



Demographic and Pathological Characteristics of Thyroid Cancer in Libya

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Authors' contributions

This work was carried out in collaboration between all authors. Author ABF participate in the design and preparation of the manuscript and participate in performed the statistical analysis. Author GMH provided the clinical data, and participated in the analysis the data. Author EAM conceived of the study, and participated in the organizing of clinical data. Author BMJ participate in the design and coordinate the research and drafted the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: The study evaluates the prevalence and incidence of thyroid cancer in Libya, and describes demographic and clinopathological features.

Patients and Methods: The study was conducted on 64 patients with thyroid carcinoma, admitted to the Misurata hospitals, Libya during the years 2000-2012. The clinopathological features were collected from pathology reports and hospital files of the patients.

Results: The mean age of thyroid cancer patients in Libya was 46 years, which is much higher than in benign lesions (36.5 years). Libyan thyroid cancer prevalence and incidence was evaluated as 12.4 and 2.9 per 100,000 females, respectively. The histological types of the thyroid cancer in Libyan populations showed that the papillary carcinoma was the predominant type followed by follicular carcinoma. On other hand, the medullary carcinoma was less common than anaplastic carcinoma.

Among Libyan patient the systemic involvement, LN involvement, non-papillary histological type of tumor, and tumor size larger than 4cms were strongly associated with poor survival. Although, the men patients had shorter life span than women did, this survival difference was not statistically significant.

The histological types and histopathological risk features show similar importance in respect to survival as the data from European thyroid cancer.

Conclusion: In Libya, the thyroid cancer incidence is low and more common in female than in male. Libyan thyroid cancer is dominantly seen in young adult and displays unfavorable features such as high histological grade and stage, large size, frequent lymph node involvement and systemic metastases.

Keywords: Thyroid cancer; Libya, North Africa; Europe; demography; prevalence; histopathology; survival, incidence.

1. INTRODUCTION

Thyroid cancers like benign thyroid diseases; commonly present in clinical practice as a thyroid nodules. Approximately 5% to 10% of thyroid nodules are thyroid cancer [1,2,3].

Thyroid cancer is the most common endocrine cancer worldwide, contributing to approximately 1.0% to 1.5% of all annually diagnosed cancers [2]. Globally, Thyroid cancer is the fifth most common cancer in women below the age of 45 years, and the second in young adult Italian female. In several countries, thyroid cancer accounts for 0.5 death cases per 100.000 persons, and it is stable and relatively low mortality rate [4,5].

In general, Thyroid cancer incidence is increasing worldwide in the recent 3 decades, but it varies from areas to areas [6,7]. For example, in the USA, the incidence has been increasing steadily by more than two folds during the last 30 years and showed mean of both gender annual percent change (APC) of 6.6% during period from 1997 to 2009 [4,6,8]. In Switzerland, the incidence rose by 85.7% in female and 5.3% in male during the last 3 decade, whereas, in Italy, thyroid cancer incidence has been dramatically increasing by 145% in women and 127% in men during the last 30 years. Similarly, in France, the incidence of particularly papillary carcinoma has been intensely increasing by about 150% and by annually rate increase of 8.1% and 6.2% in women and in men, respectively [6]. Seeming this increase in incidence may be related to improve the diagnostic procedures including the use of FNAC with radiological guiding [4,6]. In Korea the most frequent cancer in both female and male is thyroid cancer (17.8%) with rapidly annually rate increase of 24.2% from 1999 to

2010 [9]. However, in few countries such as Spain, Norway and Sweden the thyroid cancer incidence is decreased [6]. In some Nordic countries, the incidence of thyroid cancer has been decreasing steadily during the last 30 years. The incidence in Sweden reduced 18% for both male and female population. In Norway, there is reduction in female incidence by 5.8%. On other hand, in Spain the female thyroid cancer incidence decreased by 25.9% [6,10,11].

In the African and Arabic countries, the studies are not fully covering. In Egypt, thyroid cancer incidence is about 3.0 new patients per 100.000 persons [12]. The background of Arabic thyroid cancer incidences may be more related to other African thyroid cancer incidences than to European thyroid cancer incidences.

