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Research Article

A 18-Year Study of Thyroid Cancer Mortality, A Retrospective Single Centre Study in Saudi Based Community Hospital

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Abstract

Background

Thyroid carcinoma (TC) is the second most common malignancy in Saudi Arabia. We describe and interpret trends in the frequency of TC mortality in Saudi population during the 2000-2017 period.

Methods

Retrospective study of TC received at the department of pathology, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia from January 2000 to December 2017

Results

Over the 18-year period, 347 patients with TC were studied; 275 cases (79.3%) were female and 72 cases (20.7%) were male. The age of the studied cases ranged from 12 to 89 years with a mean and median age of 45.2±16.0 years. There were 287 (82.7%) cases of Papillary TC. The next common malignancy was Follicular TC with 32 (9.2%) cases followed by Hurthle cell cancer with 11 (3.2%) cases. Lymphomas was found only in 7(2%) cases. Anaplastic and medullary carcinomas had 6 (1.7%) and 4 (1.2%) cases respectively. Mortality occurred in 18 cases (5.2%). There were no significant differences between male and female patients, 3 cases (4.2%) and 15 cases (5.5%) respectively, p=0.7. Patients in the mortality group were older, 64.1±15.2 vs. 44.1±15.4, p<0.0001. Patients ≥45 years have higher mortality compared to younger than 45 years, 16 cases (9.5%) vs. 2 cases (1.2%) respectively, p=0.001. The highest mortality between different TC types were in the anaplastic cancer patients (33.3%). The frequency rates of TC per 100,000 residents for the period from 2000 to 2002 was 1.6 for 100,000 per year, for the period from 2014 to 2017 was 3.3 for 100,000 per year. However, the mortality rates per 100,000 residents for the period from 2000 to 2002 was 0.13 for 100,000 per year, for the period from 2014 to 2017 was 0.17 for 100,000 per year. The mortality percentage has not changed over 18 years (5.6%). Most of the available data showed mortality was related to respiratory diseases. The survival analysis revealed that The mean time between diagnosis and death was of 10.6 years (CI95%: 7.8-13.3 years) and median 13 years (CI95%: 6.8-19.2 years).

Conclusion

This hospital based study has shown that TC deaths are uncommon and occur in older patients than 45 years. The reason for the very low mortality rate in young TC patients remains unexplained. Hurthle cell cancers were under-represented (0%) in our series with non-fatal TC.

Introduction

The reported rate of thyroid carcinoma (TC) among all malignancies is 1% [1,2]. Thyroid cancers are the 4th most common malignancy in Saudi Arabia and it accounts for 6.6% of all cancers [1-5]. TC is the ninth most common site of all cancers in women in the world and the second most common malignancy after breast cancer in Saudi Arabia [1-5].

The vast majority of TCs (> 90%) originate from follicular cells and are defined as differentiated thyroid cancers (DTC) and the two histological subtypes are the papillary TC with its variants and the follicular TC [6]. DTC is usually an indolent disease that with adequate treatment has an excellent prognosis [6]. Recent study in Saudi Arabia showed there were 82.7% cases of papillary TC. The next common malignancy was follicular TC with 9.2% cases. There were low incidence of anaplastic TC, medullary TC, Hurthle cancer and thyroid lymphoma (1.7%, 1.2%, 3.2 and 2%, respectively) [7]. The literature reports that less than 5% of patients die from the disease within 10 years [8-10]. Furthermore, due to the generally favourable outcome of TC, the number of patients on long-term follow-up is high. In the USA, it is expected that 64300 new

patients have been diagnosed with TC in 2016 and only 0.3% have died from it. Similar trends have been observed in many parts of the world [11,12]. The purpose of this retrospective study was to assess mortality of TC at our institution and to compare that with internationally published data.

