

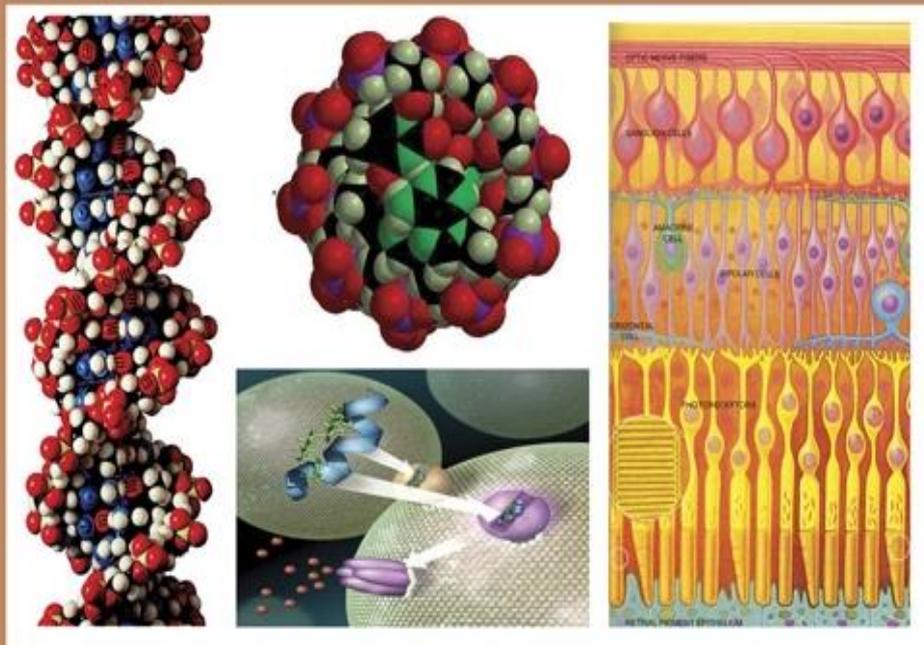


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## Epidemiology, Clinic-histopathological features and Surgical treatment of Papillary Thyroid Cancer: A Retrospective Descriptive Study in Northwestern Algeria

Elcherifa Sasaa<sup>1,2\*</sup>, Khadidja Haoud<sup>1,2</sup>, Amine Elmokhtar Drici<sup>1,2</sup>, Abderrahim Hadjadj<sup>3</sup>, Yasmina Cherifi<sup>1,2</sup>, and Boumediene El-Habachi<sup>4</sup>

1-Department of Biology, Faculty of Life and Natural Sciences, Djillali Liabes University, Sidi-Bel-Abbes, Algeria.

2-Laboratory of Molecular Microbiology, Proteomics and Health, Algeria.

3-Department of nuclear medicine, Anti-Cancer Centre, Sidi-Bel-Abbes, Algeria.

4-Department of General Surgery, University Hospital Center, Sidi-Bel-Abbes, Algeria.

\*E-mail: [cherifalsa6@gmail.com](mailto:cherifalsa6@gmail.com)

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### ABSTRACT

**Background and objectives:** The incidence rates of papillary thyroid cancer have increased over the past three decades. We aim to establish an epidemiological profile of papillary thyroid cancer, collect additional data about clinical and etiological features, and highlight how the disease is managed in Northwestern Algeria. **Patients and Methods:** An epidemiological retrospective descriptive study was conducted at the nuclear medicine department of the Anti-Cancer Center in Sidi Bel Abbes region (western Algeria), between January 2020 and December 2022, using a database of 103 papillary thyroid cancer patients. In order to analyze the medical records data, SPSS 22.0 was used. **Results:** The majority of patients were women (92.2%, mean age  $44.16 \pm 12.78$  years). 43.7% of the studied population had a previous history of thyroid diseases, and 20.4% of them have a family history of thyroid disorders. The majority of patients (91.3%) underwent a total thyroidectomy. Only 17.5% of patients underwent a lymph node dissection. Most patients (73.8%) were diagnosed with the lowest risk of thyroid carcinomas. The number of cancers associated with capsular refraction was low, and none of the patients had any signs of vascular invasion or recurrence. **Conclusion:** These results provide important information about the epidemiology of papillary thyroid cancer in Northwestern Algeria and can help to identify risk factors and the etiology of the disease. This information can be used to improve the management of patients with papillary thyroid carcinoma and to develop strategies for early detection and prevention of the disease.

