

Papillary thyroid carcinoma and obesity: Impact of BMI on clinicopathological aggressiveness criteria

Carcinome papillaire de la thyroïde et obésité: Impact de l'IMC sur les critères clinicopathologiques d'agressivité

Jihène Houas¹, Monia Ghammam¹, Heyfa Belhadj-Miled¹, Sana Bhiri², Kermani Wassim¹, Mohamed Abdelkefi¹

1. ENT Department and Cervical Surgery Farhat Hached Hospital, University of Sousse, Tunisia

2. Prevention and Security of Care Department, Sahloul Hospital, University of Sousse, Tunisia

ABSTRACT

Background: The global incidence of papillary thyroid carcinoma (PTC) has risen significantly, with obesity emerging as a potential risk factor. This study aims to assess the association between obesity, overweight, and aggressive characteristics of PTC.

Methods: A retrospective study was conducted at our hospital, including patients operated for PTC between 2014 and 2024. Body mass index (BMI) was classified per WHO criteria: normal weight (BMI < 25 kg/m²), overweight (25–29.9 kg/m²), and obese (≥30 kg/m²). Clinical and histopathological characteristics were analyzed using SPSS v26.0. Statistical significance was set at $p < 0.05$.

Results: A total of 120 patients were treated for PTC over a 11-year period, including 95 women and 25 men. Of these, 41 patients had a normal BMI, 40 were overweight and 39 were classified as obese. The results of this study show that, although obesity was associated with variations in patient age ($p=0.004$) and sex ($p=0.009$), it did not have a statistically significant impact on tumor size ($p=0.117$), ETE ($p=0.736$), multifocality ($p=0.119$) or bilaterality ($p=0.754$). Furthermore, the presence of vascular invasion ($p=0.472$) or lymph node metastases ($p=0.700$) was not influenced by BMI. Finally, the rates of post-operative complications ($p=0.970$) and recurrence ($p=0.844$) were low and comparable between the different groups.

Conclusion: Obesity does not appear to significantly influence PTC aggressiveness in this cohort. While trends in multifocality warrant further investigation, larger prospective studies are needed to clarify the impact of BMI on PTC prognosis.

Keywords: obesity, body mass index, papillary thyroid carcinoma, prognosis

RÉSUMÉ

Introduction: L'incidence du carcinome papillaire de la thyroïde (CPT) est en augmentation, et l'obésité est suspectée comme un facteur de risque potentiel. Cette étude évalue l'association entre l'IMC et les critères d'agressivité du CPT.

Méthodes: Étude rétrospective incluant 120 patients opérés pour un CPT entre 2014 et 2024. Les patients ont été classés selon leur IMC en poids normal (<25 kg/m²), surpoids (25–29,9 kg/m²) et obésité (≥30 kg/m²). L'analyse statistique a été réalisée avec SPSS v26.0, avec un seuil de significativité de $p < 0,05$.

Résultats: L'échantillon comprenait 95 femmes et 25 hommes, répartis en 41 patients normopondéraux, 40 en surpoids et 39 obèses. L'obésité était associée à des variations d'âge ($p = 0,004$) et de sexe ($p = 0,009$) mais n'avait pas d'impact significatif sur la taille tumorale ($p = 0,117$), l'extension extrathyroïdienne ($p = 0,736$), la multifocalité ($p = 0,119$), la bilatéralité ($p = 0,754$), l'invasion vasculaire ($p = 0,472$) ou les métastases ganglionnaires ($p = 0,700$). Les taux de complications post-opératoires ($p = 0,970$) et de récurrence ($p = 0,844$) étaient comparables entre les groupes.

Conclusion: L'obésité ne semble pas influencer significativement l'agressivité du CPT dans cette cohorte. Des études prospectives à plus grande échelle sont nécessaires pour mieux préciser son impact pronostique.