Methods

This is a retrospective study of TC reported at the department of pathology, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia from January 2000 to December 2017. Pathological and clinical Records of patients seen at the endocrinology or other services were thoroughly analyzed. The demographic data included age at the time of diagnosis and gender while the histopathological features included TC subtype according to the recommended classification by the International Classification of Diseases for Oncology, third edition [13]. The type of tumor was assessed from the pathology reports and classified mainly as papillary, follicular, anaplastic, medullary, hurthle cell and lymphoma. 347 Patients older than 12 years with a proven histopathological diagnosis of TC were included in this analysis.

Age-standardized, yearly TC incidence and mortality rates were calculated for the entire cohort and for each year between 2000 and 2017. Incidence and mortality rates were age adjusted using the direct method based on age distribution for the mid-average the year 2000 (1.8 million) and 2017 (2.8 million) for Jeddah population. With the direct method of standardization, age-specific rates from the study population were applied to the age distribution of the standard Jeddah population to yield the number of events that would have been expected if the study population had the same age distribution as the standard population. Incidence and mortality rates were shown as the number of cases per 100,000 individuals. Incidence and mortality TC cases were calculated as a percentage of the total number of unique patients per year. Ethical approval was obtained from Research and Ethics committee of King Fahad Armed Forces Hospital.

Statistical Analysis

Continuous variables were described using means±Standard Deviations. Unpaired t-test was used for univariate analysis of baseline demography between groups and Chi square test were used for categorical data comparison. The statistical analysis was conducted with the Statistical Package for Social Science (SPSS Inc., IBM, US), version 22. P value <.05 indicates significance.

Results

Over the 18-year period, 347 patients with TC were studied; 275 cases (79.3%) were female and 72 cases (20.7%) were male. The age of the studied cases ranged from 12 to 89 years with a mean and median age of 45.2±16.0 years. There were 287 (82.7%) cases of Papillary TC. The next common malignancy was Follicular TC with 32 (9.2%) cases followed by Hurthle cell cancer with 11 (3.2%) cases. Lymphomas was found only in 7(2%) cases. Anaplastic and medullary carcinomas had 6 (1.7%) and 4 (1.2%) cases respectively, Table 1. Mortality occurred in 18 cases (5.2%). There were no significant differences between male and female patients, 3 cases (4.2%) and 15 cases (5.5%) respectively, p=0.7, table 2. Patients in the mortality group were older, 64.1±15.2 vs. 44.1±15.4, p<0.0001. Patients ≥45 years have higher mortality compared to younger than 45 years, 16 cases (9.5%) vs. 2 cases (1.2%) respectively, p=0.001. The highest mortality between different TC types were in the anaplastic cancer patients (33.3%), table 3.

Table 1: *Frequency of thyroid cancer types [Number (%)]*

Thyroid cancer type	Frequency of cases
Papillary	287(82.7)
Follicular	32(9.2)
Anaplastic	6(1.7)
Medullary	4(1.2)
Hurthle cell	11(3.2)
Lymphoma	7(2)
Total	347

Table 2: *Gender and age at diagnosis of the study population [Number (%)]*

Parameters		Mortality rates	P value
Gender	Male	3(4.2)	0.7
	Female	15(5.5)	
	Total	18(5.2)	
Age at diagnosis (years)	<45	2(1.2)	0.001
	≥45	16(9.5)	
	Mean±SD	64.1±16.2	<0.0001

Table 3: *Frequency and rates per 100000 residents of thyroid cancer mortality [Number (%)]*

Thyroid cancer type	Mortality rates	Mortality rates per 100,000
Papillary	5(27.8)	0.2
Follicular	4(22.2)	0.17
Anaplastic	6(33.3)	0.2
Medullary	1(5.6)	0.04
Hurthle cell	0	0
Lymphoma	2(11.1)	0.09
Total	18 (5.2)	0.8

The frequency rates of TC per 100,000 residents for the period from 2000 to 2002 was 1.6 for 100,000 per year, for the period from 2014 to 2017 was 3.3 for 100,000 per year, figure 1 A. However, the mortality rates per 100,000 residents for the period from 2000 to 2002 was 0.13 for 100,000 per year, for the period from 2014 to 2017 was 0.17 for 100,000 per year, figure 1 B. Clinical outcome and mode of death of thyroid cancer was shown in table 4. The mortality percentage has not changed over 18 years (5.6%), figure 2. Most of the available recorrds showed mortality was related to respiratory diseas. The survival analysis revealed

that the mean time between diagnosis and death was of 10.6 years (CI95%: 7.8-13.3 years) and median 13 years (CI95%: 6.8-19.2 years), Figure 3.