In this study, we would like to characterize some demographic and clinopathological features that associated with thyroid cancer in Libya. To the best of our knowledge, such results on Libyan database have not been published previously. In this connection, we were able to estimate the prevalence and incidence of female thyroid cancer in Western Libya based on the data collected from Misurata health facilities.

2. MATERIALS AND METHODS

2.1 Patients and Methods

i). Clinical and pathological features. A retrospective pathological study was conducted on 64 patients (Table 2). All were treated at the Misurata Hospitals, Libya particularly (Misurata Central Hospital and Misurata Cancer Center) during the years 2000-2012. The pathological features were collected from pathology reports and patients hospital files. The estimated clinical or pathological characteristics included sex, age,

marital status, menopausal status at diagnosis, presenting complain, laboratory investigations (such as Thyroid function test, level of Calcium, hemoglobin and blood group), location and size of tumor, LN status, stage, histological grade, histological type, different types of treatment and follow-up of the patient. Patients were followed-up until they died or to the end of the observation period in the end of 2012. Some patients were lost during follow-up prior to 2012. For these patients, the last date of contact was defined as the date for the end of follow-up.

The follow-up period ranged from 1 to 166 months with an average of 23.0 months.

ii). The evaluation of incidence and prevalence. Estimation of the incidence statistics was consequently based on the histologically verified new cases of year 2010. The collection of data is an active method including visits by authors to five different data sources from majority of the public and private health facilities in Misurata in which cancer may be diagnosed that basically have pathology laboratories (Misurata cancer center, Misurata central Hospital, Assaffwa International private Hospital, and Crescent Hospital). Data are also collected at the Misurata Central pathology laboratory. The data used in this study for evaluation the prevalence are related to the whole thyroid cancer cases that diagnosed during the period from 1 January to 31 December 2010, for residents in the Misurata geographical area covered by the above hospitals. Cases that are not from this area were excluded. Furthermore, to avoid recording duplicate cases from these different data sources, a careful comparison of the data was done.

2.2 Statistical Analysis

The variables of the Libyan patients were grouped and descriptive statistics calculated for the continuous variables by using SPSS software packages for Windows, versions 19.0 (SPSS, Inc., Chicago, USA). For survival analysis, Kaplan- Meier curves were plotted, and differences between the curves analyzed using the log-rank test. Pearson and Spearman's correlation tests were used for comparison between two variables. P-values below 0.05 were regarded as significant. Comparison of numerical data was done by the chi-square test. Student t-tests and ANOVA were also used to

test differences between the groups. Microsoft Excel 2007 was used to draw graphs and to evaluate relationships between variables.

3. RESULTS AND DISCUSSION

3.1 Thyroid Cancer Incidence

There were 11 new thyroid cancer patients, 9 patients are females, and 2 patients are males diagnosed the Misurata hospitals in 2010.

All the mentioned patients were from the Misurata region. The population of this region in 2010 was 378,928 as reported by the Libyan Census Committee. The male female ratio in the Libyan population was 1.05:1 [13]. Based on this data, the incidence was 2.9 new cases per 100.000 Libyan. On other hand, the thyroid cancer incidences in female and male were 4.87 and 1.03 new cases per 100.000 person, respectively.

The incidence in Libya was in line with results published from other North African countries (for example, the male and female incidence was 3.3 and 1.0 for Tunisian, 4.5 and 1.1 for Egyptian, and 3.9 and 0.9 for Moroccan patients respectively [12,14].

The thyroid cancer incidences is relatively lower in Libya, and other North African countries compared with Europe and North America in which the incidence is more than 2.0 per 100.000 for male and more than 6.0 per 100.000 for female [14,15].

Life style differences and radiation exposure may be involved, but the variation in genetic marker distribution between North African, and European populations may also be involved [16].

The incidence rates of thyroid cancer have increased in most countries since 1970,s while mortality rates of this cancer have mostly stabled.

In current study, it was found some evidence that thyroid cancers in western Libya have been slightly increased (Fig. 1). This may be attributed to development in health care, including early detection of small tumors and improved diagnostic facilities such as radiography and FNAC in the last few years.

3.2 Thyroid Cancer Prevalence

The 10 years prevalence was calculated to assess the cancer burden of thyroid diseases, which reflects new and pre-existing cancer patients diagnosed during a given point of time and who are still alive at that given time [15].