### INTRODUCTION

Thyroid cancer (TC), a relatively rare cancer affecting the endocrine system, is the most common form of cancer affecting the endocrine system. It is usually manifested as a thyroid nodule (Curado *et al.*, 2007). There has been an increase in TC incidence over the past decades in all countries, including those in which women have substantially higher incidence rates than men (10.1 per 100,000) (Pizzato *et al.*, 2022). In Algeria, according to the International Agency for Research on Cancer 2018, TC was the third most common cancer among women and the eighth most common cancer among men.

TC incidence was 8.1 per 100,000 for women and 1.9 per 100,000 for men, with regional differences (6.2 per 100,000 to 9.1 per 100,000 for women and 1.4 per 100,000 to 2.1 per 100,000 for men) (Bray *et al.*, 2018). There are several risk factors associated with TC, including a history of cervical irradiation as a child (Sarnecki & Schneider, 1996), as well as family and/or personal history of thyroid diseases, hormonal factors, iodine intake, and other dietary factors (Dal Maso *et al.*, 2009; Nikiforov & Fagin, 1997).

Concerning the genetics of TC, seven types of mutations represent the vast majority of somatic mutations currently known, which have the greatest impact on the diagnosis and prognosis of TC, and they are involved in the etiology of the disease: point mutations of BRAF, RAS, rearrangements of RET/PTC and PAX8/PPAR $\gamma$ . Medullary thyroid carcinomas can be classified into familial and sporadic forms based on constitutional mutations of RET gene. BRAF V600E activating mutation is the most frequent and specific oncogenic event in papillary thyroid carcinoma (Vu-Phan & Koenig, 2014).

Differentiated thyroid carcinomas (DTC) are diagnosed in approximately 80% to 90% of cases. The majority of these patients are afflicted with papillary thyroid carcinomas (PTC), 4.5% with follicular thyroid carcinomas, and 1.8% with Hurthle cell tumors. 1.6% of the cases are of medullary thyroid carcinomas, while 0.8% are of anaplastic thyroid carcinomas (Krajewska *et al.*, 2020).

In the study of (Rajjoub *et al.*, 2018), PTC was identified as the most common type of DTC. In spite of its high prevalence, TC, and specifically PTC, are uncommon causes of death. PTCs are usually indolent, which makes them suitable for less invasive treatment modalities with excellent oncologic outcomes. According to (Nixon *et al.*, 2012), PTC is classified as "low-risk" based on their size, location, and nodal status.

Since TC diagnostic equipment (ultrasound and cytopuncture) has improved over the past thirty years, there is also evidence against overtreatment. Advanced imaging technology and the risk of over-detection of disease are important to understand (Miranda-Filho *et al.*, 2021). We aim to provide data on PTC incidence based on its demographic profile, to demonstrate surgical approaches, and to determine clinical and histopathological characteristics as well as the etiology of PTC in Northwestern Algerians.

## MATERIALS AND METHODS

### Study Population:

We conducted a retrospective descriptive study of 103 patients with papillary thyroid disease who underwent surgery between January 2020 and December 2022 in various general surgery departments in the western region of Algeria.

### Data Collection:

The data on clinically diagnosed PTC patients was extracted from medical records and pathology reports of patients at the level of the nuclear medicine department of the cancer center of Sidi Bel Abbes region (western Algeria). Among the data included in the study are demographic information such as gender, age, marital status, parity, origin, and medical histories of thyroid disorders, as well as circumstances surrounding the discovery of the disease; surgery treatment: partial thyroidectomy (PT) or total thyroidectomy (TT), with or without lymph node dissection; clinic-histopathological features that include tumor localization, TNM, capsular retraction, vascular invasion, and recurrence.

