THYROID CANCER IN SURGICALLY TREATED MULTINODULAR GOITER: INCIDENCE AND HISTOPATHOLOGICAL OUTCOMES

NCT NUMBER not available.

Date of document: 15/12/2023

ABSTRACT

INTRODUCTION

Thyroid cancer, the most common endocrine malignancy, has been extensively studied due to its rising global incidence and diverse clinical presentations. Among thyroid disorders, multinodular goiter (MNG) is frequently encountered in clinical practice, with a prevalence ranging from 0.4% to 7.2% in iodine-sufficient regions and affecting approximately 25– 33% of the population in iodine-deficient areas.

The association between MNG and thyroid cancer is well-documented, although reported incidence rates vary significantly among studies and populations, ranging from 5% to 35% in the literature

This study aims to investigate, based on existing knowledge, the incidence of occult thyroid carcinoma in a cohort of patients with MNG, providing new insights into the prevalence and characteristics of thyroid malignancies in MNG. It seeks to contribute to optimizing diagnostic evaluations for patients with multinodular goiter.

MATHERIALS AND METHODS

This retrospective study included patients with a preoperative diagnosis of multinodular goiter who underwent total or partial thyroidectomy from January 2018 to May 2024 at the Department of Medical and Surgical Sciences at the University Hospital “Ospedali Riuniti” in Foggia. The study's objective was to investigate the incidence of thyroid carcinoma in patients undergoing thyroidectomy for MNG, also analyzing associated demographic and clinical variables.

RESULTS

Out of the 223 patients, 32 cases of thyroid carcinoma were diagnosed, corresponding to an incidence rate of 14.4% . Among these, 24 were female (75%) and 8 were male (25%), with a female-to-male

ratio of 3:1. Thyroid carcinoma was identified in 13.3% of all females and 19% of all males. Although a difference in incidence between the sexes was observed, it was not statistically significant (chi=0.929; p=0.335).

Papillary thyroid carcinoma (PTC) was the most common type, identified in 25 cases (78.1%).
The mean age of patients with thyroid carcinoma was 49.4 years (SD 16.7), with an age range of 22 to 72 years. A significant difference was observed between this group and the mean age of patients without carcinoma (mean: 56.2 years, SD 13.1). Statistical analysis indicated a significant difference between the two groups in terms of age (t=-2.686; p=0.008). Additionally, evaluating the correlation between age and malignancy revealed that for each additional year of age, the probability of carcinoma decreased by 3.7% (OR=0.963; p=0.009).

CONCLUSION

The results of this study highlight a significant incidence of thyroid carcinoma in patients with multinodular goiter. The predominant histotype was papillary carcinoma, with no observed sex-based differences in incidence. The identified risk factors, such as age and thyroid weight, while potentially useful for stratifying risk in patients with multinodular goiter, are insufficient—due to study limitations and the significant variability among populations from different regions—to justify modifications to existing thyroid nodule screening criteria.

Keywords: multinodular goiter; incidental thyroid cancer; total thyroidectomy; endocrine surgery

Introduction

Thyroid cancer, the most common endocrine malignancy, has been extensively studied due to its rising global incidence and diverse clinical presentations. Among thyroid disorders, multinodular goiter (MNG) is frequently encountered in clinical practice, with a prevalence ranging from 0.4% to 7.2% in iodine-sufficient regions and affecting approximately 25– 33% of the population in iodine-deficient areas. [1] It is characterized by an enlarged thyroid gland containing multiple nodules. The pathogenesis of MNG involves various genetic, environmental, and dietary factors leading to the development of multiple thyroid nodules.

The association between MNG and thyroid cancer is well-documented, although reported incidence rates vary significantly among studies and populations, ranging from 5% to 35% in the literature [2]. Bove et al. reported an overall incidence of 8.9% in 2023, including 6.1% microcarcinoma cases and 2.8% thyroid carcinoma cases [3]. In 2021, a study involving 3,233 patients found thyroid carcinoma in 1,026 of them, corresponding to an incidence of 31.7% [4-5]. Another study conducted in Southern Italy, focusing on a genetically homogeneous population in Calabria with mild to moderate iodine deficiency, reported an overall prevalence rate of incidental thyroid carcinoma of 12.5% [6].