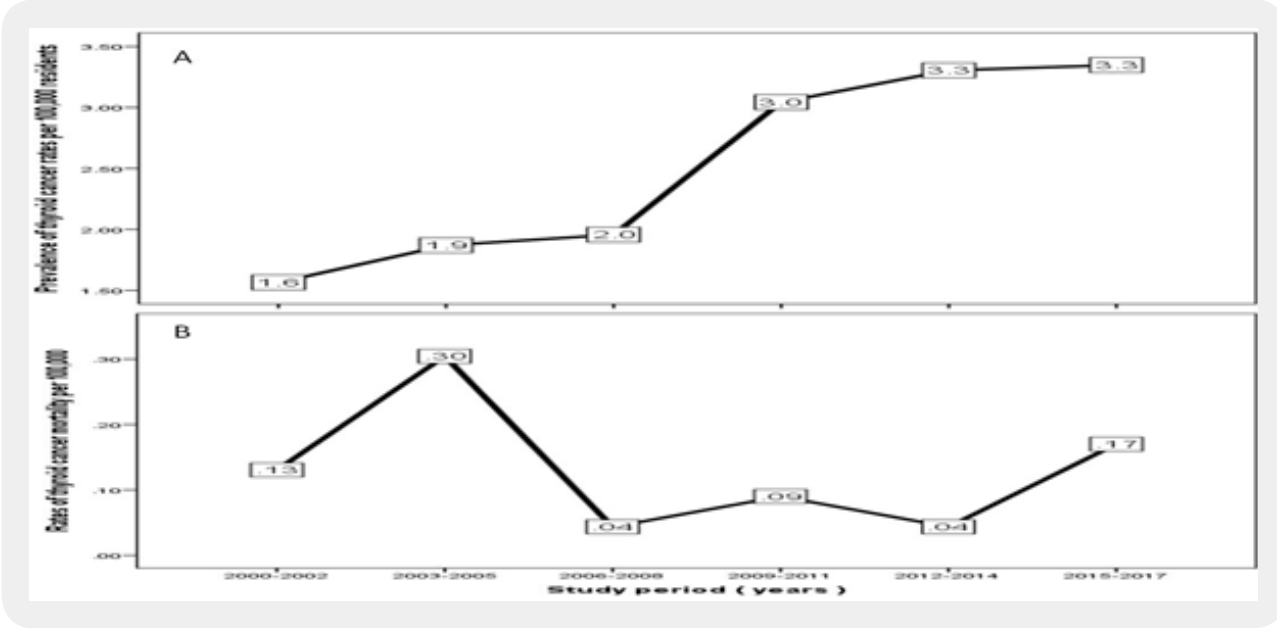

Figure 1A and 1B: *Trends in relative frequency and mortality rates per 100000 residents of thyroid cancer during the study period 2000 to 2017*

Table 4: *Clinical outcome and mode of mortality of thyroid cancer*

Patients	Age at diagnosis	Gender	Histopathology	Reason for death	Years Post Diagnosis
1	63	Female	Lymphoma	Unknown	15
2	66	Female	Lymphoma	Unknown	1
3	39	Male	Anaplastic	Unknown	17
4	33	Male	Anaplastic	Unknown	13
5	62	Female	Anaplastic	Unknown	8
6	81	Female	Anaplastic	Unknown	2
7	89	Female	Anaplastic	Septic shock, Chronic liver disease	4
8	55	Female	Follicular	Pneumonia	13
9	83	Female	Follicular	Community acquired pneumonia	14
10	67	Female	Follicular	Unknown	15
11	73	Female	Follicular	Aspiration pneumonia	2