### Statistical Analysis:

All data were analyzed using SPSS 22.0 software (Statistical Package for the Social Sciences, IBM Corporation; Chicago, IL. August 2013). The frequencies and percentages of categorical variables were reported, even as the means and standard deviations (SD) of continuous variables.

## RESULTS

A total of 103 patients with PTC

were studied (Ninety-five women [92.2%], aged 48–52; 8 men [7.8%], aged 38–42). Their ages ranged from 23 to 80 years old (mean age of  $40.50 \pm 13.58$  years). The mean age at TC diagnosis was  $44.16 \pm 12.78$  years for women and  $41.36 \pm 19.17$  years for men. The study population was 82.5% married (79 women [92.9%]) and 16.5% single (15 women [88.2%]). There is a large proportion of patients from Mascara (42.7%), followed by Sidi Bel Abbes (31.1%), SAIDA (15.5%), TIARET (6.8%),

and other western regions (3.9%) (Table 1). The study found that 20.4% of patients had hypertension, 10.7% had diabetes, and 43.7% already had thyroid disease. Furthermore, 20.4% of all cases were accompanied by a family history of thyroid disease. In 58.2% of patients, the disease history began with a feeling of cervical swelling; 19.4% experienced dysthyroidism as an incidental result of another health consultation (13.6%); dysphagia (4.9%) and dysphonia (3.9%) (Table 2).

**Table 1:** Demographic and epidemiological characteristic of 103 PTC patients

Variables	Number (%) or Mean $\pm$ SD
<b>Demographic data</b>	
<b>Gender</b>	
Female	95 (92.2)
Male	8 (7.8)
Age of patients	40.50 $\pm$ 13.58
Age of women	44.16 $\pm$ 12.78
Age of men	41.36 $\pm$ 19.17
<b>Age group at diagnosis, years</b>	
23-33	25 (24.3)
34-44	30 (29.1)
45-55	26 (25.2)
56-66	17 (16.5)
> 66	5 (4.9)
Total	103 (100)
<b>Age group for women, years</b>	
23-27	10 (10.5)
28-32	10 (10.5)
33-37	15 (15.8)
38-42	13 (13.7)
43-47	7 (7.4)
48-52	16 (16.8)
53-57	7 (7.4)
58-62	6 (6.3)
63-67	8 (8.4)
68-72	3 (3.2)
Total	95 (100)
<b>Age group for men, years</b>	
23-27	2 (25)
28-32	1 (12.5)
33-37	1 (12.5)
38-42	2 (25)
58-62	1(12.5)
78-82	1 (12.5)
Total	8 (100)
<b>Marital status</b>	
<b>Married</b>	85 (82.5)
Women	79 (92.9)
Men	6 (7.1)
<b>Divorced</b>	01 (1)
<b>Single</b>	17 (16.5)
Women	15 (88.2)
Men	2 (11.8)
<b>Parity</b>	79 (92.9)
Nulliparous	2 (2.5)
Parous	77 (97.5)
1-2	23 (29.8)
$\geq 3$	54 (70.2)
<b>Origin</b>	
MASCARA	44 (42.7)
SIDI BEL ABBES	32 (31.1)
SAIDA	16 (15.5)
TIARET	7(6.8)
Other wilayahs	4(3.9)

**Table 2:** Medical history of 103 PTC patients

Variables	Number (%)
<b>Personal medical history</b>	
Hypertension	21 (20.4)
Diabetes	11 (10.7)
<b>Thyroid diseases</b>	45 (43.7)
Goiter	29 (64.4)
Other diseases	16 (35.6)
<b>Family history of thyroid disorders</b>	
Yes	21 (20.4)
No	82 (79.6)
Total	103 (100)
<b>Circumstances of the discovery of disease</b>	
Cervical swelling	60 (58.2)
Dysthyroidism	20 (19.4)
Incidentally	14 (13.6)
Dysphagia	5 (4.9)
Dysphonia	4 (3.9)

A total of 103 eligible patients were included in this study, 94 of whom underwent TT (87 women and 7 men), and 9 of whom underwent PT (8 women and 1 man), with lymph nodes dissected in 17.5 percent of the cases (Table 3).