Mots-clés: obésité, indice de masse corporelle, carcinome papillaire de la thyroïde, pronostic

Correspondance

Jihène Houas

ENT Department and Cervical Surgery Farhat Hached Hospital, University of Sousse, Tunisia

Email: jihene.houas@famso.u-sousse.tn

INTRODUCTION

Over the past three decades, the global incidence of thyroid cancer has increased by 87.5%, primarily attributed to the rise in papillary thyroid carcinoma (PTC) [1]. This trend is likely multifactorial, with improved detection due to greater access to healthcare, higher-quality ultrasonography, and increased utilization of fine-needle aspiration cytology (FNAC) [2,3]. Among contributing factors, radiation exposure is the most extensively studied, increasing the risk of thyroid cancer by 5% to 50% [4,5]. Other risk factors, such as estrogens, smoking, diabetes, obesity, metabolic syndrome, and insulin resistance, have also been identified [6]. Obesity, considered the second leading modifiable cause of cancer after smoking, plays a significant role in the development of thyroid cancer.

This retrospective study aims to examine the association between obesity, overweight, and aggressive characteristics of papillary thyroid carcinomas.

METHODS

A retrospective, descriptive, single-center study was conducted within the Department of Otolaryngology and Head and Neck Surgery at Farhat Hached University Hospital of Sousse, spanning an 11-year period (January 2014 to December 2024). The study included patients who underwent surgical intervention for papillary thyroid carcinoma (PTC), whether a total thyroidectomy or a thyroidectomy combined with lymph node dissection. Only patients with available weight and height data in their medical records were included, allowing for the calculation of body mass index (BMI). BMI was stratified according to World Health Organization (WHO) criteria into three categories: normal weight (BMI < 25 kg/m²), overweight (BMI between 25 and 29.9 kg/m²), and obese (BMI ≥ 30 kg/m²). A review of the histopathological slides was performed by a pathologist, in accordance with the 2022 WHO classification of endocrine tumors. Statistical analysis was performed using SPSS version 26.0 software. The study evaluated the association between BMI and clinical, histopathological variables, and markers of tumor aggressiveness, including tumor size, multifocality, extrathyroidal extension, lymph node involvement, postoperative complications, recurrence, and the presence of metastases. A statistical significance threshold of $p < 0.05$ was used for all statistical tests. The multivariate model was adjusted for age and sex. Initial tumor stage was not included due to missing data.

RESULTS

Our study population, consisting of patients surgically treated for papillary thyroid carcinoma at our department, comprised 120 cases. The distribution of patients according to the three predefined body mass index (BMI) groups was as follows: Group 1 (BMI < 25 kg/m²) included 41 patients (34.2%), Group 2 (25 kg/m² ≤ BMI < 29.9 kg/

m²) included 40 patients (33.3%), and Group 3 (BMI ≥ 30 kg/m²) consisted of 39 patients (32.5%) (Table 1).

The mean age of the study population was 46.7 years, with a statistically significant difference observed across BMI groups ($p = 0.004$). Participants in the obese group (BMI ≥ 30 kg/m²) were significantly older (mean age: 51.5 years) compared to those in the normal-weight group (BMI < 25 kg/m²; mean age: 40.4 years). A female predominance was noted overall (79.2%), which was more pronounced in the obese group (94.9%; $p = 0.009$). Tumor size trended smaller in the obese group (64.1% of tumors ≤ 2 cm vs. 39% in the normal-weight group), though this difference lacked statistical significance ($p = 0.117$). Classic papillary carcinoma was the predominant histological subtype (79.1%), with similar distribution among BMI categories. Multifocality was more frequent in overweight (47.5%) and obese (44.7%) groups compared to normal-weight individuals (26.8%), though this trend was non-significant ($p = 0.119$). Bilaterality rates were consistent across groups (mean 13.6%; $p = 0.754$). Extrathyroidal extension (ETE) was observed in 30.9% of cases, with a marginal increase in prevalence alongside higher BMI, but no significant differences were noted for microscopic ($p = 0.736$) or macroscopic ETE ($p = 0.462$). Vascular invasion was slightly elevated in the overweight group (12.8%; $p = 0.472$), while lymph node involvement (47.5% overall; $p = 0.700$) and distant metastases (4.9% normal-weight vs. 5.1% obese; $*p = 0.407$) showed no significant associations. Postoperative complications ($p = 0.970$) and recurrence rates ($p = 0.844$) were comparable across all BMI categories.