12	69	Female	Papillary	Unknown	18
13	51	Female	Papillary	Pneumonia, End stage renal disease	15
14	86	Female	Anaplastic	Pulmonary embolism	7
15	66	Female	Medullary	Unknown	17
16	62	Female	Papillary	Unknown	15
17	58	Female	Papillary	Pulmonary embolism	4
18	51	Female	Papillary	Pneumonia	10

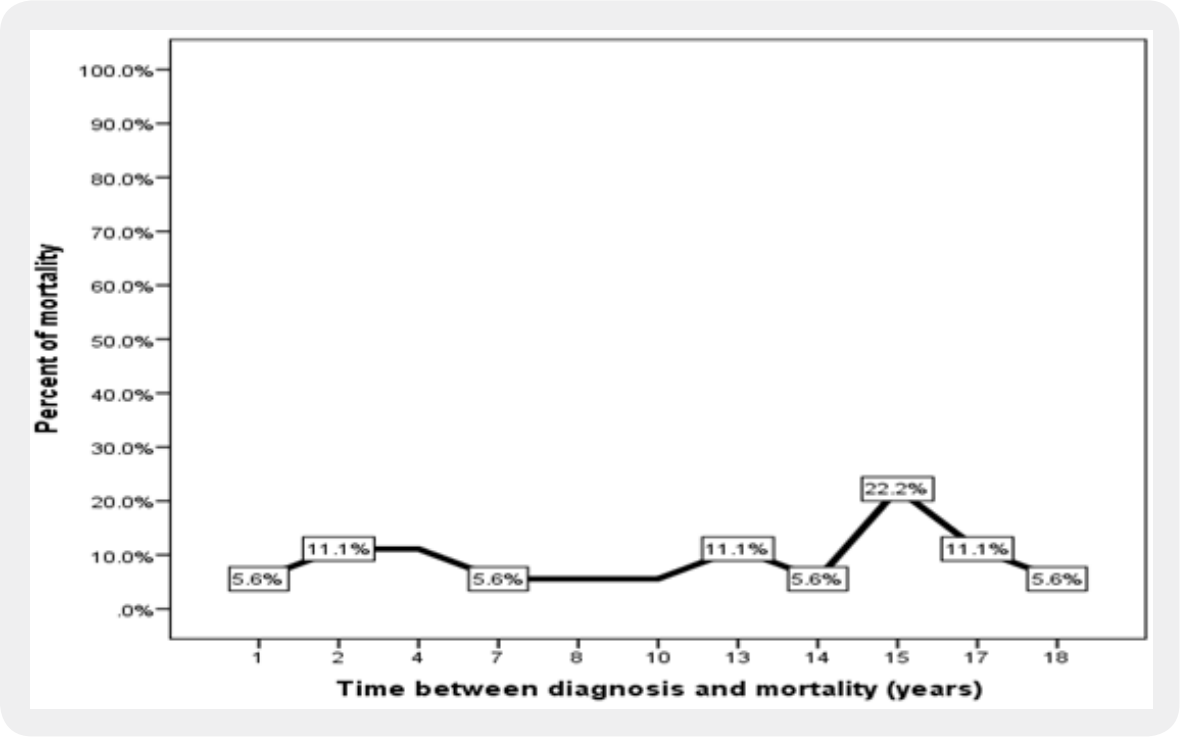

Figure 2: *Percent of mortality for thyroid cancer (2000-2017)*

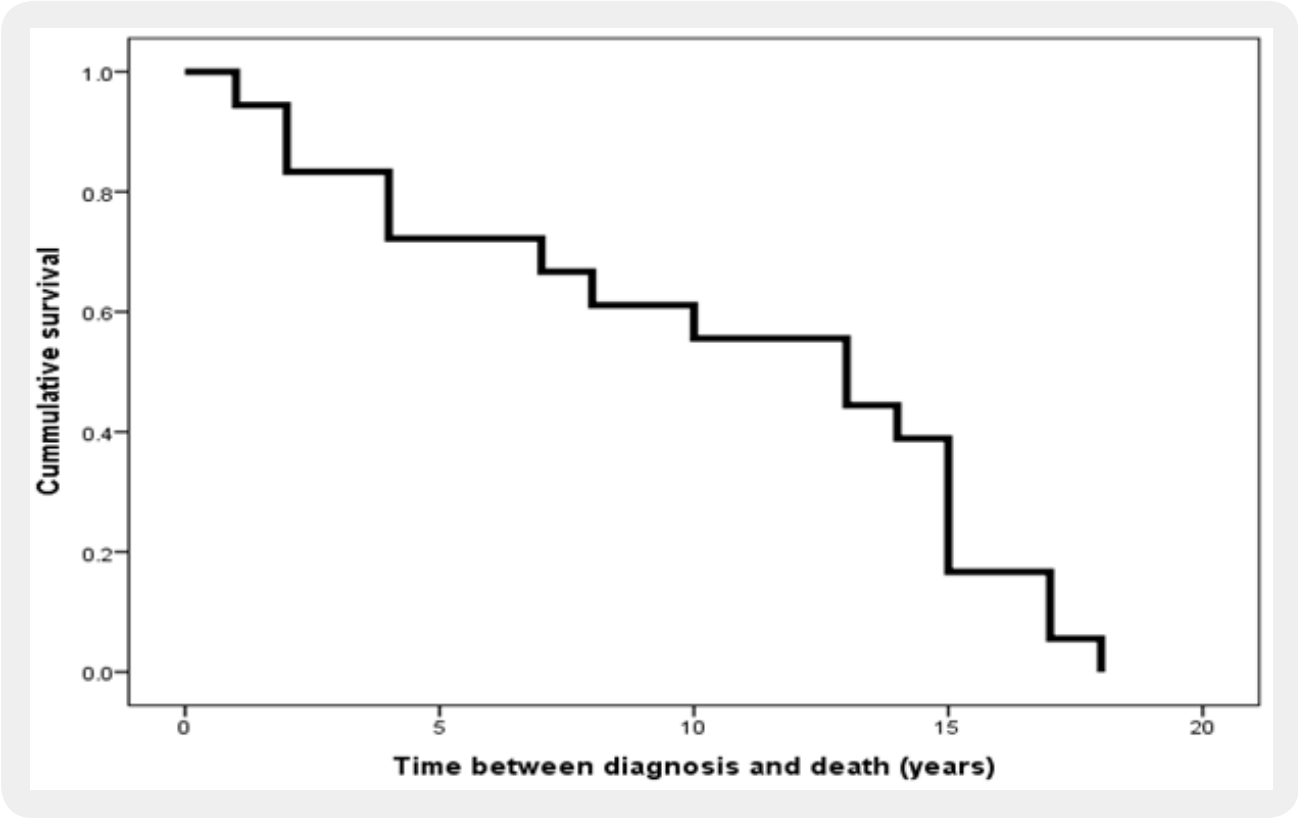

Figure 3: *Kaplan-Meier plot of cumulative survival for thyroid cancer*

Discussion

A major advantage of the present study is the good and complete number of TC cases collected during a relatively long time (18 years). Selection bias has not thereby been avoided, and there has been substantial change in the general health service during this period. Furthermore, there has been a complete record of all patients with respect to survival, and information concerning causes of death has been obtained by death summary and certificates. Although the general validity of death certificates may be discussed, the number of errors are known to be low for malignant tumors [14].

Over the study period (18 years), It approximates to one TC death per year and can be contrasted with the average 19 newly diagnosed TC patients seen by our service in the last 18 years [7]. Moreover, mortality (5.6%) has not been changed over the same period. There are two main messages in the present updated analysis of TC mortality and incidence including: the persistent no change in death rates and the continuous rise in the incidence of thyroid cancer over the last two decades. The incidence of reported TC and study sample size varied from one study to another study. From the 1970s, incidence rates of TC increased in most European countries, although a decrease was recorded in some countries, such as Sweden and Norway [15]. Rising incidence trends are also observed in US and Canada [16,17]. Saudi Arabia is not an exception. Our previous report indicated an increase in TC incidence in Saudi Arabia between 2000 to 2017 in concordance with other national studies [7].

