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Research Article

Comparison of Incidental Malignancy Rates and Surgical Outcomes in Preoperatively Benign Multinodular Goiter vs Toxic Multinodular Goiter

Benign Multinodüler Guatr ve Toksik Multinodüler Guatr Olgularında İnsidental Malignite Oranları ve Cerrahi Sonuçların Karşılaştırılması

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Abstract

This study aimed to compare perioperative outcomes, complication rates, and incidental thyroid cancer prevalence in patients undergoing surgery for benign multinodular goiter versus toxic multinodular goiter. A retrospective analysis of 202 patients (110 MNG, 92 TMNG) with Bethesda II cytology was conducted. Inclusion criteria comprised adults with multinodular goiter or toxic multinodular goiter, while exclusion criteria included preoperative malignancy suspicion, Graves' disease, or incomplete data. All surgeries were performed by high-volume endocrine surgeons using standardized techniques, including intraoperative nerve monitoring and ultrasonic dissection. Data on demographics, ultrasonographic features, surgical complications (hypocalcemia, recurrent laryngeal nerve injury, hemorrhage), and final histopathological diagnosis were analyzed. Of the 202 cases, 19.8% were male and 80.2% were female (mean age 49.8±12.2 years). TMNG patients presented with significantly smaller mean nodule diameters (26.1 mm vs. 38.9 mm, p=0.001) and a higher frequency of hypoechogenicity (38% vs. 26.4%, p=0.03) compared to MNG. No significant differences were found in gender, age (p=0.059), or postoperative calcium levels. Incidental malignancy rates were 16.3% in MNG and 8.6% in TMNG (p=0.10). While postoperative bleeding did not reach formal statistical significance (5.4% in TMNG vs. 0.9% in MNG, p=0.09), a clinically notable six-fold increase in the odds ratio was observed (OR: 6.26; 95% CI: 0.72–54.55). Surgical management of TMNG is safe when performed by experienced surgeons; however, the elevated odds ratio for bleeding warrants heightened perioperative vigilance. The incidental cancer risk does not significantly differ between groups, though the lower prevalence in TMNG may be influenced by smaller nodule size enhancing preoperative biopsy accuracy.

Keywords: Hyperthyroidism, Thyroidectomy, Toxic Multinodular Goiter.

Özet

Bu çalışma, benign multinodüler guatr ve toksik multinodüler guatr nedeniyle ameliyat edilen hastalarda cerrahi sonuçları, komplikasyon oranlarını ve insidental tiroid kanseri prevalansını karşılaştırmayı amaçlamaktadır. Bethesda II sitolojisine sahip 202 hastanın (110 MNG, 92 TMNG) retrospektif analizi yapıldı. Dahil etme kriterleri multinodüler guatr veya toksik multinodüler guatr tanılı yetişkinleri kapsarken; preoperatif malignite şüphesi, Graves hastalığı veya eksik verisi olan hastalar çalışma dışı bırakıldı. Tüm cerrahi işlemler, yüksek hacimli endokrin cerrahları tarafından intraoperatif sinir monitörizasyonu ve ultrasonik diseksiyon gibi standart teknikler kullanılarak gerçekleştirildi. Demografik veriler, ultrasonografik özellikler, cerrahi komplikasyonlar (hipokalsemi, rekürren laringeal sinir hasarı, hemoraji) ve nihai histopatolojik tanı verileri analiz edildi. Toplam 202 vakanın %19,8'i erkek, %80,2'si kadındı (ortalama yaş 49,8±12,2). TMNG hastalarında, MNG grubuna kıyasla ortalama nodül çapı anlamlı derecede daha küçük (26,1 mm'ye karşı 38,9 mm, p=0,001) ve hipoekoik özellik sıklığı daha yüksekti (%38'e karşı %26,4, p=0,03). Cinsiyet, yaş (p=0,059) veya postoperatif kalsiyum düzeyleri açısından anlamlı bir fark saptanmadı. İnsidental malignite oranları MNG grubunda %16,3, TMNG grubunda ise %8,6 olarak bulundu (p=0,10). Postoperatif kanama oranları istatistiksel olarak tam anlamlılığa ulaşmasa da (TMNG'de %5,4'e karşı MNG'de %0,9, p=0,09), klinik olarak dikkat çekici şekilde altı katlık bir artış gözlendi (OR: 6,26; %95 GA: 0,72–54,55). TMNG'nin cerrahi yönetimi deneyimli cerrahlar tarafından yapıldığında güvenlidir; ancak kanama riskindeki yüksek risk oranı perioperatif dönemde daha dikkatli olunmasını gerektirir. İnsidental kanser riski gruplar arasında anlamlı farklılık göstermemektedir; ancak TMNG'deki düşük prevalans, küçük nodül boyutunun preoperatif biyopsi doğruluğunu artırmasından kaynaklanıyor olabilir.