As seen in (Table 1) the thyroid cancer patients in this study, in general population during (2000-2010) was 47 survival patients (10 were died).

Therefore, the Prevalence of malignant thyroid tumor in general population during (2000-2010) was 12.4 per 100,000 ($47/378928 \times 100.000$).

The fraction of malignant tumor out of study population (remain alive) during (2000-2010) = $47/437 \times 100 = 10.7\%$, i.e. out of 100 patients there are 11 patients have malignant tumors.

3.3 Age at Presentation

The occurrence of thyroid cancer in female Libyan population is strongly related to the young age with nearly 65.0% of cases arising in-patient

who are 50 years or younger. The mean age was 46.4 (Fig. 2). However, medullary carcinoma and undifferentiated cancers had higher mean age than well-differentiated cancers (Table 2). The difference between the mean ages of men and women patients is statistically significant (p value = 0.02).

Thyroid cancer in males is age related. The highest number of cases in UK was recognized in older men [15].

In this study, more than 50% of male thyroid cancers aged more than 60 years. On contrast with female thyroid cancer, we found that in females aged younger than 40yrs there is about 58% of total female thyroid cancers. In Korean, the thyroid cancer was the most common cancer in middle-aged females, whereas, in Italy, thyroid cancer is the second most frequent cancer in females [6,9]. However, there is statistical difference in the mean age at diagnosis between female and male patients [43.6 and 56.2 respectively] with p -value = 0.024. The younger age female have more risk for thyroid cancer, this might partly be related to estrogen factor.

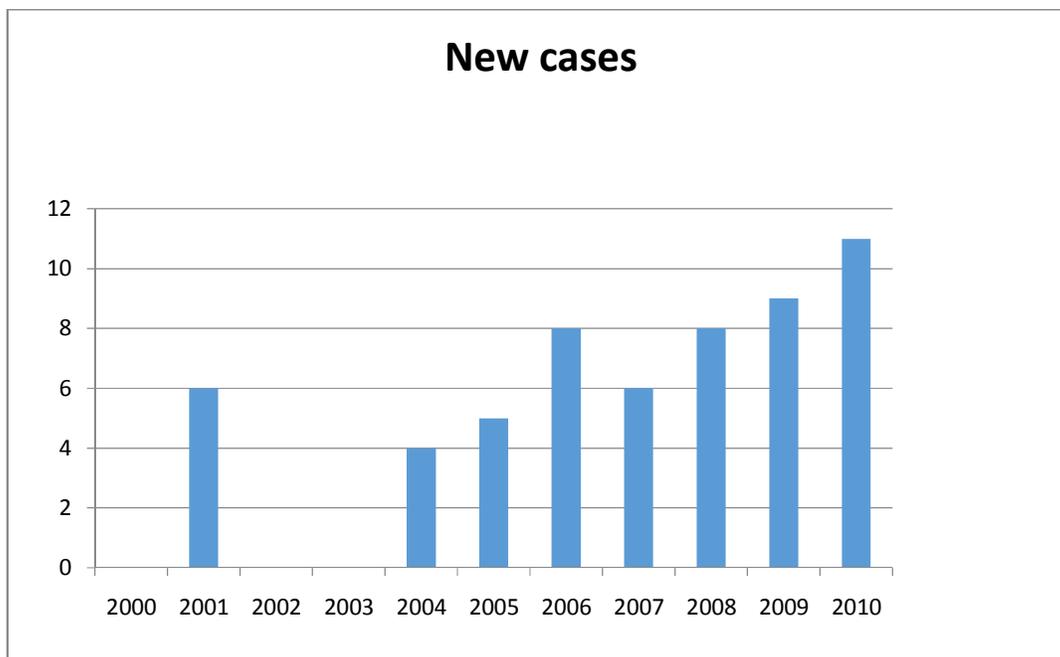


Fig. 1. New thyroid cancer cases in Misurata Cancer Registry over the 10-year period 2000-2010

Table 1. Distribution of thyroid tumors in Misurata health facilities during (2000-2012)

Type of tumor	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
PTC	0	4	0	0	3	5	7	4	8	7	9	0	3
FTC	0	1	0	0	1	0	1	0	0	1	2	1	1
UDC	0	1	0	0	0	0	0	1	0	1	0	0	1
MTC	0	0	0	0	0	0	0	1	0	0	0	1	0
Total malignant	0	6	0	0	4	5	8	6	8	9	11	2	5