The right lobe was most affected by the disease in the current study, followed by the left lobe, with a rate of 41.8% and 40.8% respectively. In 5.8% of cases the disease affected both lobes, while in 3.9% of cases, the disease affected the isthmus and in 2.9%

of cases, it affected the right lobo-isthmic region. In 4.8% of cases, the surgical specimen was not oriented. The primary tumor size in our study was T1 (tumor measuring  $\leq 2$  cm) at 73.8%, followed by T2 (tumor measuring  $>2$  but  $<4$  cm) at 26.2% based on the TNM classification. The lymph nodes of 85.4% of cases were not examined, while 14.6% of cases had no evidence of regional lymph node metastasis 8.7% of patients had capsular refraction (Table 4).

**Table 3:** Surgical treatment of 103 PTC patients, with or without lymph node dissection

Extent of surgery	Number (%)
<b>TT</b>	94 (91.3)
<b>PT</b>	09 (8.7)
Total	103 (100)
<b>Lymph node dissection</b>	
Yes	18 (17.5)
No	85 (82.5)
Total	103 (100)

TT: Total Thyroidectomy; PT: Partial Thyroidectomy.

**Table 4:** Clinic-histopathological features of 103 PTC patients

Variables	Number (%)
<b>Tumor localization</b>	
Right lobe	43 (41.8)
Left lobe	42 (40.8)
Both lobes	6 (5.8)
Isthmus	4 (3.9)
right lobo-isthmic	3 (2.9)
Surgical specimen was not oriented	5 (4.8)
Total	103 (100)
<b>Tumor size</b>	
T1	76 (73.8)
T2	27 (26.2)
Total	103 (100)
<b>Lymph node</b>	
Nx	88 (85.4)
N0	15 (14.6)
Total	103 (100)
<b>Recurrence</b>	0 (0)
<b>Capsular refraction</b>	9 (8.7)
<b>Vascular invasion</b>	0 (0)

## DISCUSSION

In the current study, the dominant gender is female (92.2%) compared with male (7.8%), a finding consistent with the literature (LeClair *et al.*, 2021). The average age of the patients was  $40.50 \pm 13.58$  years with an extreme of 23-80 years (mean age at PTC diagnosis was  $44.16 \pm 12.78$  years for women and  $41.36 \pm 19.17$  years for men). The most affected age was between 48-52 years in the female gender and 38-42 in the male gender. In contrast to previous studies, men's TC diagnosis is often very young compared to women's (Bendouida *et al.*, 2015). Age plays an important role in the risk stratification of TC (Datta *et al.*, 2006). It increases the incidence of clinically relevant thyroid nodules but decreases the likelihood that these nodules will be malignant. However, TC detected in older individuals may have a high-risk histological phenotype (Kwong *et al.*, 2015).

According to our study, 92.9% of women are married. Out of these married women, 70.2 percent have at least three children. There have been several studies suggest that productive factors, particularly pregnancy, are associated with TC risk (Galanti *et al.*, 1995; Horn-Ross *et al.*, 2011). Female sex hormones, especially

estrogen, may contribute to the gender disparity in TC incidence (Rahbari *et al.*, 2010). It is an effective stimulator of both benign and malignant thyroid nodules. The studies showed that estrogen receptors  $\alpha$  and  $\beta$  mediate Estradiol-induced proliferation of PTC and FTC cells (Kumar *et al.*, 2010; Manole *et al.*, 2001). However, some studies indicate a contrasting association between the use of contraceptives and the risk of TC, which may be due to the low concentrations of  $17\beta$ -estradiol (E2) of currently used contraceptives (Cornet, 2013; Kabat *et al.*, 2012; Sakoda & Horn-Ross, 2002).