These differences may partially stem from genetic variability among populations and sociocultural factors, particularly diet. However, the relationship between iodine intake and thyroid cancer remains controversial. After iodine intake increased due to salt iodization and iodine supplementation, the incidence of thyroid cancer, particularly papillary thyroid carcinoma (PTC), rose despite a decrease in follicular thyroid carcinoma (FTC) incidence. Conversely, some meta-analyses on the association between iodine intake and thyroid cancer have found that higher iodine intake correlates with a lower risk of thyroid cancer [7]. Other studies indicate an association between excessive body fat, obesity, and overweight status with thyroid neoplasia [8; 9]. These findings highlight the intricate relationship between diet and thyroid pathology, emphasizing the need for optimal dietary strategies.

Although most nodules in MNG are benign, the presence of multiple nodules complicates the identification of potentially malignant ones. It has long been believed that the risk of cancer in MNG is much lower than in solitary nodules. However, recent literature indicates that if a nodule in MNG

grows consistently, becomes markedly dominant, or changes in consistency, its risk of malignancy matches that of a solitary nodule. Fineneedle aspiration (FNA) can differentiate thyroid nodules with a high risk of malignancy, warranting surgical removal, from benign goitrous nodules manageable with pharmacological therapy. FNA is associated with falsenegative rates of approximately 3% for solitary nodules [9]. However, the diagnostic process is complicated by the number of nodules and the need to select those for biopsy, which may reduce the sensitivity of the procedure [10-11]. The application of TIRADS ultrasound criteria can aid in identifying suspicious nodules, guiding further diagnostic assessments.

Advancements in molecular testing have also contributed to evaluating thyroid nodules. Nikiforov et al. (2011) discussed the use of molecular markers such as BRAF, RAS mutations, and RET/PTC rearrangements in predicting thyroid cancer. Their study demonstrated that integrating molecular testing with traditional diagnostic methods improves malignancy detection accuracy in MNG [12]. Similarly, Agrawal et al. (2012) highlighted the potential of molecular diagnostics to refine risk stratification and management of thyroid nodules [13].

The association between gender and thyroid cancer has yielded conflicting results. A recent study found that men had a higher risk of incidental papillary thyroid carcinoma [4], whereas others reported a higher prevalence of incidental thyroid carcinoma in the female population [3; 6].

The collective findings from these studies underscore the complex and only partially understood interaction between MNG and thyroid cancer. Although the incidence of malignancy within MNG is relatively low, a rigorous diagnostic approach is essential for the timely and accurate identification of tumors. Integrating ultrasound imaging, FNA, and molecular tests has enhanced diagnostic precision, enabling more informed clinical decisions. Moreover, identifying correlations with demographic and clinical factors could help refine risk stratification and patient management in MNG.

This study aims to investigate, based on existing knowledge, the incidence of occult thyroid carcinoma in a cohort of patients with MNG, providing new insights into the prevalence and characteristics of thyroid malignancies in MNG. It seeks to contribute to optimizing diagnostic evaluations for patients with multinodular goiter.

Materials and Methods

Patients

This retrospective study included patients with a preoperative diagnosis of multinodular goiter who underwent total or partial thyroidectomy from January 2018 to May 2024 at the Department of Medical and Surgical Sciences at the University Hospital “Ospedali Riuniti” in Foggia. The study's objective was to investigate the incidence of thyroid carcinoma in patients undergoing thyroidectomy for MNG, also analyzing associated demographic and clinical variables.

Diagnoses of multinodular goiter were confirmed through clinical and ultrasound examinations. Tissue samples obtained during surgery were analyzed by expert pathologists to identify thyroid carcinoma.