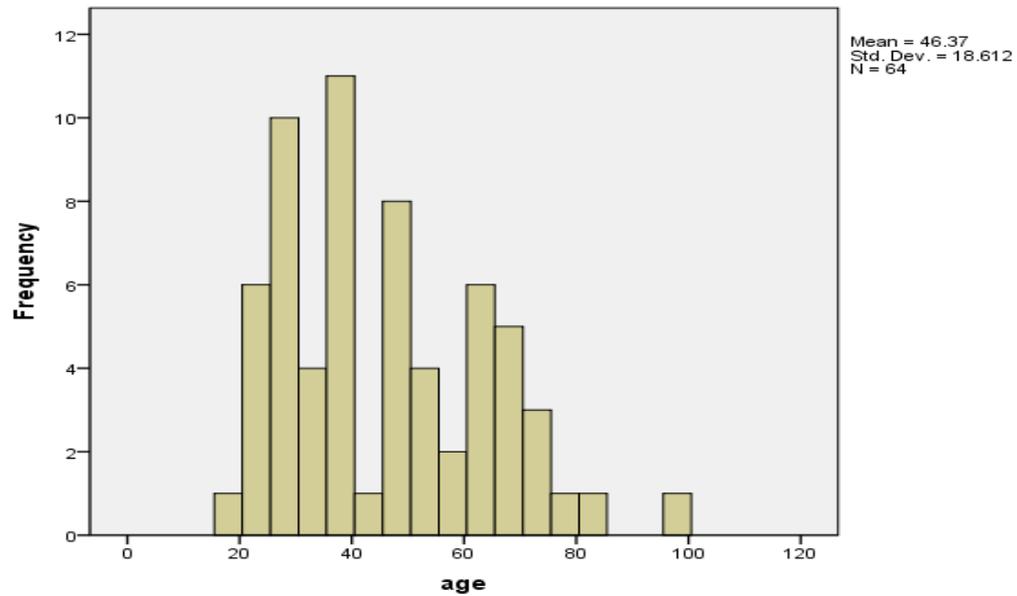


Fig. 2. Age distribution at diagnosis of histologically verified thyroid cancer patients in Western Libya (Misurata region) in 2000-2012. The graph is based on 64 patients

Table 2. Pathological type of thyroid carcinoma, along with their clinicopathological characteristics and their relative 5-year survival

Histological type	Frequency (%)	Mean age (year)	Mean size of tumor (cm)	Nodal involvement (%)	Systemic disease (%)	5 years survival (%)
Papillary carcinoma	78.1	45.3	3.2	23.1	18.0	96.0
Follicular carcinoma	12.5	46.8	3.3	25.0	25.0	80.0
Anaplastic carcinoma	6.3	53.0	6.3	100.0	100.0	25.0
Medullary carcinoma	3.1	58.5	5.8	100.0	100.0	50.0

3.4 Married Status and Parity Roles

Although, the fraction of unmarried female patient is not uncommon in current study. As the fraction of unmarried women (between ages 34 and 40) was higher among Libyan female population than in North African population in general (23.8% and 15 to 21%, respectively) [17]. It was clearly that Libyan women had higher parity; about threefold in respect to the European female population who had a higher mean age of first pregnancy (25.6 years). Which might be an additional factor that has resulted in an increasing of parity in Libyan women and decrease the effect of estrogen hormone. The decrease in estrogen role could be responsible for the low incidence of thyroid cancer in Libyan patients.

3.5 Gender

In Libya, nearly 78.1% of thyroid cancer patients were women, which left 21.9% for men patients

(Fig. 3). It is well known that the female gender has thyroid carcinoma incidence about 4times greater than in the male. In Europe and United States thyroid cancer, the men accounts 28% of all thyroid cancers [15]. In Jordan thyroid cancers is ranked 4th in females. It is one of the few tumors which is by far more frequent in females than males, affect (4.7%) of all female cancer and (1.6%) of all male cancer with ratio nearly 3:1 [18]. In Korean the thyroid cancer was the most common cancer in middle-aged females [9]. Several epidemiological studies have examined several reproductive traits, but the cause of this increased prevalence of thyroid cancer in women is unclear [19]. However, in some African countries, the thyroid cancer incidence in male is more predominant than in female. The latter is true especially in Sudan where the incidence in Sudanese male and female population was 1.8 and 0.4 per 100,000, respectively [12]. Male thyroid cancer patients usually have higher age than female patients do.

