and to correlate the outcome to the epidemiological data, histopathological features and ER expression, so we could select high risk patients for more aggressive therapy and could probably benefit from more radical lymph node dissection and should also be under more intense follow-up.

Patients and Methods

This retrospective study was carried out at the Pathology and Clinical Oncology & Nuclear Medicine Departments, Mansoura University Hospital, Egypt and reviewed 644 patients retrospectively with histologically proven thyroid carcinoma during the period from January 2003 to December 2011.

Patients' data were collected from the files in our departments. The studied variables were data regarding general characteristics of patients including: age, sex, primary tumor size, lymph node status, type of thyroid carcinoma, multifocality (*MF*) of the primary lesion, extrathyroid extension (*ETE*), treatment modalities (*type of surgical resection*, *postoperative treatment*), presence or absence of local recurrence, presence or absence of distant metastasis (*DM*), and survival including overall survival and disease free survival (*OAS and DFS respectively*).

Histological types of thyroid carcinoma were determined according to the system of World Health Organization [14]. TNM staging system was performed for these cases according to The American Joint Committee on Cancer [15].

The original H&E sections were retrieved from the archive of the pathology department and reassessed regarding the histological type, extent of tumor invasion and lymph node metastasis as well as the adequacy of the specimen. The selected sections contained normal thyroid epithelium to compare the normal tissue with the tumor tissue. Thereafter, the available paraffin blocks for 152 cases during the period of 2008 and 2011 were retrieved from the archive and repeated cutting at the thickness of 3-4u on coated slides. The slides were then submitted for immunohistochemistry for oestrogen receptor-α(*ER*).

All specimens were fixed in 10% formalin and routinely processed for paraffin embedding for immunohistochemistry. Xylene deparaffinization and rehydration in descending grades of alcohol into water were performed. Antigen retrieval procedure was performed using citrate buffer at pH 6 and heating in microwave for 10 minutes. The sections were incubated in 3% H_2O_2 blocking medium for five minutes then washed with distilled water. After those a monoclonal antibody against ER-α antigen was used. The monoclonal antibody for ER-α was mouse antihuman antibody (*clone*; *1D5*, *1*:*50*, *Genemed Biotechnologies*, *South San Francisco*, *CA 94080*, *U.S.A.*). A slide from breast carcinoma was used as a positive control with each run of immunostaining. The antibody was incubated for 60 min at room temperature. Immunodetection was performed with the Dako REAL™EnVision™ system, peroxidase/DAB+, Rabbit/Mouse (*Code*: *K5007*, *DAKO*, *Glostrup*, *Denmark*) for use with Dako automated immunostaining instruments. The staining was performed according to the manufacturer instructions. The visualization of the immunoreaction was done by adding DAB (*Code*: *K5007*) for three minutes. The slides were counterstained with Dako REAL hematoxylin (*Code*: *S2020*) for 1 min and cover slipped with the mounting media. Negative controls were assessed by replacing the primary antibody by PBS. Hormone receptor expression was scored by assigning proportion and intensity scores, according to Allred's procedure [16]. In brief, a proportion score represented the estimated proportion of positive nuclear staining in tumor cells, as follows: 0 (none);1(<1%);2(1–10%);3(10–33%);4(33–66%);5(>66%). A second score was determined and represented the average intensity of positive tumor cells (*0*, *none*; *1*, *weak intensity*; *2*, *intermediate*; *3*, *strong*). The Allred score was obtained by the addition of the proportion score to the intensity score. This score ranged from 0 to 8 and determined the tumor's positivity. An Allred score>2 was used to define tumor ER positivity. The positive cases were sub grouped into a low range category including scores 3, 4, 5 and a high range category including scores 6, 7, 8.

Follow up of patients with DTC was done by means of three to six monthly outpatients' returns in first 2 years then annually. Follow up included physical examination, biochemistry tests for thyroid hormones assessments, thyroid stimulating hormone (*TSH*), and thyroglobulin levels (*at 6*, *12 months then annually*), periodic ultrasonography of the neck. whole body iodine scan (*WBI ^{131}Scan*) every 6 to 12 months till it will become free twice, radiological studies (*including chest X-ray*, *abdominal ultrasound and bone scan*, *when indicated*) were employed for detection of relapse. The survival data (*overall survival*, *disease free survival*) were retrieved from the archive of Clinical Oncology and Nuclear Medicine Department. The statistical analysis for studying the histopathological factors affecting the survival of the thyroid cancer was performed for whole patient and the 152 cases for which estrogen receptor immunohistochemistry was done for more accuracy. We also analyzed the factors affecting the

outcome of 97 cases of PTC. Regarding FTC, MTC and anaplastic carcinomas we didn't study them in details due to the very few number for performing accurate statistical analysis.