Inclusion criteria were: (1) patients diagnosed with multinodular goiter via thyroid ultrasound, with or without FNA cytology, (2) patients who underwent surgery, and (3) availability of complete clinical data. Exclusion criteria were: patients with a history of thyroid carcinoma or other thyroid neoplasms, those who did not complete postoperative follow up, and patients with preoperative FNA results indicating malignancy (TIR 4–5), suspicion of malignancy (TIR 3), or indeterminate significance (TIR 1) per the 2014 criteria of the Italian Society of Pathological Anatomy and Cytology (SIAPEC).

Demographic, clinical, and pathological data were collected from paper and/or electronic medical records. These included age, sex, results of any FNA cytology, type of surgery, weight of the resected thyroid, and definitive histopathological findings.

Statistical Analysis

Continuous variables were represented as mean values along with standard deviation (SD), while categorical variables were presented as counts and percentages. Percentages were compared using Pearson’s chi-square test, a statistical method employed to assess whether the observed frequency distribution differs significantly from the expected distribution in a given sample. In essence, it evaluates whether two categorical variables are independent.

To investigate potential correlations between continuous variables and the presence of malignancy, an independent samples Student's t-test was conducted. This test determines whether there are statistically significant differences between the means of two groups.

Logistic regression analysis was performed to examine the potential relationship between age and incidental thyroid carcinoma (ITC). Logistic regression is a statistical test used to analyze the relationship between a binary dependent variable (e.g., yes/no, 0/1) and one or more independent variables. This method estimates the impact of independent variables on the dependent variable. The resulting odds ratios (OR) were reported with 95% confidence intervals (CI). A significance level of 0.05 was selected to determine statistical significance. Statistical analysis was conducted using SPSS software.

Results

Charateristics	Mean (SD) or Number (%)
Male, nº	42 (18,8%)
Female, nº	181 (81,2%)
Age, years	55,3 (±13,5)
Benign FNA (TIR2), nº	151 (67,7%)
FNA not done, nº	72 (32,3%)

Total thyroidectomy, n°	202 (90,6%)
Lobectomy, n°	21 (9,4%)
Thyroid wheight, grams	68,4 (±57,9)

Table 1: carateristics of the study partecipants

The study included a cohort of 223 patients diagnosed with multinodular goiter (MNG) at our center between January 2018 and May 2024. The cohort consisted of 181 females (81.2%) and 42 males (18.8%), with a mean age of 55.3 years (SD 15.5). All cases were benign multinodular goiter, with 151 patients (67.7%) undergoing fine-needle aspiration (FNA) yielding benign results, and 72 patients (32.3%) not undergoing FNA. All patients underwent surgical treatment for symptomatic goiter (compressive symptoms, hypo-/hyperthyroidism), with 202 (90.6%) undergoing total thyroidectomy and 21 (9.4%) undergoing lobectomy (Table 1). Patients diagnosed with incidental carcinoma post-total thyroidectomy were referred directly for endocrinological and oncological follow-up, while those who underwent lobectomy received the same guidance following completion of thyroidectomy.

Charateristics	Mean (SD) or Number (%)
Carcinoma, n°	32 (14,4%)
M	8 (25%)
F	24 (75%)
Benigne neoplasms, n°	22 (10,9%)
Age, years	49,4 (±16,7)
Benign FNA (TIR2), n°	18 (56,3%)
FNA not done, n°	18 (56,3%)
Total thyroidectomy, n°	29 (90,6%)
Lobectomy, n°	3 (9,4%)
Thyroide weight, grams	50,9 (±48,1)

Table 2: charateristics of patient with carcinoma

Out of the 223 patients, 32 cases of thyroid carcinoma were diagnosed, corresponding to an incidence rate of 14.4% (Table 2). Among these, 24 were female (75%) and 8 were male (25%), with a female-to-male ratio of 3:1. Thyroid carcinoma was identified in 13.3% of all females and 19% of all males. Although a difference in incidence between the sexes was observed, it was not statistically significant (chi=0.929; p=0.335).