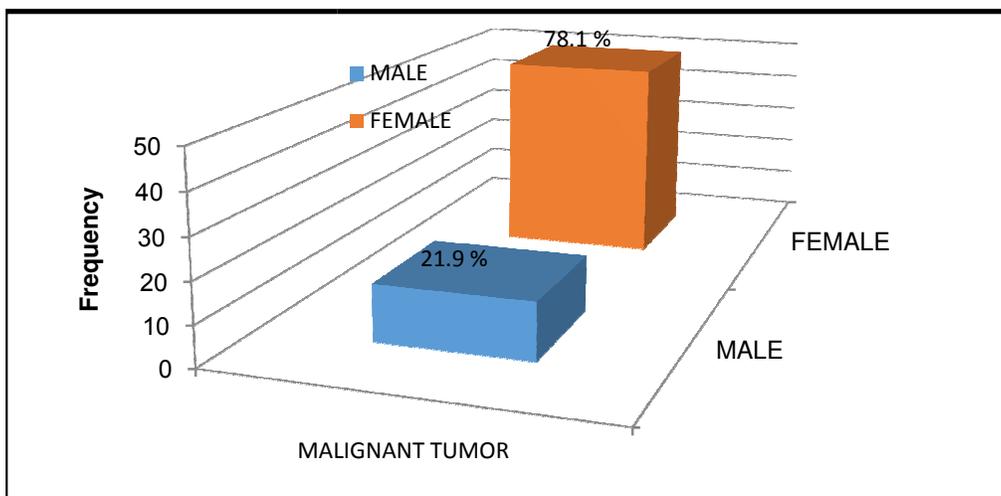


Fig. 3. Shows gender distribution with malignant tumors

3.6 Tumor Size

The mean size of all histological types of thyroid cancer was 3.5 cm for both female and male Libyan patients; only 13 patients (20.3%) had tumor size 2cm or less (T1). Libyan and North African data of tumor size are similar, but the data from developed countries suggests the efficiency of more sophisticated and advanced diagnostic facilities in detect smaller lesions in that population [20,21,22]. This suggests that the start of FNAC associated with advanced diagnostic facilities should be considered in Libya.

The mean tumor size of well-differentiated carcinoma (PC and FC) is mostly similar (about 3.2 cm), which when compared with other type of thyroid carcinomas, it was clearly that the average tumor size of well-differentiated carcinoma was smaller than the mean size of medullary and undifferentiated carcinomas (5.8 cm and 6.3 cm, respectively), (Table 2). Which suggests the aggressiveness of those type of tumors.

3.7 Lymph Node Status and Distant Metastases

One third of Libyan thyroid cancer patients had regional lymph node involvement at the time of surgery (Table 2), of them all cases of MC and AC (9.4%). Distant metastases (to multi-organ including bone, lung and liver) were present in 16.1% of our patients. In current study, systemic and regional lymph nodes metastases were significantly more common in AC and MC than in PC and FC (Table 2).

The significant increasing of systemic and regional lymph nodes metastases in Libyan patients may suggest a delay in diagnosis in developing countries, and lack or inefficacy of advanced diagnostic facilities. However, the aggressiveness of biological features in African thyroid cancer should also be considered.

3.8 Histological Type

The histological type's distribution in Libya are shown in (Table 2) with relation to clinco-pathological features. The frequencies for each of histological types of thyroid cancer were found in the present study is in line with other studies. Papillary and follicular thyroid carcinomas are the most common thyroid

cancers in most regions worldwide. In the current study, papillary carcinoma was the predominant type (78%) among both men and women, compared with (70-80%) in the other countries. FC and AC form 12.5% and 6% respectively. These figures in line with international fraction range which are (15-25%) for FC and (4-10%) for AC. Medullary carcinoma is more common in Europe (5-8%) than in our populations (3%) which might be related to genetic factor differences. [23,24,25].