The risk of TC did not appear to be associated with hormonal or reproductive factors such as the age of menarche or menopause, parity, or bilateral oophorectomy in a retrospective cohort study of 145 007 postmenopausal women. However, an increased risk of PTC was observed in women who gave birth to their first live child between the ages of 20 and 24 years of age (Kabat *et al.*, 2012). The variations in the incidence of TC may be attributed to iodine deficiency in certain regions of northwestern Algeria.

There was a high prevalence of endemic goiter in Algeria because of iodine deficiency (Hafdi-Nejjari *et al.*, 2018). It was first implemented in 1967 in areas with

a high prevalence of endemic goiter and then nationwide since 1990 (Guidoum *et al.*, 2015). The results of a population-based investigation in Algeria (1993-2013) by (Boukheris *et al.*, 2020b) suggest a shift from an iodine deficiency state to sufficient to excessive iodine supplementation.

The examination of the patient's medical history found that 43.7 % of the studied population had already thyroid diseases, of which goiter is a major disorder (64.4%). As well as, 20.4 % of all cases had a family history of thyroid disorders. The study confirmed previous findings that TC is more likely to occur in patients with a history of goiter or nodules or any benign thyroid alteration (Memon *et al.*, 2002; Schiffmann *et al.*, 2020). In contrast, TC occurs too rarely to warrant screening all patients with goiter or nodules (From *et al.*, 2000). The presence of first-degree relatives with PTC strongly predicts the risk of developing malignant thyroid disease, while a family history of TC increases the risk of its development. Alternatively, benign thyroid disorders in the family history are not associated with TC (Kust *et al.*, 2018).

Approximately 20.4% of the cases in the current study had hypertension. Antihypertensive agents and cancer development have been extensively examined with conflicting results. According to the most recent studies, patients who receive antihypertensive drugs do not experience an increased cancer risk (Milan *et al.*, 2014). According to a previous Algerian study, the risk of dying from cancer is low in most cases. However, cardiometabolic risk factors are prevalent (Kaouache, Merabet, *et al.*, 2022). In our cohort population, 10.7 % of patients were diabetics. According to the literature, diabetes increases the risk of DTC (Aschebrook-Kilfoy *et al.*, 2011; Oberman *et al.*, 2015). A recent Algerian study demonstrated that the mortality risk by TC is low. However, diabetes and prediabetes are prevalent (Kaouache, Zouraghen, *et al.*, 2022).

It has been suggested that the

association between diabetes and TC is due to insulin's role in thyroid carcinogenesis. The IGF-1 receptors on follicular cells are similar to insulin, which stimulates follicular cell growth. Furthermore, the IGF-1 receptor activates the mitogen-activated protein (MAP) kinase and the PI3k pathway, regulating genes, differentiation, mitosis, and apoptosis (Fröhlich & Wahl, 2012; Shih *et al.*, 2012).

Our patients also experienced cervical swelling in 58.2% of cases, which led to the discovery of the disease. Dysthyroidism in 19.4%, 13.6% fortuitously, during a consultation for another health issue, 4.9 % with dysphagia, and 3.9 % with dysphonia. The majority of PTC was diagnosed by self-neck checks, and most initially appeared as cervical swelling or thyroid nodules (Bendouida *et al.*, 2015; Boukheris *et al.*, 2020b). This is consistent with our results.

Our retrospective descriptive study comprising 103 patients found that the majority of patients undergo TT (94 TT for 9 PT), with lymph node dissection in 17.5 % of them. TT and PT are the main surgical approaches to DTC with a low to intermediate recurrence risk (Chen *et al.*, 2022). Studies published in 2005 and thereafter found no difference in survival among patients with DTC undergoing TT or PT (Hafdi-Nejjari *et al.*, 2018; Haigh *et al.*, 2005; Song *et al.*, 2019). The American Thyroid Association revised its 2015 guidelines in order to approve lobectomy as the primary treatment option for DTC of 1 to 4 cm in diameter with low-to-intermediate risk (Haugen *et al.*, 2016). On the other hand, several studies suggest that TT is associated with a lower recurrence and mortality rate, possibly as a result of a complete nodal dissection at the time of initial surgery (Macedo & Mittal, 2015).