The diagnosis of carcinoma was confirmed through postoperative histopathological examination, which classified the subtypes of thyroid carcinoma present in the sample. Papillary thyroid carcinoma (PTC) was the most common type, identified in 25 cases (78.1%), including 16 cases (50%) of microcarcinoma (pT1a; <1 cm) and 9 cases of classic PTC. Follicular thyroid carcinoma was diagnosed

in 5 cases (15.6%), while 1 case of anaplastic carcinoma and 1 case of Hurthle cell carcinoma were identified.

No cases of medullary carcinoma were reported (Figure 1).

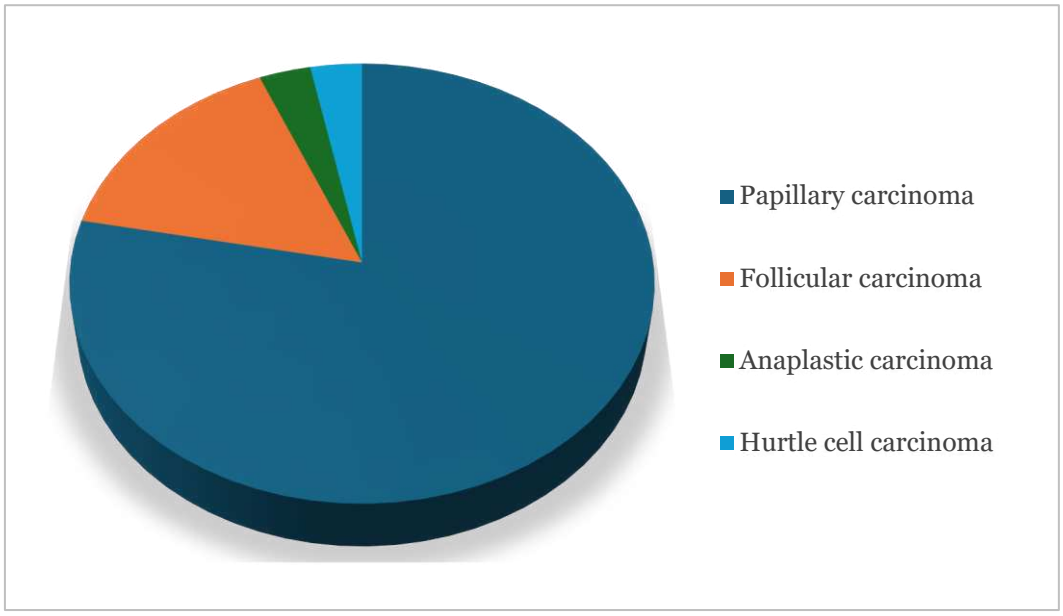

Figure 1: subtypes of thyroid carcinoma

Regarding benign neoplasms, 20 follicular adenomas, 1 Hurthle cell adenoma, and 1 NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features) were identified.

The mean age of patients with thyroid carcinoma was 49.4 years (SD 16.7), with an age range of 22 to 72 years. A significant difference was observed between this group and the mean age of patients without carcinoma (mean: 56.2 years, SD 13.1; Figure 2). Statistical analysis indicated a significant difference between the two groups in terms of age (t=-2.686; p=0.008). Additionally, evaluating the correlation between age and malignancy revealed that for each additional year of age, the probability of carcinoma decreased by 3.7% (OR=0.963; p=0.009).