The multivariate analysis (Table 2), after adjusting for confounding variables, revealed that tumors larger than 2 cm were significantly more frequent in the normal BMI group ($p = 0.046$; OR = 2.178), suggesting an increased risk of such tumors in these patients compared to the overweight and obese groups. Specifically, patients with normal BMI had approximately 2.18 times higher odds of having a tumor larger than 2 cm compared to the combined overweight and obese groups. This indicates that obesity is not associated with increased tumor size in this study. Although the multivariate analysis suggested an association between normal BMI and reduced multifocality (OR = 0.428), the wide confidence interval [0.18–0.97] and lack of significance in the obese group ($p = 0.423$) warrant caution. These results may reflect residual confounding or unmeasured. Finally, no significant association was found between tumor bilaterality and obesity ($p = 0.803$), suggesting that obesity does not influence the likelihood of developing bilateral tumors in papillary thyroid carcinoma within this cohort.

Table 1. Univariate analysis of factors influencing the aggressiveness of papillary thyroid cancer according to weight

		Total (n=120)	Group 1 (n=41)	Group 2 (n=40)	Group 3 (n=39)	p value
Age		46.7±15.7	40.4±17.6	48.5±14.3	51.5±12.7	0.004
Gender	Female	95 (79.2%)	31 (75.6%)	27 (67.5%)	37 (94.9%)	0.009
	Male	25 (20.8%)	10 (24.4%)	13 (32.5%)	2 (5.1%)	
Tumor size	T ≤ 2cm	62 (51.7%)	16 (39%)	21 (52.5%)	25 (64.1%)	0.117
	T : 2-4 cm	38 (31.7%)	19 (46.3%)	11 (27.5%)	8 (20.5%)	
	T > 4cm	20 (16.7%)	6 (14.6%)	8 (20%)	6 (15.4%)	
Histological type						0.440
Multifocality		47 (39.5%)	11 (26.8%)	19 (47.5%)	17 (44.7%)	0.119
Bilaterality		16 (13.6%)	6 (14.6%)	6 (15.8%)	4 (10.3%)	0.754
ETE	Micro	23 (19.2%)	9 (22%)	8 (20%)	6 (15.4%)	0.736
	Macro	14 (11.7%)	3 (7.3%)	5 (12.5%)	6 (15.4%)	
Vascular invasion		11 (9.4%)	3 (7.3%)	5 (12.8%)	3 (7.9%)	0.472
N+	N1a	19 (15.8%)	5 (12.2%)	6 (15%)	8 (20.5%)	0.700
	N1b	37 (30.8%)	14 (34.1%)	13 (32.5%)	10 (25.6%)	
M1		4 (3.3%)	2 (4.9%)	0	2 (5.1%)	0.407
Complications		26 (21.8%)	9 (22.5%)	9 (22.5%)	8 (20.5%)	0.970
Recurrence		5 (4.3%)	1 (2.6%)	2 (5.3%)	2 (5.3%)	0.844

ETE : Extrathyroidal extension, **Micro**: microscopic, **Macro** : macroscopic, **N+** : lymph node involvement, **N1a** : central lymph node involvement , **N1b** : lateral lymph node involvement, **M1**: distant metastasis

Table 2. Multivariate analysis of factors influencing the aggressiveness of papillary thyroid cancer according to weight

	Group 1 (n=41)		Group 2 (n=40)		Group 3 (n=39)	
	p	OR [IC]	p	OR [IC]	p	OR [IC]
Tumor size >2	<u>0.046</u>	2.178 [1.008-4.706]	0.626	1.313 [0.439-3.924]	0.059	0.471 [0.214-1.034]
Multifocality	<u>0.040</u>	0.428 [0.188-0.973]	0.204	1.648 [0.761-3.570]	0.423	1.376 [0.629-3.010]
Bilaterality	0.803	1.149 [0.386-3.421]	0.897	0.951 [0.445-2.033]	0.462	0.638 [0.192-2.125]