Statistical Analysis

Data was analyzed by using Statistical Package for Social Sciences (*SPSS Inc*., *Chicago*, *IL*, *USA*) program version 17. Qualitative data were presented as number and percent. Association between ER immunoreactivity and different clinicopathological parameters was evaluated using Chi-square and Fisher's exact probability test. The logistic regression model with the presence of lymph node metastases serving as the dependent variable was done to assess the correlation of ER expression with lymph node metastasis. Survival curves were estimated by the Kaplan-Meier method with a log rank test to assess significance. Multivariate Cox proportional hazard regression models were used to evaluate any independent prognostic effect of the variables with 95% confidence interval. A p-value of <0.05 was considered to reflect a significance. DFS was calculated from the date of surgery till the date of recurrence (*either local or distant*) and OAS was calculated from the date of diagnosis till the date of death of the patient or lost follow up.

Results

The records of unselected 644 patients with histologically proven thyroid carcinomas were reviewed and retrospectively analysed with median follow period was 44 months. Of these patients, 31.2 % were males and 68.8% were females (*male to female ratio was 1*:*2.2*) with an age range (8–84) years and a median age of 43 years. The remaining patients' characteristics are shown in Table 1. Forty nine patients died during the follow up period (*7.6*%). The patients in our study received different lines of treatment as shown in Table 2. The different lines of treatment were mentioned as descriptive results only as the relation between treatment and survival is outside our scope in this study.

Prognostic Features in the Whole Series

Univariate analysis of various prognostic factors in the whole patients' series in relation to OAS showed that older age group, large primary tumor size, involvement of lymph nodes, DM, ETE, and anaplastic carcinoma were significantly poor prognostic factors. Performing the analysis with the same variables in relation to DFS had shown similar relations in addition to sex of the patient and multifocality of the tumor were associated with lower survival (Table 3)

Table 1 Clinicopathological features of the whole thyroid carcinoma series

Variable	Number	(%)
Gender		
- Female	443	(68.8)
- Male	201	(31.2)
Patients' age		
- Less than 45 years	345	(53.6)
- More than or equal to 45 years	299	(46.4)
Primary tumour size		
- 1 cm or less	62	(9.6)
- More than 1 cm but not more than 2 cm	125	(19.4)
- More than 2 cm but not more than 4 cm	280	(43.5)
- More than 4 cm	177	(27.5)
Lymph node stage		
- N0	401	(62.5)
- N1	243	(37.5)
Histological type		
- PTC	477	(74.1)
- FTC	81	(12.6)
- Medullary	35	(7.9)
- Anaplastic	51	(5.4)
Development of distant metastasis		
- No	588	(91.3)
- Positive	56	(8.7)
Extrathyroid extension		
- No	594	(92.2)
- Probable	50	(7.8)
Multifocality		
- No	602	(93.5)
- Yes	42	(6.5)
ER expression*		
- Negative	83	(54.6)
- Positive:	69	(45.4)
Low score	35	(50.7)
High score	34	(49.3)

*Total number of cases investigated for ER receptors were 152

Multivariate COX hazard analysis showed that only the large primary tumor size, involvement of lymph nodes, DM, and tumor types retained the independent prognostic feature in relation to OAS. While the multivariate COX hazard analysis in relation to DFS showed that the age of the patient, the large primary tumor size, involvement of lymph nodes, tumor types and ETE retained the independent prognostic feature (Table 4).

ER Expression Results in 152 Cases of Thyroid Cancer

Sixty nine out of 152 cases (45.4%) were positive for ER expression among which only 13.1% were males and 86.9%

Table 2 Lines of treatment in whole patients' series of thyroid cancer

Lines of treatment	Patients no (%)
Surgery	
-Radical (total or near total thyroidectomy)± Node dissection	419 (65.1)
-Subtotal thyroidectomy	169 (26.2)
-Palliative resection	56 (8.7)
Radiotherapy*	46 (7.1)
Chemotherapy	15 (2.3%)
Radioactive iodine^{131}	535 (83.1%)
Combined**	48 (7.6)

*Including radical and postoperative RT

**Combination of two or three of RT, chemotherapy or RAI ^{131}

were females with a statistical significance ($p=0.005$). Among the positive cases 63.8, 18.8, 8.7 and 8.7% were PTC, FTC, MTC and ATC respectively with no statistical significance ($P=0.9$) (Fig. 1). The relation of ER- expression to other clinicopathological parameters showed significant positive association lymph node stage ($p<0.001$), TNM stage ($p<0.001$), ETE ($p<0.001$), disease recurrence (<0.001) and MF ($p=0.04$). The results are summarized in Table 5. When we used the logistic regression analysis with the presence of lymph node metastases serving as the dependent variable, we found a positive correlation between ER expression and lymph node metastasis [($p=0.000$, *odds ratio*;*5.196 and 95% CI*;*2.6–10.4*), *this result didn't be presented in table*].