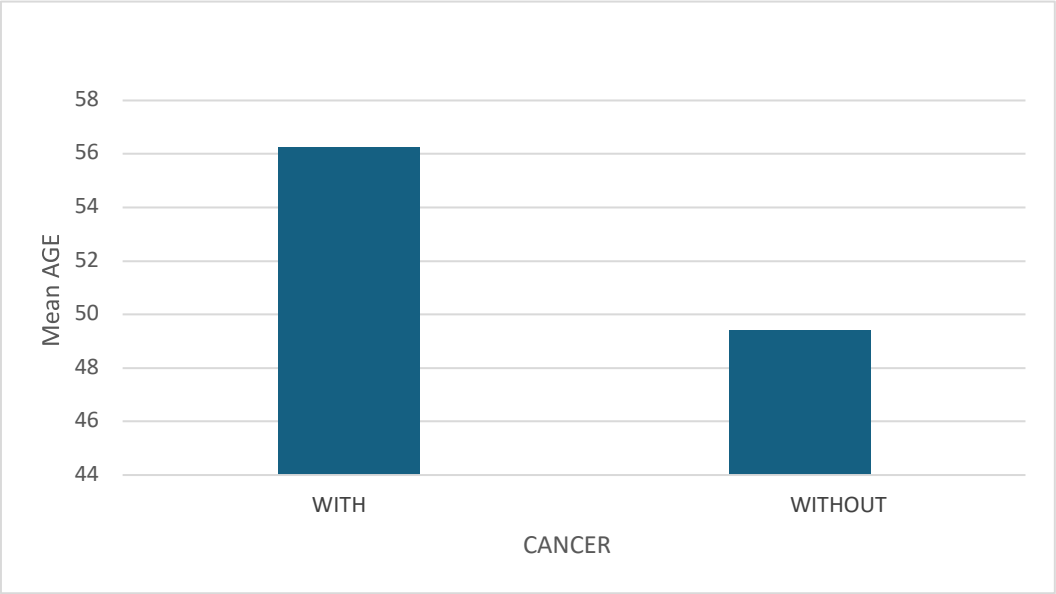

Figure 2: age in the groups whit an without carcinoma

No significant differences were found between the mean ages of male and female patients with carcinoma.

Following surgical removal, the weight of the thyroid glands was assessed as an indicative parameter of size, volume, and the density of the thyroid parenchyma, serving as a characteristic that integrates multiple structural factors of the organ affected by MNG.

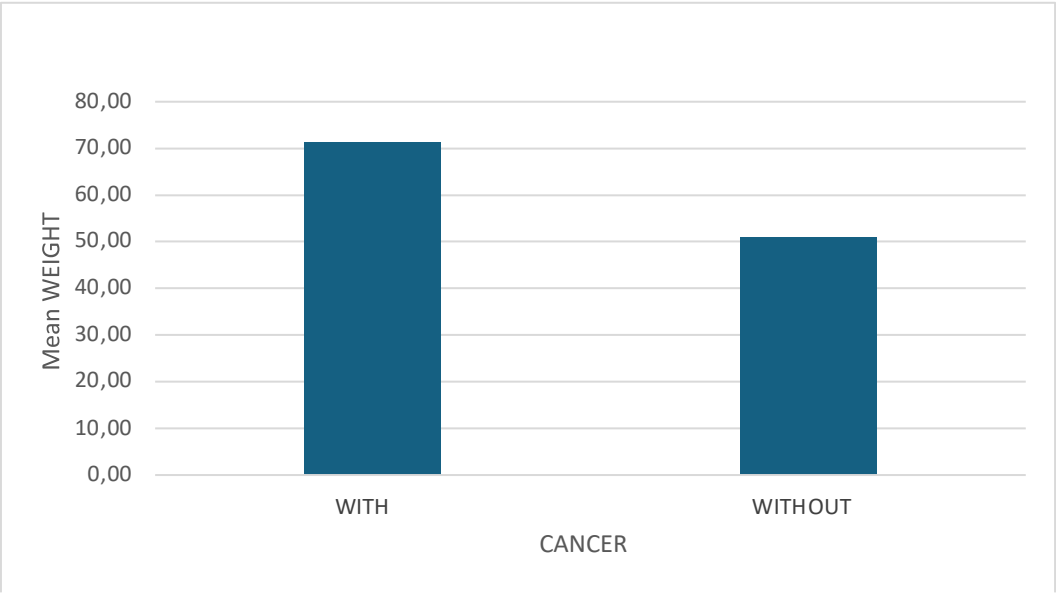

Figure 3: weight in the groups with and without carcinoma

The mean thyroid weight in patients with ITC was 50.9 grams (SD 48.1), compared to 71.3 grams (SD 59.0) in patients without ITC (Figure 3). This difference was statistically significant (t=-1.855; p=0.032). No significant differences in carcinoma incidence were observed between patients with benign FNA results and those who did not undergo FNA.