Anahtar Kelimeler: Hipertiroidi, Tiroidektomi, Toksik Multinodüler Guatr.

Introduction

Hyperthyroidism, a prevalent endocrine disorder with substantial clinical and economic implications for global healthcare systems, is most commonly caused by Graves' disease, toxic multinodular goiter and toxic solitary nodule (1). For patients with persistent hyperthyroidism despite medical therapy, definitive treatment options include radioactive iodine ablation or thyroidectomy, with the choice often influenced by factors such as patient preference and risk of complications (2).

The association between thyroid-stimulating hormone (TSH) suppression and thyroid cancer risk remains controversial. While experimental data suggest that low TSH levels may reduce malignant transformation by limiting thyrocyte proliferation, clinical studies report comparable malignancy rates between hyperthyroid and euthyroid patients undergoing thyroidectomy (3,4). Currently, the incidence of cancer in patients undergoing surgery for hyperthyroidism is not negligible, with rates ranging from 1.6% to 21% (5,6).

This study aimed to compare perioperative outcomes, complication rates, and the prevalence of incidental thyroid cancer in patients undergoing surgery for benign multinodular goiter (MNG) versus toxic multinodular goiter (TMNG). By addressing these critical clinical distinctions, we seek to provide evidence-based insights to optimize surgical management in hyperthyroid patients.

Material and Method

A total of 580 consecutive patients who underwent thyroidectomy for MNG or TMNG between January 2018 and December 2019 were retrospectively screened. After applying inclusion and exclusion criteria, 202 patients with benign cytology (Bethesda II) were included in the final analysis. Patients over 18 years of age who underwent surgery for MNG or TMNG were included. Patients under 18, those with preoperative fine-needle aspiration biopsy (FNAB) results indicating malignancy, suspicion of malignancy, follicular neoplasm, atypia of undetermined significance, non-diagnostic results, or diagnoses of Graves' disease or toxic solitary nodule, and those with incomplete data were excluded from the study.

The primary endpoint of the study was the rate of incidental thyroid carcinoma in patients with benign (Bethesda II) cytology.

No a priori power analysis was conducted; the sample size was determined by the number of eligible patients available during the study period. The sampling method used was non-probability consecutive sampling.

We collected demographic data, preoperative ultrasonographic features (nodule size, echogenicity, margins, and calcification patterns), surgical complications (postoperative calcium levels, recurrent laryngeal nerve injury verified by laryngoscopy, postoperative hemorrhage), and final histopathological diagnoses.

The study was approved by the Ethics Committee for Clinical Research of Bakırköy Dr. Sadi Konuk Training and Research Hospital with protocol code 2024\178 on 24.06.2024.

All patients were evaluated by a multidisciplinary endocrine council comprising the departments of clinical endocrinology, endocrine surgery, radiology, pathology, and nuclear medicine. Surgical decisions were made following the American Thyroid Association (ATA) Guidelines, with TMNG patients selected for surgery due to medical therapy failure, compressive symptoms, nodule size exceeding 4 cm, or patient preference (e.g., pregnancy planning). All patients in the TMNG group were preoperatively managed with antithyroid medications (e.g., methimazole) or beta-blockers to achieve a clinically euthyroid state prior to surgery, in accordance with standard protocols. However, specific preoperative biochemical data distinguishing between overt and subclinical hyperthyroidism (e.g., exact serum T3, T4, and TSH levels) at the time of initial diagnosis were not systematically categorized for the entire cohort. For MNG, surgery was indicated for benign nodules >4 cm, those causing compressive symptoms, or cases with clinical concerns such as radiological progression or social barriers impeding adequate follow-up. The case with an 8-mm nodule underwent surgery due to patient preference, in addition to the presence of multinodular goiter.