Prognostic Features in 152 Cases of Thyroid Cancer

Recurrences were found to have occurred in 46 % of the patients. The median time of recurrence was 24.00 months ranged from 0.00 to 54 months. The Kaplan Meier survival analysis revealed significant association between ER expression and DFS ($p<0.001$) Fig. 2 with median survival of 20.00 months in cases with ER expression and 25.00 months in cases negative for ER expression. Univariate and multivariate analysis of various prognostic factors in the ER studied whole patients' series in relation to DFS are shown in Table 6.

Table 3 Prognostic variables in relation to OAS and DFS in the whole patients' series of thyroid cancer

Variable	Overall Survival (%)	Log rank	*p* value	Disease free survival (%)	Log rank	*p* value
Gender		0.460	0.498		0.905	0.002
- Male	91.1			62.4		
- Female	92.8			76.2		
Patients' age		35.793	<0.001		70.629	<0.001
- Less than 45 years	97.2			83.3		
- More than or equal to 45 years	85			58.4		
Primary tumour size		91.993	<0.001		147.592	<0.001
- 1 cm or less	100			90.4		
- More than 1 cm & less than 2 cm	99			89.4		
- More than 2 cm & less than 4 cm	96.7			78		
- More than 4 cm	73.9			37.9		
Lymph node stage		42.725	<0.001		130.166	<0.001
- N0	97.3			88.2		
- N1	82.1			45		
Histological type		375.923	<0.001		279.299	<0.001
- PTC	97			78.1		
- FTC	89			64.4		
- Medullary	90.6			59.4		
- Anaplastic	45.7			34.8		
Development of distant metastasis		77.399	<0.001	–	–	–
- No	94.6					
- Yes	60.8					
Extrathyroid extension		20.784	<0.001	75.5	76.677	<0.001
- No	92.9			30.4		
- Probable	76.1					
Multifocality		0.856	0.355		7.601	0.006
- No	91.9			73.4		
- Yes	87.2			51.3		

Table 4 COX proportional hazard analysis of the predictors of OAS and DFS in the whole series of thyroid cancer patients

Variable	OAS				DFS			
	P value	Hazard ratio (HR)	95 % CI		*P* value	Hazard ratio (HR)	95 % CI	
			Lower	Upper			Lower	Upper
Gender	–	–	–	–	0.674	1.071	0.778	1.475
Age	0.067	2.104	0.950	4.660	<0.001	2.255	1.570	3.239
Tumour size	0.008	2.496	1.264	4.927	<0.001	1.576	1.239	2.005
LN stage	0.003	3.083	1.479	6.426	<0.001	4.256	2.951	6.139
Tumour types	<0.001	2.339	1.787	3.063	<0.001	1.729	1.479	2.022
DM	0.010	2.248	1.214	4.164	–	–	–	–
MF	–	–	–	–	0.388	1.284	0.728	2.265
ETE	0.195	1.595	0.788	3.229	<0.001	2.312	1.465	3.650

It was found that only tumor type, ETE and ER expression retained the independent prognostic features ($p<0.05$).

Thirty four deaths (22.3%) out of 152 cases were reported. The Kaplan Meier survival analysis revealed no significant association between ER expression and OAS ($p=0.67$) with median survival of 27 months in cases with ER expression and 25.00 months in cases negative for ER expression Fig. 3.

Univariate and multivariate analysis of various prognostic factors in the whole patients' series in relation to OAS are shown in Table 6. It was found that only the histological tumor type remained as an independent prognostic factor ($p<0.001$).

ER Expression Results in 97 Cases of Papillary Thyroid Carcinoma

Forty four out of 97cases (45.3%) were positive for ER expression in papillary thyroid carcinoma. The association of ER expression with the clinicopathological features of PTC are summarized in Table 7. There were also significant positive correlation between ER expression and lymph node metastasis by using logistic regression analysis (*p=0.000*, *odds ratio*; *11.467 and 95% CI*; *4.409–29.8*), also this result didn't be presented in table.