Discussion

The observed incidence of 14.4% higlight a significant risk of thyroid carcinoma development in patients with MNG compared to the general population. This finding aligns with recent studies conducted in various Italian populations [14, 15], including those by Bove et al. (2023), Spaziani et al. (2023), and Chiefari et al. (2024) [3, 16, 6]. However, unlike these studies, which reported a significant prevalence in females, and the study by Apostolou et al. (2021) [4], which showed an increased incidence in males, our data revealed no notable sex-based differences in carcinoma distribution. This finding deviates from existing literature.

Although prevalence indices vary slightly, our findings regarding histotype distribution confirm, in agreement with numerous other studies [2-6, 15], that papillary thyroid carcinoma is the most prevalent subtype among patients with MNG, followed by follicular thyroid carcinoma.

It is noteworthy that Hurthle cell carcinoma, reported as such based on the 2018 histopathological classification, is now defined to as “oncocytic carcinoma” according to the 2022 WHO guidelines [18]. Given that half of the cases were papillary microcarcinomas, it is essential to emphasize their favorable prognosis despite their scientific interest. Although progression rates are below 15% over 10 years, they tend to increase with younger age at diagnosis [18, 19]. Older patients are ideal candidates for active surveillance with ultrasonographic monitoring, while younger patients may benefit more from surgery. However, most young patients would also qualify for active surveillance, as surgery may not be required during their lifetime [20, 21].

Regarding age as a risk factor for thyroid carcinoma in MNG patients, the literature reports conflicting data. Some studies found no significant relationship between age and malignancy [4, 22], whereas others, consistent with our findings, reported higher tumor prevalence in younger patients [23, 24].

Benign neoplasms, of which 22 cases were identified, require only conservative surgical management without the need for radioactive iodine therapy or ultrasonographic surveillance due to their low progression rates. Thyroid weight has been implicated as a potential risk factor for ITC [4, 22,

25,26,27]. Based on the existing literature [4, 22], clinical observations, and diagnostic pathways for malignancies in goitrous thyroids, we hypothesized that smaller thyroids with lower nodular density (cystic or spongiform appearance) are more prone to ITC, owing to diagnostic challenges with ultrasonography and FNA. This hypothesis was confirmed by our findings. Thyroid weight should therefore be considered a potential risk factor in the clinical management of MNG patients to ensure early detection of associated thyroid malignancies [28, 29].

The primary limitations of this study include the small sample size, the fact that the patients were recruited from a single center, and their representation of a genetically homogeneous population. While the latter reduces potential statistical errors related to genetic factors, it limits the generalizability of the findings.

The difficulty in collecting certain parameters due to incomplete data allowed for the evaluation of only a limited number of disease-related aspects, although these proved to be significant.

Conclusion

The results of this study highlight a significant incidence of thyroid carcinoma in patients with multinodular goiter. The predominant histotype was papillary carcinoma, with no observed sex-based differences in incidence. The identified risk factors, such as age and thyroid weight, while potentially useful for stratifying risk in patients with multinodular goiter, are insufficient—due to study limitations and the significant variability among populations from different regions—to justify modifications to existing thyroid nodule screening criteria.

These results are an excellent starting point and instead underscore the need for multicenter studies aimed at developing specific monitoring protocols for this patient population. Such protocols could enable timely and targeted interventions, ultimately improving clinical outcomes and reducing morbidity associated with thyroid carcinoma.

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