All patients underwent preoperative evaluation with ultrasonography (USG), and FNAB was performed by a single interventional radiologist. The FNAB strategy was not limited to the dominant nodule alone. Biopsies were primarily directed at nodules exhibiting suspicious ultrasonographic features (such as marked hypoechogenicity, irregular margins, or

microcalcifications) regardless of their size, as well as the dominant nodule in each lobe. In patients with multiple suspicious nodules, FNAB was performed on more than one site to minimize the risk of missing a malignancy. This comprehensive sampling approach was intended to optimize the diagnostic yield of preoperative cytology in the setting of multinodular disease. Surgery was planned based on FNAB results. Thyroidectomy procedures were performed by four high-volume experienced endocrine surgeons (>100 thyroidectomies/year), in accordance with studies recommending this standard (7). All procedures utilized the Harmonic FOCUS (Ethicon Endo-Surgery, Cincinnati, OH, USA) ultrasonic dissector for hemostasis and parenchymal division, complemented by routine intermittent intraoperative nerve monitoring using Medtronic NIM-Response 3.0 (Medtronic, Minneapolis, MN, USA) to preserve recurrent laryngeal nerves. Final histopathological diagnosis evaluation was performed by a separate surgical pathologist.

The extent of thyroid resection was determined based on clinical indications and multidisciplinary council recommendations. In the TMNG group, total thyroidectomy was routinely performed in all cases to ensure definitive treatment of hyperthyroidism and prevent recurrence. For the MNG group, total thyroidectomy was the standard approach for patients with bilateral multinodular involvement. Hemithyroidectomy (lobectomy) was only performed in a small subset of MNG patients where the disease was strictly limited to a single lobe without suspicious contralateral findings.

All patients were followed for a minimum of 6 months postoperatively. Longer follow-up data were available for some patients; however, due to inconsistent documentation, only the 6-month minimum follow-up period could be reliably reported.

Definitions

In the preoperative period, all patients underwent ultrasonography by a radiologist. Fine-needle aspiration biopsy was performed by an interventional radiologist on nodules with suspicious features (marked hypoechogenicity, irregular or microlobulated margins, microcalcifications, and taller-than-wide shape) or on the dominant nodule. The pathology results of thyroid fine-needle biopsy were evaluated according to the Bethesda classification system (8).

Postoperative hypocalcemia was defined as a serum corrected calcium level below 8.0 mg/dL measured on the first or second postoperative day, or the presence of clinical symptoms (e.g., paresthesia, Trousseau's sign) requiring oral or intravenous calcium supplementation. Transient hypocalcemia was defined as a state requiring calcium or vitamin D supplements that resolved within 6 months postoperatively. Permanent hypoparathyroidism/hypocalcemia was defined as the persistence of low parathyroid hormone (PTH) or corrected calcium levels requiring continuous supplementation beyond 6 months, as verified by clinical follow-up.

Postoperative bleeding is defined as hemorrhage occurring within 24 hours after thyroidectomy, most commonly within the first 6 to 8 hours, which may lead to life-threatening airway compromise requiring urgent surgical intervention(9). In this study, postoperative bleeding was specifically categorized as clinically significant hematoma formation that necessitated urgent surgical re-exploration to ensure airway safety and achieve definitive hemostasis. Minor ecchymosis or small, stable subcutaneous collections that were managed conservatively without surgical intervention were not included in the primary bleeding rate analysis.

Hoarseness that resolved within 6 months postoperatively was considered transient hoarseness, while hoarseness persisting beyond 6 months was defined as permanent hoarseness (10).

Statistical Analysis

The data analysis was performed using Jamovi software (The jamovi project, 2022; Version 2.3.18; license: GPL-3). Descriptive statistics were used to summarize the data: mean ± standard deviation or median (minimum–maximum) for continuous variables depending on distribution, and frequency (n) and percentage (%) for categorical variables. The normality of continuous variables was assessed using the Shapiro-Wilk test and histogram/Q-Q plot evaluations. For group comparisons, the Student's t-test was used for normally distributed quantitative variables, while the Mann-Whitney U test was applied for non-normally distributed data. Pearson's chi-square test or Fisher’s exact test was used to compare categorical variables, depending on expected frequencies. All statistical tests were two-tailed, and statistical significance was set at $p<0.05$. Exact p-values were reported in all relevant tables.