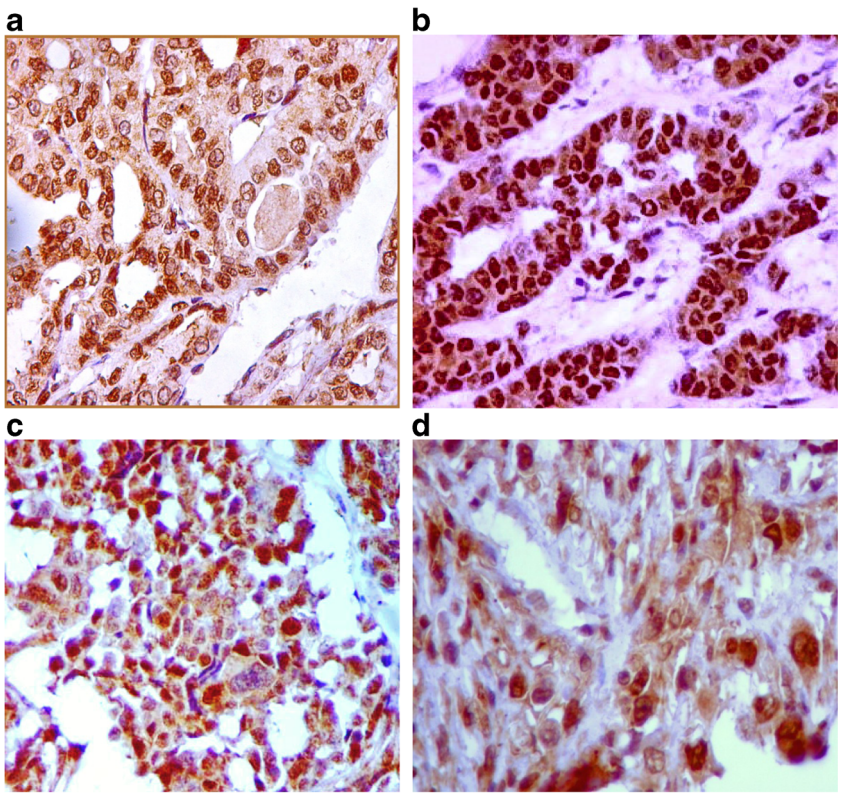

Fig. 1 Immunohistochemistry for estrogen receptor αshowing positive nuclear staining in **a**) follicular variant of papillary thyroid carcinoma x200 **b**) follicular thyroid carcinoma x400 **c**) medullary thyroid carcinoma x400 **d**) anaplastic thyroid carcinoma x400

Table 5 Association of ER expression with the clinicopathological features of 152 cases of thyroid cancer

	ER expression		*P* value
	Negative	Positive	
Gender			
- Male	33 (39.8%)	9 (13.1%)	0.005
- Female	50 (60.2%)	60 (86.9)	
Patients' age			
- Less than 45 years	30 (36.1%)	40 (58%)	0.8
- More than or equal to 45 years	53 (63.9%)	29 (42%)	
Histological type			
- PTC	53 (63.9%)	44 (63.8%)	0.9
- FTC	13 (15.7%)	13 (18.8%)	
- MTC	8 (9.6%)	6 (8.7%)	
- ATC	9 (10.8%)	6 (8.7%)	
Lymph node status			
- N0	66 (74.7%)	25 (36.2%)	<0.001
- N1	17 (25.3%)	44 (63.8%)	
TNM stage			
- Stag I	48 (57.8%)	28 (40.6%)	<0.001
- Stage II	11 (13.3%)	2 (2.9%)	
- Stage III	10 (12.0%)	28 (40.6%)	
- Stage IV	14 (16.9%)	11 (15.9%)	
DM			
- No	78 (93.9%)	61 (77.7%)	0.3
- Yes	5 (6.1%)	8 (11.5%)	
Extra thyroid extension			
- No	82 (98.9%)	54 (74.1%)	<0.001
- Yes	1 (1.1%)	15 (25.9%)	
Multifocality of tumour			
- No	81 (97.6%)	61 (88.4%)	0.04
- Yes	2 (2.4%)	8 (11.6%)	

The median time of recurrence was 25.00 months ranged from 6 to 54 months. The Kaplan Meier survival analysis revealed significant association between ER expression and DFS ($p=0.000$) as shown in with median survival of 23.00 months in cases with ER expression and 30.00 months in cases negative for ER expression. Univariate and multivariate analysis of various prognostic factors in relation to DFS are shown in Table 8. It was found that only ER expression remained as an independent prognostic factor ($p=0.002$).