3.9 Stage

The staging system currently in use for thyroid cancer is based on the age of patient, size of primary tumor, degree of spread to lymph nodes and presence of systemic metastasis. The Libyan thyroid cancer staging in our study is based on the TNM classification of 2006 [26]. Many of Libyan patients were seen in stage 3 and 4. Anaplastic and medullary carcinomas patients had advanced stage than differentiated papillary and follicular carcinomas patients (Table 2). The large fraction of patients in advanced stages may reflect delayed presentation and late diagnosis, which was also obvious in the study of Ermiah et al. [27]. On other hand, FNAC guided by high quality radiological facilities has been quit not practiced in Libya. However, FNAC obviously has not been able to improve the early diagnosis of follicular carcinoma. The reason is not possible of cytological detection of follicular carcinoma [28].

3.10 Survival analysis

By the end of follow-up, 12 patients were known to have died, Mean survival for the whole series of 64 patients was 23 months (range 1 - 166 months).

3.11 Clinco-pathological Features

The Libyan and other North African thyroid cancer patients have little worse prognosis than that recognized by studies in European patients. However, in respect to progressive pathological indicators, the North African thyroid cancer behaves as the European thyroid cancer as shown by current study (Figs. 4, 5). For example, patient have systemic involvement, LN involvement, and tumor size larger than 4cms were strongly associated with shortened survival rate (Kaplan-Meier and log rank ($p < 0.0001$, 0.008, and 0.01 respectively)). On other hand, early clinical stage associated with better survival

rate but with only marginal significance (Kaplan-Meier and log rank ($p = 0.04$). The cut-point of tumor size at 4cm was the most significant cut-point (Log Rank test, $p = 0.01$). This online with that other studies which showed, that patients

have larger size tumors (4.0+ cm), lymph node involvement and distant stage tumors were associated with local recurrence, and poorer survival among both men and women [25,29], (Fig. 4).