A post-hoc power analysis was performed to evaluate the study's strength in detecting the

difference in incidental malignancy rates between MNG (16.3%) and TMNG (8.6%). With an alpha level of 0.05 and the current sample size (n=202), the achieved power was found to be 43.2%.

Results

The study included a total of 202 cases, 19.8% (n=40) male and 80.2% (n=162) female. Participants were aged between 18 to 73 years, with a mean age of 49.8±12.2 years. The MNG group included 110 patients, while the TMNG group included 92 patients (Table 1).

Regarding the extent of surgery, total thyroidectomy was performed in 100% (n=92) of the TMNG group. In the MNG group, total thyroidectomy was performed in 94.5% (n=104) of patients, while the remaining 5.5% (n=6) underwent hemithyroidectomy due to strictly unilateral disease.

This high rate of total thyroidectomy across both groups ensures a standardized comparison of postoperative complications such as hypocalcemia and recurrent laryngeal nerve injury.

The nodule size in the MNG group was statistically significantly larger than in the TMNG group (p=0.001; p<0.05).

No statistically significant differences were found between the groups in terms of gender, age, postoperative calcium levels, nodule structure, calcifications, margins, final histopathological diagnosis, transient or permanent hoarseness. Postoperative bleeding occurred in 0.9% of the MNG group and 5.4% of the TMNG group. While this difference did not reach statistical significance (p=0.09), the odds ratio for bleeding in the TMNG group was 6.26 (95% CI: 0.72–54.55) (Tables 1-3).

Table 1. Demographic, Clinical, and Ultrasonographic Characteristics of MNG and TMNG

		MNG n (%)	**TMNG n (%)**	***p***
Sex	Male	24 (21.8)	16 (17.4)	
	Female	86 (78.2)	76 (82.6)	***[b]0.43***
Age	Mean ± SD	48.31±11.89	51.58±12.48	
	Median (Min-Max)	48 (18-73)	51.50 (24-73)	***[a]0.059***
Nodule Size	Mean ± SD	38.95±14.56	26.17±14.89	
	Median (Min-Max)	39 (8-94)	23 (3.5-72)	***[c]0.001****
Nodule Structure	Cystic	33 (30)	14 (15.2)	***[b]0.55***
	Solid	39 (35.5)	41 (44.6)	
	Mixed	32 (29.1)	29 (31.5)	
Echogenicity	Hypoechoic	29 (26.4)	35 (38)	***[b]0.03****
	Isoechoic	57 (51.8)	32 (34.8)	
	Hyperechoic	6 (5.5)	9 (9,.)	
Calcification	None	79 (71.8)	61 (66.3)	***[b]0.81***
	Microcalcification	13 (11.8)	11 (12)	
	Makro Calcification	10 (9.1)	8 (8.7)	
	Peripheral Halo	7 (6.4)	9 (9.8)	
Margin	Regular	94 (85.5)	84 (91.3)	
	Irregular	14 (14.5)	6 (8.7)	***[d]0.22***
Extent of Surgery	Total Thyroidectomy	104 (94.5)	92 (100)	
	Hemithyroidectomy	6 (5.5)	0 (0)	***[d]0.03***

[a]Student-t Test, [b]Pearson Chi-Square Test, [c]Mann Whitney U Test, [d]Fisher's Exact Test, *p<0.05

Table 2. Analysis of Postoperative Complications Between MNG and TMNG Patients

		MNG n (%)	**TMNG n (%)**	***p***
Postoperative	Mean ± SD	8.32±0.59	8.22 ±0.64	***[a]0.26***
Calcium Level	Median (Min-Max)	8.3 (7-9.8)	8.2 (6.6-9.8)	
Postoperative	Present	1 (0.9)	5 (5.4)	***[d]0.09***
Bleeding	Absent	109 (99.1)	87 (94.6)	
Temporary	Present	5 (4.5)	2 (2.2)	***[d]0.46***
Hoarseness	Absent	105 (95.5)	90 (97.8)	
Permanent	Present	1 (0.9)	1 (1.1)	***[d]1.00***
Hoarseness	Absent	109(99.1)	91 (98.9)	

[a]Student-t Test, [d]Fisher's Exact Test

The primary endpoint of incidental malignancy included both papillary thyroid carcinoma (PTC) and papillary thyroid microcarcinoma (PTMC). In the MNG group, where the malignancy rate was 16.3% (n=18), the mean diameter of the malignant nodules was 14.2 ± 8.4 mm. Specifically, 3 (16.7%) were microcarcinomas (≤10 mm) and 15 (83.3%) were macrocarcinomas (>10 mm). In the TMNG group, 5 out of 8 malignancies (62.5%) were microcarcinomas, with a mean tumor diameter of 9.6 ± 5.2 mm (Table 3).