Eleven deaths (11.3%) out of 97 cases were reported with no significant association between ER expression and OAS ($p=0.301$) with equal median survival of 31 months in positive and negative cases for ER expression. Univariate and multivariate analysis of various prognostic factors in relation to OAS are shown in Table 8. It was found that only extrathyroid extension remained as an independent prognostic factor.

Relation of Survival With Intensity of Oestrogen Positive Expression

Among 69 cases with positive ER expression, there were 34 (49.3%) case with high score (score 6, 7, 8) while low score (score 3, 4, 5) was detected in 35 cases. In PTC (50.7%), high score was detected in 23 cases (52.3%), while 21(47.7%) case were in low score. We didn't record any significant difference in either DFS or OAS survival between the low range and high range groups of ER positive expression in whole thyroid or papillary thyroid carcinoma patient ($p=0.875$, $p=0.429$, $p=0.631$, $p=0.21$, respectively).

Discussion

Thyroid cancer is the most common malignancy of the endocrine system and the incidence rates differs among the different parts of the world [17]. Most thyroid carcinomas originating from follicular cells are differentiated carcinomas (*DTC*), including papillary and follicular carcinoma that generally have an indolent character and show a favorable prognosis if treated appropriately [18]. Approximately 80–85% and 10–15% of all thyroid malignancies are papillary cancers and follicular carcinoma, respectively [5]. Other uncommon types of thyroid cancer include anaplastic (1–2%) and medullary thyroid carcinomas (3–4%). [6, 7]. In agreement with our results, these incidences show close similarity to the current study regarding the tumor type distribution as we reported 74, 13, 8 and 6% for PTC, FTC, MTC and ATC respectively. This is indicating that thyroid cancer patients in Egypt show no noticeable differences in incidence and distribution.

The age of thyroid cancer in our study ranged from 8 to 84 years and a mean of 43 years. Other literatures reported a range from 25 to 65 yearswith the median age at diagnosis was 49 years of age [19]. In our study, the very old age can be attributed to the presence of anaplastic carcinomas (common in old age) and the very young age was a case of papillary thyroid carcinoma. This agrees with the other studies which reported that, papillary and follicular carcinomas can occur in children and account for 80% and 10-20% respectively, followed by medullary carcinoma (5%) and anaplastic carcinoma, which is rare [20].

Females were more common than males in our study with a ratio of 2.2:1 and this was true for both PTC and FTC, which agrees with other literatures [19]. The predominance of thyroid cancer in female in reproductive years explained by the presence of estrogen receptor in thyroid carcinoma, however for other ages, the incidence in males and females is similar [21]. Others reported that, although the majority of patients with PTC are women, no convincing hormonal associations have been elucidated [22].

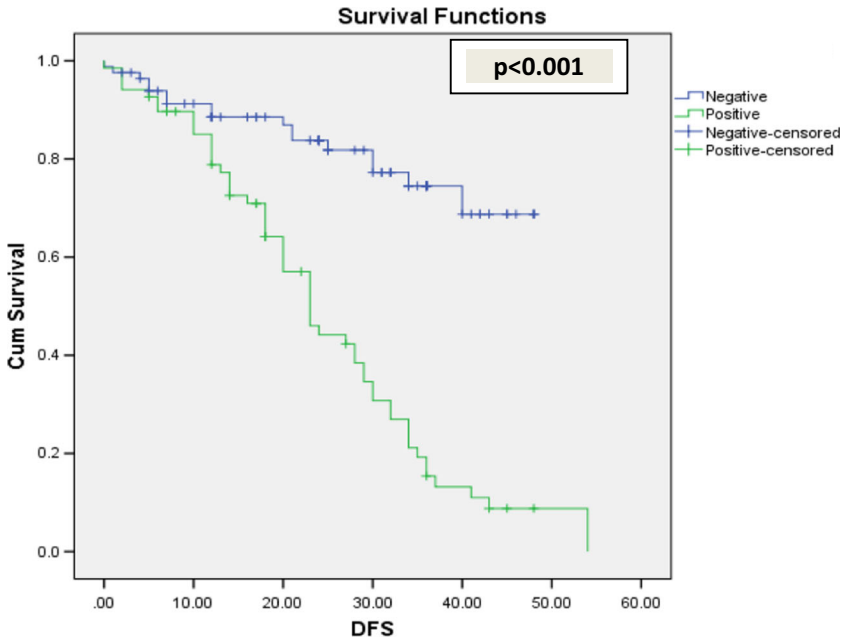

Fig. 2 Disease free survival rates (in months) according to ER expression status in 152 cases of thyroid carcinomas