DISCUSSION

The impact of obesity on the increased risk of cancer is widely studied in the scientific literature, especially in the context of global public health concerns related to rising BMI levels [9]. Obesity has been linked to an increased risk of aggressiveness in various types of carcinomas [10]. Chronic inflammation in adipose tissue, leading to genotoxic stress, may play a role in carcinogenesis and cancer initiation [11]. Obesity causes insulin resistance, which has been associated with thyroid cancer through insulin-like growth factor-1 (IGF-1) signaling, thyroid-stimulating hormone (TSH), inflammation, and oxidative stress [12]. Hyperinsulinemia reduces the synthesis of IGF binding proteins (IGFBP), increasing the free circulating IGF-1 concentration. Both insulin and IGF-1 have mitogenic effects and have been linked to various cancers. Increased IGF-1 levels in vitro lead to enhanced cell proliferation. In thyroid cancer cells, IGF receptors are overexpressed compared to normal thyroid cells [12]. Epidemiological studies have shown a relationship between obesity and the incidence of several cancers, including thyroid cancer [10,13]. A Norwegian study with 2 million participants demonstrated an increased risk of developing papillary thyroid carcinoma (PTC) with rising BMI in both men and women [14]. A meta-analysis of cohort studies revealed associations between obesity and higher thyroid cancer incidence in both genders

[15]. Another recent meta-analysis of five prospective studies concluded that BMI is independently and positively associated with the risk of thyroid cancer in both men and women [16]. However, in a retrospective study of 13,995 PTC cases, Li et al. found that obesity was significantly more prevalent in men than in women, with no statistically significant relationship with age [17]. In our study, although age and gender are not direct factors of tumor aggressiveness, they show a statistically significant difference related to the increase in BMI.

The literature does not fully address the relationship between tumor size and aggressiveness, which may explain why clinical diagnoses often overlap with incidental findings. In O'Neil's meta-analysis, tumor size was significantly larger in overweight patients compared to those with a normal BMI [10]. Li et al. also found that obesity increased tumor size (T) [17]. In the study by Tresallet et al., obese patients with papillary thyroid carcinoma larger than 10 mm had an increased risk of disease recurrence (OR = 3.8, 95% CI 1.6-8.8, P = 0.03) [18].

In contrast, our results from both univariate and multivariate analysis did not find any association between obesity and increased tumor size in this study. In O'Neil's meta-analysis, the rate of multifocality was higher in overweight and obese patients [10]. According to Choi et al., multifocality was a predictive factor for advanced stage regardless of BMI [19]. However, Tresallet et al. observed similar rates of multifocality across the three

BMI groups [18].

Multifocality was more common in groups 2 (47.5%) and 3 (44.7%), but without a statistically significant difference ($p = 0.119$). However, this trend is similar to the findings of O'Neil et al. These results may suggest a potential role of obesity in the multifocal proliferation of tumors, although this was not confirmed in our multivariate analysis.

Regarding bilaterality, no significant difference was observed when comparing overweight or obese groups to participants with a normal BMI in three studies from the literature [18,20,21], which aligns with the results of our cohort. In O'Neil's meta-analysis, eleven studies reported data on extrathyroidal extension, and the rate of extrathyroidal extension was higher in overweight patients [10].

In the study by Kim et al., extrathyroidal extension (ETE) was observed in 16.8% of patients with a BMI < 24.9, 22.8% of those with a BMI between 25 and 29.9, and 18.2% of patients with a BMI ≥ 30 ($p = 0.19$) [22]. According to Choi et al., in patients with PTC, BMI was associated with ETE [19]. Lastly, Tréssallet et al. found that obese patients had a higher rate of microscopic ETE, with a BMI < 30 (32% vs 23%, $p < 0.016$) [18]. Furthermore, numerous studies have linked BMI with an increased likelihood of minimal extrathyroidal extension, although the prognostic role of this characteristic has recently been questioned [19,21,23,24].