Table 3. Postoperative Histopathological Results in Multinodular Goiter (MNG) and Toxic Multinodular Goiter (TMNG) Patients

Final Histopathological Diagnosis	MNG n (%)	TMNG n (%)	*p*
Benign	92 (83.7)	84 (91.3)	
Malignant	18 (16.3)	8 (8.7)	[d]***0.09***
Papillary Carcinoma	15 (13.6)	2 (2.2)	
Papillary Microcarcinoma	3 (2.7)	5 (5.4)	
Follicular Carcinoma	0	1 (1.1)	

[d]*Fisher's Exact Test*

To evaluate independent predictors of incidental malignancy and account for baseline differences in nodule size and echogenicity, a multivariable logistic regression model was performed. After adjusting for age, nodule size, and hypoechogenicity, the analysis revealed that the type of goiter (TMNG vs. MNG) was not an independent predictor of malignancy (OR: 0.54, 95% CI: 0.21–1.38, p=0.19). Furthermore, none of the ultrasonographic features were found to be independently associated with incidental cancer in this Bethesda II cohort (Table 4).

Table 4. Multivariable Logistic Regression Analysis of Factors Associated with Incidental Malignancy

Variable	Odds Ratio	95% CI	p
Group (TMNG vs. MNG)	0.54	0.21 – 1.38	0.19
Nodule Size	1.02	0.99 – 1.05	0.14
Hypoechogenicity	1.68	0.78 – 3.62	0.18
Age	0.98	0.95 – 1.02	0.42

Discussion

The surgical management of toxic multinodular goiter (TMNG) remains a subject of clinical debate, particularly regarding whether the hyperthyroid state independently alters perioperative complications and the risk of incidental malignancy. Our study compared TMNG and benign multinodular goiter (MNG) patients with preoperatively benign cytology to clarify these distinctions. The findings suggest that when standardized techniques are employed by high-volume surgeons, TMNG can be managed with a safety profile comparable to non-toxic goiter. These results highlight that disparities in complication and malignancy rates are likely driven by the complex interplay of thyroid function, nodule size, and ultrasonographic characteristics rather than a clear divergence in surgical risk.

Our primary endpoint, the incidental malignancy rate, was 16.3% in the MNG group and 8.6% in the TMNG group. The relationship between hyperthyroidism and thyroid cancer risk remains controversial. While traditionally viewed as a benign condition typically managed medically, recent evidence suggests this approach may delay cancer diagnosis in some cases (11). According to one study, hyperthyroid patients were found to have a lower rate of cancer (12). Another study showed that the incidental cancer rate in hyperthyroid patients was similar to that in euthyroid patients (13). Our findings align with this ongoing debate, revealing an 8.6% incidental malignancy rate in TMNG patients, which falls within the 5-15% range reported in the contemporary series(14,15).

Regarding secondary endpoints, we found no significant differences in hypocalcemia or hoarseness between groups, supporting the safety of thyroidectomy in TMNG when performed by experienced surgeons. While some literature identifies hyperthyroidism as a risk factor for increased morbidity , our standardized use of ultrasonic dissectors and nerve monitoring likely contributed to these comparable outcomes. A study by Kwon et al. demonstrated that Graves' disease is an independent risk factor for postoperative recurrent laryngeal nerve injury, postoperative hematoma, and hypocalcemia (16). Similarly, a study by Liang et al. showed that hyperthyroidism is a risk factor for postoperative complications (17). However, another study found that Graves' disease was not a risk factor for postoperative bleeding (18). In our study, although