Our study revealed on the univariate analysis that age> 45 years, tumour size>4 cm, involvement of lymph nodes, extrathyroid extension, distant metastasis and tumour type were significantly poor prognostic factors for OAS in the whole patient series. Multivariate analysis showed that, only the large primary tumour size, involvement of lymph nodes, distant metastasis, and tumour types (anaplastic carcinoma) retained the independent prognostic feature. Chunxia et al., also found that patients with lymph node and distant metastasis had poorer prognosis, which agree with us [23]. On the other hand, the sex of the patient had no significant effect of on OAS, although, Shah et al., reported that female gender is a favourable prognostic factor [24]. The poor prognosis of anaplastic carcinoma agrees with other literatures with a death rate of 90% within 6 months [20].

The same previous prognostic factors were found to influence DFS on univariate analysis in whole patients' series, but in addition, female gender and multifocality were also significant prognostic factors. The significance of multifocality as a factor influencing DFS but not OAS can be related to incomplete thyroidectomy. Also multiplicity and recurrence are common in PTC, which is the predominant type of thyroid cancer but with very rare distant metastasis and excellent prognosis, so multiplicity is related to DFS but not to OAS. Multivariate analysis showed that only age of the patient, the large primary tumour size, involvement of lymph nodes,

Table 6 Cox proportional hazard model showing prognostic factors of DFS in 152 cases of thyroid cancer

	DFS				OAS			
	Univariate		Multivariate		Univariate		Multivariate	
	P value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)
Age	0.03	1.02 (1.002–1.04)	0.7	0.99 (0.97–1.02)	0.005	1.03 (1.008–1.05)	0.16	1.02 (0.99–1.04)
Sex	0.6	0.9 (0.5–1.5)	–	–	0.68	1.1 (0.6–2.05)	–	–
Histological type	<0.001	1.8 (1.4–2.1)	<0.001	1.729 (1.479–2.022)	<0.001	1.5 (1.3–1.5)	<0.001	2.129 (1.554–3.021)
LN	<0.001	2.8 (1.7–4.6)	0.37	1.3 (0.7–2.3)	0.3	1.3 (0.78–2.2)	–	–
TNM stage	<0.001	1.6 (1.3–1.9)	0.5	1.1 (0.77–1.6)	0.008	1.4 (1.09–1.7)	0.77	1.06 (0.7–1.5)
DM	0.04	2.08 (1.03–4.2)	0.99	1.002 (0.4–2.3)	0.6	0.77 (0.3–2.1)	–	–
ETE	<0.001	7.1 (4.03–12.4)	0.001	3.9 (1.8–8.6)	0.04	1.8 (1.04–3.03)	0.77	1.1 (0.5–2.5)
MF	0.001	2.4 (1.4–3.96)	0.3	0.7 (0.4–1.3)	0.9	1.03 (0.5–1.96)	–	–
ER expression	<0.001	4.7 (2.7–8.1)	0.01	2.2 (1.15–4.3)	0.76	1.08 (0.6–1.8)	–	–

*The histological type (PTC versus FTC) was found to be a highly significant factor

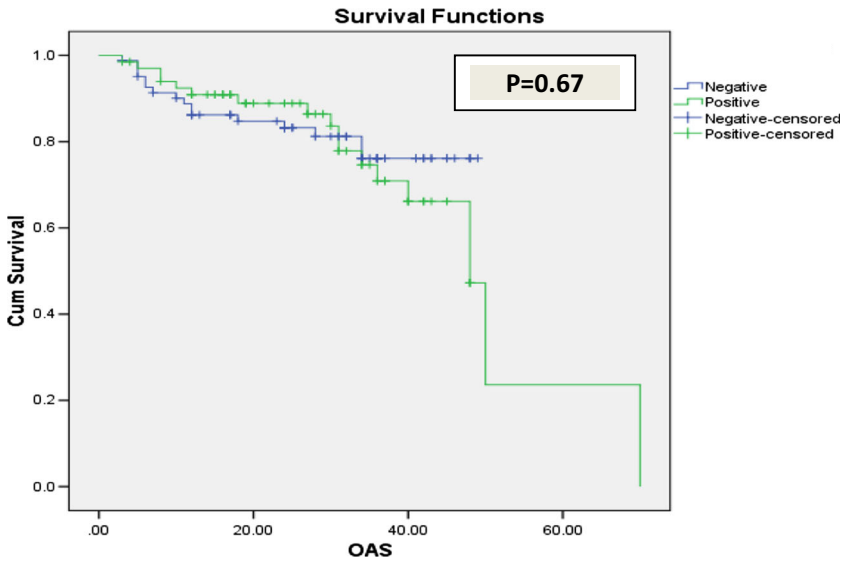

Fig. 3 Overall survival rates (in months) according to ER expression status in 152 cases of thyroid carcinomas

extrathyroid extension and tumor types, which lead to residual tumour causing recurrence, retained the independent feature in relation to DFS. Others noticed the factors affecting DFS significantly on multivariate analysis are family history of DTC, advanced stage, and total thyroidectomy [25].