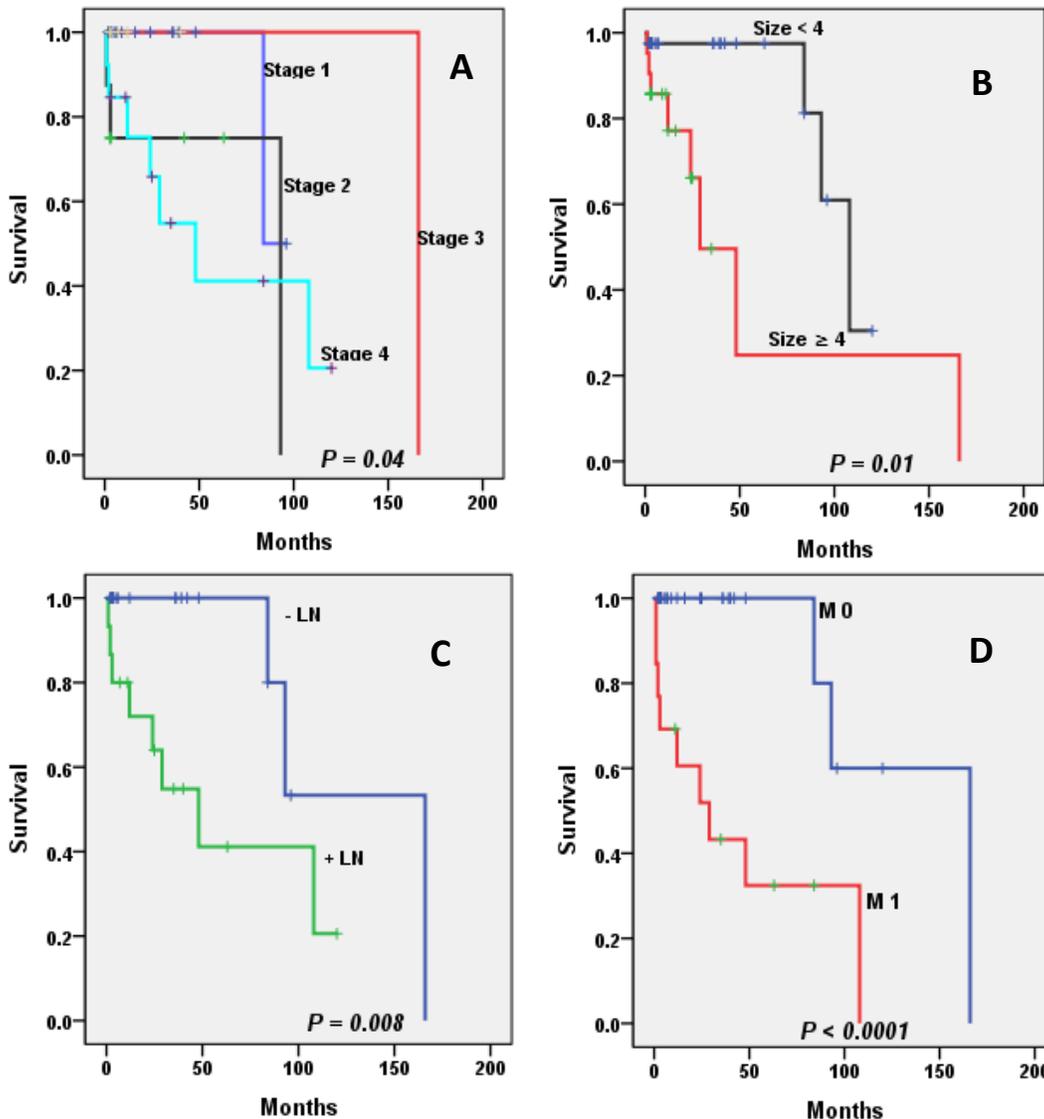


Fig. 4. A. Survival curves of Libyan thyroid cancer patients in different clinical stages: The group of patients with stage 1 had the best 5-year survival ($p < 0.0001$). B. Survival curves associated with tumor size: The group of patients with size cut-point less than 4cm had the best survival ($p = 0.001$). C. Survival curves and lymph node involvement: The group of patients without involvement had better 5-year survival than the group with nodal involvement ($p = 0.008$). D. Survival curves and systemic metastasis: The group of patients without metastasis had better 5-year survival than the group with systemic metastasis LN status ($p < 0.0001$)