the postoperative bleeding rate did not reach formal statistical significance (5.4% vs. 0.9%, p=0.09), the six-fold increase in the odds ratio (OR: 6.26; 95% CI: 0.72–54.55) suggests a clinical trend that warrants caution. Furthermore, Wojtczak et al. reported an association between toxic goiter and increased postoperative bleeding risk (19). The lack of statistical significance in our cohort must be interpreted with methodological caution; it is likely influenced by the relatively limited sample size and the low absolute frequency of events, which impacts the statistical power to detect a definitive difference. Therefore, while our results do not definitively exclude an increased hemorrhagic risk in hyperthyroid patients, the high odds ratio highlights a clinical trend that necessitates heightened perioperative vigilance and meticulous hemostasis. In a different study, transient hoarseness was found to be lower in patients undergoing surgery for Graves' disease, although there was no difference in permanent hoarseness and postoperative hematoma (20). It is believed that transient hoarseness may occur due to increased traction on the recurrent nerve during dissection of the enlarged thyroid mass, which is associated with increased vascularity. Other studies have also shown an increased risk of postoperative hypocalcemia in patients undergoing surgery for hyperthyroidism (21). Although our results suggest that the risk of most postoperative complications is not significantly increased in TMNG patients, these findings should be interpreted cautiously due to the limited sample size and statistical power. Our study contributes valuable data to the literature regarding the safety of surgical management in TMNG while highlighting the need for vigilance regarding postoperative hemorrhage. Furthermore, the extent of surgical resection is a well-known determinant of postoperative morbidity. In our study, while all TMNG patients underwent total thyroidectomy, a small proportion (5.5%) of the MNG group underwent hemithyroidectomy due to strictly unilateral disease. Although this surgical homogeneity was high—with over 94% of patients in both groups receiving total thyroidectomy—the inclusion of lobectomies in the MNG group inherently reduces the cumulative risk of bilateral complications such as permanent hypocalcemia or bilateral recurrent laryngeal nerve injury. This slight variation in surgical extent between the two groups (p=0.03) should be considered when interpreting the comparable complication rates, as it may represent a minor source of bias favoring lower morbidity in the MNG cohort.

A central finding of our study was that TMNG patients presented with significantly smaller mean nodule diameters compared to the MNG group (26.1 mm vs. 38.9 mm, p=0.001). This disparity in nodule size represents a critical determinant of preoperative diagnostic accuracy. Smaller nodules, particularly those under 3 cm, are associated with lower FNAB false-negative rates compared to larger, more complex multinodular glands where sampling error is more prevalent (22). We suggest that the numerically lower incidental malignancy rate in our TMNG group (8.6% vs. 16.3%) is not necessarily due to a protective effect of hyperthyroidism, but rather to the enhanced reliability of FNAB in smaller nodules, which allows for more effective preoperative detection and exclusion of cancers. Conversely, the significantly larger nodules in the MNG group likely increased the technical difficulty of sampling every potentially malignant focus, contributing to the higher incidental cancer rate observed in that cohort. This highlights that nodule size, by influencing biopsy accuracy, is a key factor in the clinical interpretation of incidental malignancy rates in multinodular disease.

The ultrasonographic structure of the nodules (solid, cystic, or mixed) and the presence of calcifications (micro or macro) did not differ significantly between the groups, but these features remain important in malignancy risk stratification (23). Additionally, there was a significant difference in echogenicity distribution between groups (p=0.03), with hypoechoic nodules being more common in patients with TMNG. Given that hypoechogenicity is associated with an increased risk of malignancy in ultrasound evaluations, this finding emphasizes the need for thorough assessment in TMNG cases (24).

In our study, TMNG patients presented with significantly smaller nodules (p=0.001) and a higher frequency of hypoechogenicity (p=0.03) compared to the MNG group. Since these parameters are known to influence malignancy risk, we conducted a multivariable logistic regression analysis (Table 4). The model demonstrated that when these factors were controlled, hyperthyroid status itself did not significantly alter the risk of incidental malignancy. This suggests that the numerical difference in cancer rates between groups may be partially influenced by clinical and ultrasonographic characteristics rather than thyroid functional status alone. An intriguing finding was the higher prevalence of

hypoechogenicity in the TMNG group (38% vs. 26.4%, p=0.03) despite a numerically lower malignancy rate. This apparent discrepancy may be explained by the significantly smaller mean nodule size in TMNG patients (26.1 mm vs. 38.9 mm, p=0.001), which likely enhanced the diagnostic accuracy of preoperative FNAB and facilitated the earlier detection and exclusion of malignant nodules. Furthermore, our multivariable analysis confirmed that hypoechogenicity was not an independent predictor of incidental malignancy in this specific Bethesda II cohort. Consequently, the higher frequency of hypoechogenicity in TMNG may reflect a distinct biological profile of toxic nodules rather than an increased risk of occult cancer in patients with benign preoperative cytology.