In our study, the presence of microscopic or macroscopic extrathyroidal extension showed no significant differences between groups, suggesting that obesity does not have a major impact on the local extension of the tumor, a conclusion that is largely consistent with the literature findings.

In the prospective study by Grani et al. involving 432 patients, no influence of BMI on vascular invasion was found [25]. In the recent meta-analysis by O'Neil, twelve studies (including those by Choi et al. and Yu Tsu et al.) reported data on regional lymph node involvement, involving 19,590 patients with normal BMI, 10,830 overweight patients, and 2,996 obese patients. The rate of regional lymph node involvement was higher in obese patients, but this was not significant in overweight patients [10,19,21]. According to Choi et al., lymph node metastasis rates showed no difference between groups of PTC patients based on BMI [19]. Zaman et al. observed higher frequencies of lymph node metastases in obese patients, though these differences were not statistically significant [26]. Lastly, Kim et al. reported that a higher BMI was associated with greater lymph node involvement ($p < 0.004$) in patients under 45 years of age [27].

Our results show that obesity is not significantly associated with lymph node involvement, which is consistent with several studies mentioned above. None of the studies included in O'Neil's meta-analysis found a statistically significant association between BMI and disease recurrence [10], which aligns with our findings.

Furthermore, Tréssallet et al. observed that obese patients with papillary thyroid tumors larger than 10 mm had an increased risk of disease recurrence [18]. Tréssallet reported a 2.8% rate of permanent recurrent laryngeal

nerve paralysis in obese patients compared to 0.7% in patients with normal BMI ($p = 0.01$) [18]. Jin also reported higher rates of postoperative hemorrhage, infection, and accessory nerve injury in obese patients who underwent total thyroidectomy with lateral cervical dissection [28]. In our study, the complication rate ($p = 0.970$) was not influenced by BMI, suggesting that obesity does not have a direct effect on postoperative events.

This study has several limitations, notably its relatively small sample size, which limits the statistical power to detect subtle associations. As a result, non-significant findings may reflect insufficient power rather than a true absence of effect. Additionally, the lack of adjustment for important confounders, such as initial tumor stage and dietary habits, may have influenced the results.

Future research should focus on elucidating the role of insulin resistance and IGF-1 signaling in the pathogenesis of thyroid cancer. Elevated IGF-1 levels and hyperinsulinemia are known to promote cellular proliferation and inhibit apoptosis, potentially contributing to increased tumor aggressiveness in obese individuals. Investigating serum IGF-1 concentrations and markers of insulin resistance—such as HOMA-IR—in PTC patients across different BMI categories may help clarify their mechanistic association with clinical outcomes. Moreover, examining the tissue-specific expression of insulin and IGF-1 receptors in thyroid tumors could uncover novel therapeutic targets. These strategies would expand on prior findings (and help address the current gaps in understanding the influence of metabolic dysregulation on PTC behavior [6,12]

In conclusion, the rising incidence of papillary thyroid carcinoma observed over recent decades underscores the need to identify and characterize the contributing risk factors, with obesity being of increasing interest. While obesity is a recognized modifiable risk factor for several cancers, our findings suggest a limited impact on PTC aggressiveness within the present cohort. Specifically, our analyses did not demonstrate a significant association between obesity and established markers of aggressiveness, including tumor size, multifocality (although a trend was observed), bilaterality, extrathyroidal extension (ETE), lymph node involvement, distant metastases, postoperative complications, or recurrence rates.

However, it is important to acknowledge certain limitations of this study, including its single-center design and relatively modest sample size, which may limit statistical power and the generalizability of the results. Furthermore, other potential confounding factors not accounted for in this analysis could influence the relationship between BMI and PTC prognosis. These factors could include, but are not limited to, dietary habits, physical activity levels, genetic predisposition, and specific molecular characteristics of the tumors.

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