Table 7 Association of ER expression with the clinicopathological features in 97 cases of PTC

	ER expression				*P* value
	Negative		Positive		
	Number	%	Number	%	
Gender					
- Male	17	32.1%	8	18.2%	0.1
- Female	36	67.9%	36	81.8%	
Patients' age					
- Less than 45 years	23	43.4%	29	65.9%	0.24
- More than or equal to 45 years	30	56.6%	15	34.1%	
Lymph node status					
- N0	43	81.1%	12	27.3%	<0.001
- N1	10	18.9%	32	72.7%	
TNM stage					
- Stag I	37	69.8%	22	50.0%	0.001
- Stage II	7	13.2%	0	0.0%	
- Stage III	7	13.2%	20	45.5%	
- Stage IV	2	3.8%	2	4.5%	
DM					
- No	52	98.1%	43	97.7%	0.9
- Yes	1	1.9%	1	2.3%	
Extra thyroid extension					
- No	52	98.1%	35	79.5%	0.001
- Yes	1	1.9%	9	20.5%	
Multifocality					
- No	52	98.1%	38	86.4%	0.04
- Yes	1	1.9%	6	13.6%	

Emerging studies show that oestrogen receptors are present in thyroid tissue, and suggest that oestrogen may play a role in the biology of thyroid neoplasm [10]. Our study revealed higher expression of ER in PTC accounting for 63.8% of thyroid cancer followed by FTC (18.8%), MTC and anaplastic carcinoma (each accounts for 8.7%). Among PTC, FTC, MTC and ATC, 45.3%, 50%, 42.8% and 40% of cases were positive for ER respectively. Tavangar et al., found ER expression in 11 % of follicular carcinomas, 31% of papillary carcinomas, zero% for medullary carcinomas and zero % for undifferentiated carcinomas [10], also the incidence of ER positivity was found higher in well-differentiated thyroid lesions as detected by other results [26]. Cameselle-Teijeiroet et al., showed positive ER in 50.8% of PTC, 13 % of FTC and 30 % of undifferentiated carcinoma [27]. They explained the highest expression of hormone receptors in PTC by its higher female prevalence and suggested that such receptors play a genetic role. On the other hand, Cho et al., found ER was detected in 91% of medullary carcinoma which is markedly higher than ours, and other studies andsuggested that ER may play a role in MTC tumor growth and progression [28]. The difference between other studies and ours can be explained by the different scoring system, the difference in number of cases or difference in the techniques of the immunohistochemistry. A previous study found that the incidence of oestrogen receptor reactivity does not significantly differ between females and males of different age groups and it does not correlate with lymph node status, which disagrees with us. They also found no relation between ER reactivity and pregnancy, presence of capsular and vascular invasions [10].

Few studies examined the correlation between estrogen receptors content and clinicopathological features of the thyroid lesions in detail. The significance of these receptors remains unclear [10, 12]. In the current study, ER-α

Table 8 Cox proportional hazard model showing prognostic factors of DFS in 97 cases of papillary thyroid carcinomas

	DFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	P value	HR (CI95%)	*P* value	HR (CI95%)	*P* value	HR (CI95%)	*P* value	HR (CI95%)
Age	0.48	0.5 (0.49–1.03)	–	–	0.15	1.03 (0.98–1.08)	–	–
Sex	0.8	0.9 (0.5–1.8)	–	–	0.89	1.09 (0.3–4.3)	–	–
LN	<0.001	3.5 (1.7–6.8)	0.57	1.2 (0.6–2.7)	0.07	4.2 (0.9–20.3)	–	–
TNM stage	0.03	1.4 (1.04–1.9)	0.75	1.06 (0.7–1.5)	0.01	2.4 (1.2–4.7)	0.06	2.3 (0.98–5.5)
DM	0.3	2.3 (0.5–9.5)	–	–	0.11	4.5 (0.7–28.6)	–	–
ETE	<0.001	5.4 (2.7–10.5)	0.06	2.7 (0.96–7.4)	0.009	7.9 (1.7–37.4)	0.049	7.1 (1.006–50.2)
MF	0.001	3.3 (1.7–6.3)	0.8	0.9 (0.4–1.9)	0.7	1.3 (0.3–5.2)	–	–
ER expression	<0.001	8.5 (3.6–20.6)	0.002	5.1 (1.8–14.5)	0.3	2.1 (0.5–8.4)	–	–