To confirm an event-free outcome in a minority of cases, lobectomy must be combined with additional treatments and a longer follow-up period. However, TT is recommended for intermediate-risk micro- and macro-DTCs despite the greater

likelihood of post-operative complications (Colombo *et al.*, 2022). According to a recent study (Chen *et al.*, 2022), the extent of surgery does not affect the health-related quality of life (HRQOL) of patients at low or intermediate risk of DTC. A number of studies have shown that active surveillance can be an effective alternative to surgery for the treatment of low-risk PTC without increased risk of recurrence or death in order to avoid surgical risks and thyroid replacement therapy (Lohia *et al.*, 2020; Saravana-Bawan *et al.*, 2020).

The role of prophylactic central neck dissection, particularly in elderly patients, has been contradicted in recent studies. There was no difference between TT and TT associated with prophylactic central cervical dissection in terms of recurrence rates, and there was an increase in postoperative morbidity for lymphadenectomy patients and those over 75 years of age (Baud *et al.*, 2022; Gambardella *et al.*, 2019). A thorough understanding of the complications associated with lymph node dissection during thyroid surgery can assist surgeons in selecting the optimal surgical approach (Baud *et al.*, 2022).

As part of our survey, 103 patients who underwent surgery for PTC were surveyed. In 41.8 percent of cases, malignant nodules were found in the right lobe, 40.8 percent in the left lobe, 5.8 percent in the bilateral lobe, and 3.9 percent in the isthmus, 2.9 percent in right Lobo-isthmus, while in 4.8 percent surgical specimen was not oriented. Several studies have indicated that the right lobe contains an increased number of cells that may contribute to a greater risk of tumor development (Gessl *et al.*, 2010). Our findings were in contrast to that of (Bendouida *et al.*, 2016), in which the majority of patients had malignant nodules located in the left lobe. According to recent studies (Jasim *et al.*, 2021), TC risk is independent of nodule location. Nevertheless, nodule localization is associated with a distinct risk of

malignancy, with isthmus and upper lobar nodules being at the greatest risk (Jasim *et al.*, 2020; Pastorello *et al.*, 2020; Ramundo *et al.*, 2019; Zhang *et al.*, 2019).

Based on the 8th AJCC classification, T1 (tumors  $\leq 2$  cm) represented 73.8% of tumors measured in our study, and T2 (tumors measuring  $>2$  but  $<4$  cm) represented 26.2%. These data are similar to those reported by (Kaouache *et al.*, 2021).

A total of 85.4% of cases did not have regional lymph nodes assessed, while 14.6% did not have any evidence of metastasis to regional lymph nodes. In this study, 9 patients experienced capsular effraction. No vascular invasion or recurrence was observed. These results are consistent with the findings of (Boukheris *et al.*, 2020a) which demonstrated that over time, the frequency of TC with capsular effractions and angioinvasions decreased. The studies indicated that vascular invasion is not a common event in small DTC. However, vascular invasion has a significant influence on tumor recurrence and patient survival in DTC patients. The extent and presence of vascular invasion should also be considered adverse prognosis factors in DTCs (Vuong *et al.*, 2017; Galanti *et al.*, 1995; Horn-Ross *et al.*, 2011).

## CONCLUSION

Our findings showed that most papillary thyroid cancer in our patients is low to intermediate risk and that TT when performed correctly and safely, is an excellent and effective way of PTC treatment. However, it is possible to improve the management of the PTC according to the recurrence, mortality rate, and age of patients, to avoid surgical risks and thyroid replacement therapy.

Further research into the biological and molecular characteristics of TC will enhance our understanding of risk factors and etiopathogenetic mechanisms. In the future, individualized medicine will also have a major impact on the management of thyroid malignancies.

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**Conflicts of Interest:** The authors have no conflicts of interest to declare.

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