Papillary carcinoma was the most frequent DTC found in 82.7% of cases, followed by follicular (9.2%). The incidence of papillary and follicular TC are within the reported Saudi and Western experience. DTC is associated with an overall excellent prognosis and a mortality rate that has been slowly decreasing in spite of the rising incidence of thyroid cancer [18]. Overall, greater than 90% are alive at 10 years after diagnosis. This excellent prognosis results from a combination of the indolent biological behavior of most cases of DTC and effective primary treatment options. Same is true for the low incidence of Anaplastic TC, Medullary TC, Hurthle cancer and thyroid lymphoma (1.7%, 1.2%, 3.2 and 2%, respectively). These percentages contrast with significantly different percent ages in the current study reflecting a possible change in thyroid histopathological pattern and/or improvement and change in thyroid histopathological classification. Anaplastic TC, which is by far less common type of TC, was responsible for 33.3% (6/18) of our TC deaths. Followed by papillary TC 27.8% (5/18) and follicular TC 22.2% (4/18). There is higher frequency of mortality among the differentiated carcinomas, up to 50% compared to the papillary or follicular TC. It is well known that cancer patients in general are subjected to increased health care [19,20]. Hurthle cell cancer showed no mortality related to TC. In earlier reports Hurthle cell cancers were included with the much commoner follicular cancers, but Hurthle cell cancers are probably best classified separately as they behave more aggressively and are less likely to concentrate radioiodine. Anaplastic carcinomas showed a very poor prognosis, as was expected [21]. However, some cases survived for several years, and these should have been reconsidered with the possibility that they represent thyroid lymphomas [22]. The group of poorly differentiated carcinomas showed an intermediate survival, and this finding is in line with the hypothesis that they may represent transition types between differentiated and undifferentiated carcinomas [23]. Epidemiologic studies are limited by their dependence on population-specific registries, which subject them to bias from regional influences such as diagnostic practices, reporting patterns, and case definitions. Poorly differentiated carcinoma remains a controversial entity, and it is therefore difficult to evaluate whether the different prevalence rates among different geographic regions reflect true etiological differences or mere variations in diagnostic criteria.

Although a marked sex difference is present in the incidence of TC, we found the sex factor does not seem to influence tumor mortality to any significant degree [7,21,24,25]. The female to male ratio of patients dying of TC was 5.0:1 and this is higher to the ratio for our newly diagnosed patients with TC (female to male ratio was 3.8:1) reported previously [7].

Our findings are, however, in contrast to the data of Schelfout *et al.,* who showed that age had no major prognostic significance in a multivariate study of differentiated carcinomas [26]. However, most tumors occurred in our patients were older than 45 years, and the age groups used may be too small to disclose a significant effect among younger patients. The results may also indicate that other biological factors are more important to explain the aggressive behavior of this tumor type. During the 18-year study period two patient under 45 years of age at diagnosis died of TC. (The two young patients died of TC during the study period were diagnosed with anaplastic cancer). Our experience is similar to published reports of TC deaths which show that most deaths occur in patients > 45y at the time of diagnosis [27-30]. The reasons for the very low mortality rate in young TC patients remains unexplained.

The limitations of our study include the small sample size, its retrospective nature over long period, enrolled patients were managed by different teams and cases were from a single hospital and not all patients had follow up. The findings might therefore, not be reflective of the overall general population. Due to the descriptive nature of this study, it is only possible to speculate about potential explanations for the observed TC mortality. Individual-level environmental exposures and lifestyle-related factors were not captured by registries. The current study did not evaluate the influence of treatment on these trends.

In conclusion, this hospital based study has shown that TC deaths are uncommon and occur in older patients than 45 years. The reason for the very low mortality rate in young TC patients remains unexplained. Hurthle cell cancers were under-represented (0%) in our series with non-fatal TC.

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Conflict of Interests

The authors declare no conflict of interests.

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