expression showed significant association with the female sex of the patients, tumor size, lymph node metastasis, TNM stage, extrathyroid extension, disease recurrence and multifocality. However, there was no significant association with the type of the carcinoma which can be explained by the discrepancy in the number of each type in our study. One study has shown increased risk of thyroid carcinomas in women taking oral contraceptive pills and in pregnant women and suggested a role of oestrogen in the pathogenesis of thyroid diseases [9]. Regarding PTC, ER expression was significantly associated with lymph node metastasis, TNM stage, extrathyroid extension, disease recurrence and multifocality, while the sex and age of the patient didn't show and significant association.

To our knowledge there are no studies that examined the effect of ER expression on the outcome of thyroid cancer together with other clinicopathological factors. Our study revealed on the univariate analysis that age>45 years, tumour type, involvement of lymph nodes, high TNM stage, extrathyroid extension, multifocality, distant metastasis and ER expression were significantly poor prognostic factors for DFS in the whole patient series. The same previous factors affected DFS of PTC except the patient's age. Chunxia et al., found that patients with lymph node and distant metastasis had poorer prognosis, which agree with us [23]. Multivariate analysis for the whole series showed that, tumour types, ETE and ER expression retained the independent prognostic features. Regarding PTC, only ER expression was an independent prognostic factor. The sex of the patient in our study showed no significant effect of on DFS, although, Shah et al., reported that female gender is a favourable prognostic factor [24]. Others noticed the factors affecting DFS significantly on multivariate analysis are family history of DTC, advanced stage, and total thyroidectomy [25].

The factors affecting the OAS on univariate analysis in whole patients studied for ER receptors were the patient's age, tumor type, TNM stage and extrathyroid extension. Other factors including ER expression didn't show any significant effect on OAS. However the histological type was the only independent prognostic factor on the multivariate analysis. The poor prognosis of anaplastic carcinoma agrees with other literatures with a death rate of 90% within 6 months [20]. The significance of multifocality as a factor influencing DFS but not OAS can be related to incomplete thyroidectomy. Also multiplicity and recurrence are common in PTC, which is the predominant type of thyroid cancer but with very rare distant metastasis and excellent prognosis, so multiplicity is related to DFS but not to OAS.

Regarding PTC, TNM stage and extrathyroid extension affected the OAS, but on the multivariate analysis, only extrathyroid extension was an independent prognostic one with no role for ER expression. ETE was an independent prognostic factorfor OAS and DFS in PTC in other studies [29, 30]. Others found that distant metastasis was an independent prognostic factor of PTC which doesn't agree with ours [29]. Lymph node metastasis didn't show any effect on OAS of PTC either on the univariate or multivariate analysis in our study while, it was found to be independent prognostic factor in PTC in other studies [29–31].

Multifocality of tumour had no influence the OAS of PTC, while it significantly influenced the DFS of PTC on the univariate analysis, but not on the multivariate analysis, this finding was reported in previous study agrees with ours [30, 31].

The role of oestrogen activity in thyroid lesions, especially in well-differentiated tumors, such as papillary carcinomas, follicular adenomas and in goiters, need further investigation and a further study in a larger cohort with long term follow up. The small number of cases in our study might have confounded effect on the potential role of ER in thyroid carcinogenesis.

In conclusion: this study conclude that the prognosis and biological behavior of thyroid carcinoma in Egypt is similar to what happens worldwide and,to the best of our knowledge, is the first study that examined the effect of ER expression on the outcome of thyroid cancer and PTC together with other

clinicopathological factors especially in Egypt. ER expression retained the independent prognostic features for DFS for the whole series. Regarding PTC, only ER expression was an independent prognostic factor with no difference in survival between the patients with high positive and low positive ER expression. The OAS of thyroid carcinoma was affected significantly by tumour type, while in PTC extrathyroid extension was an independent factor. The significant association of ER with female sex, lymph node stage, TNM stage, extrathyroid extension, disease recurrence and multifocality can potentially provide new targets for the treatment of thyroid diseases, so we recommend further studies on ER expression in a large cohort of thyroid carcinomas especially the FTC and MTC and compare them with PTC. We also hope that hormonal therapy (antioestrogen) be studied in thyroid carcinomas and compare the outcome of such patients with those who didn't receive such treatment.

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