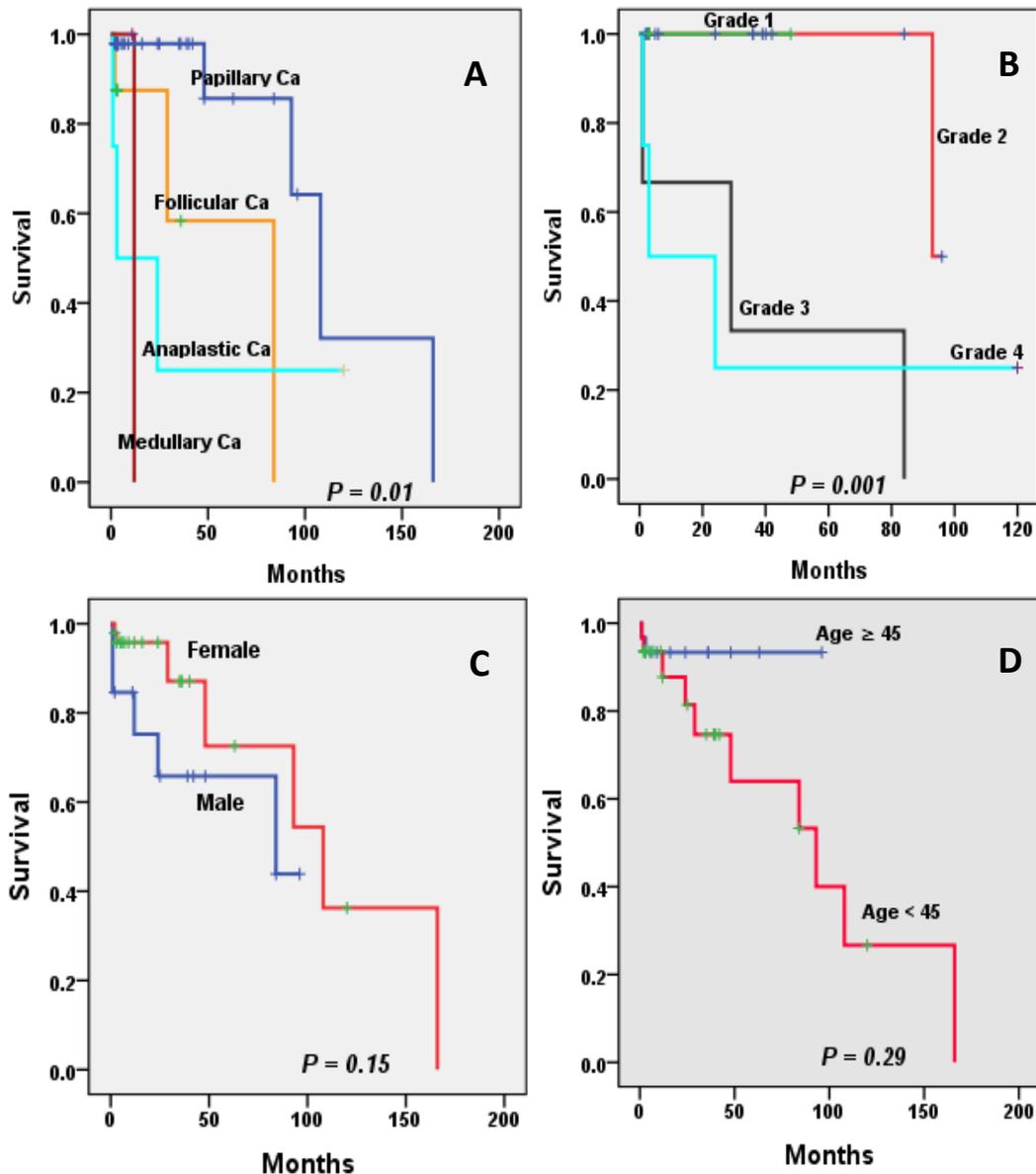


Fig. 5. A. Overall survivals of patients according to the histopathological type of thyroid carcinoma, patients with papillary type have better survival than other type ($p = 0.01$). **B.** Survival and histological grade. Low-grade patients have better survival than higher grade ($p = 0.001$). **C, D.** Survival curves associated with patients' age and sex are not show any significant

The patients with papillary carcinoma and lower grade tumors have better survival rate than the patients with other carcinomas and higher grade ($p = 0.01$ and 0.001 respectively) (Fig. 5. A, B).

Several authors provide that WDTC particularly papillary thyroid carcinoma is the most common thyroid malignancy that can be treated by total

thyroidectomy, and usually associated with an excellent prognosis with overall survival more than 90 % from cases [30,31].

On other hand, among Libyan patients the gender and age of patient did not seem to influence survival (Fig. 5. C, D). However, several studies have shown that the overall

survival of young adult's female with differentiated thyroid carcinoma is excellent [32]. In Netherlands Overall, 5-year survival was relative better for females than in males [33]. This is also true in Korea the cancer survival is better in females than in males. This is might be partially explained by that the thyroid cancers in these countries more common in females than in our population [9].

4. CONCLUSION

Prevalence of malignant thyroid tumor in Libyan general population during (2000-2010) is relatively high (12.4/ 100,000). On other hand, the last 10 years thyroid cancer incidence have been increased in Libya like in other North African countries, however, it is lower than that stated for Europe population; this difference might be due to the known variation in the distribution of genetic markers in these populations. Different environmental influences, however, cannot be excluded. Like most countries, Libyan thyroid carcinoma is affect women more than men are. Libyan thyroid cancer is dominantly seen in young age and displays unfavorable features such as high histological grade and stage, large size and frequent lymph node and systemic metastases.

The histological predominant types were also similar in Libyan, other North African and European thyroid carcinomas. The papillary carcinoma was the most common type of thyroid cancer followed by follicular carcinoma then undifferentiated carcinoma. However, medullary carcinoma is lower frequency in Libyan patients than in European patients.

Finally, in our hospital setting, the results of this study could be used as a baseline data for further research studies. Furthermore, to increase the health education and raising awareness about cancers which may lead to early detection and treatment.

CONSENT

The proposed study has been examined and approved by the Research Council of Misurata Cancer Center and informed consent was obtained from the patients for publication of this research.

ETHICAL APPROVAL

All authors hereby declare that all research processing in this study have been examined and approved by the ethics committee of Research Council of Misurata Cancer Center and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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