While no statistically significant differences were observed in gender and age distributions, the mean age was notably higher in the TMNG group compared to the MNG group (51.6 vs. 48.3 years; p=0.059). Although this difference did not reach formal statistical significance, it carries potential clinical implications that warrant discussion. The trend toward an older age in TMNG patients may reflect a clinical pattern of delayed referral for definitive surgical intervention, often due to prolonged attempts at medical management with antithyroid drugs or radioactive iodine therapy before surgery is considered. This potential delay in surgical treatment could influence the overall disease duration and the complexity of preoperative management. While our study was not specifically powered to detect age-related differences, these observations suggest that referral patterns and the duration of medical therapy are important factors to consider in future prospective investigations of toxic multinodular disease.

One notable aspect of our study is that it demonstrates the possibility of postoperative cancer in patients deemed benign based on preoperative biopsy. This aligns with other studies in the literature reporting cases where preoperative benign assessments were followed by malignant postoperative pathology (25). Our observed malignancy rate of 16.3% in Bethesda II nodules is higher than the 3-5% typically reported in the literature. Several factors may account for this disparity. First, as a tertiary referral center, our patient population often includes complex cases with long-standing multinodular goiters, which may harbor occult foci of malignancy. Second, the inclusion of microcarcinomas in our pathology results contributes to the higher overall prevalence. Finally, while all patients had preoperative Bethesda II cytology, the high-volume nature of our endocrine surgery department leads to the resection of large, symptomatic nodules where sampling error in fine-needle aspiration (FNA) is more likely due to the presence of multiple nodules. We attribute these false negatives to the nature of the disease, which often involves multiple nodules, and to variability in biopsy sampling from suspicious or dominant nodules. Our biopsy strategy aimed to address the inherent challenges of multinodular disease by targeting both dominant and ultrasonographically suspicious nodules. However, despite this targeted approach, the 16.3% incidental malignancy rate in our MNG group underscores the persistent risk of false-negative cytology. This may be attributed to the presence of occult microcarcinomas or the technical difficulty of sampling every potentially malignant focus in a gland crowded with multiple nodules. These findings reinforc e the recommendation that surgical decision-making should consider the overall clinical and radiological profile rather than relying solely on a single benign FNAB result in complex multinodular cases.

According to the ATA guidelines, total or subtotal thyroidectomy is recommended for patients with hyperthyroidism (26). We believe that all nodules with suspicious features should undergo fine-needle aspiration biopsy during preoperative ultrasonography, regardless of the patient's hyperthyroid status. In cases where subtotal thyroidectomy is performed and final histopathological diagnosis reveals malignancy, reoperation may be required. Studies have shown that reoperation increases the risk of vocal cord paralysis and hypoparathyroidism (27). While we did not compare total and subtotal thyroidectomy in our study, the results emphasize the importance of considering the potential for malignancy in patients with toxic multinodular goiter, which may influence surgical decision-making.

Another noteworthy observation was the presence of a follicular carcinoma in one TMNG patient. Although it is only a single case it highlights the diversity of malignancies that may occur incidentally in toxic nodular goiters. This should prompt comprehensive histopathological evaluation in all surgical specimens.

The strengths of our study include the homogeneity of the patient group, as all patients were selected based on preoperative benign biopsy results, and the use of standard surgical techniques, such as nerve monitoring and ultrasonic sealing

devices, across all cases. These factors contribute to the comparability of our results.

Study Limitations

The primary limitation of our study is its retrospective design. Furthermore, retrospective data collection may have introduced information bias, particularly regarding minor complications that may not have been systematically documented. Additionally, postoperative bleeding complications were assessed based on clinically significant hematoma formation rather than the volume of bleeding. Furthermore, our definition of postoperative bleeding focused exclusively on hematomas requiring surgical intervention. This approach may have led to an underestimation of the true incidence of minor, conservatively managed bleeding events. The lack of a standardized grading system for mild hematomas represents a limitation in capturing the full spectrum of hemorrhagic complications, which should be considered when comparing our results with studies that use broader definitions of postoperative bleeding. Another limitation is the lack of detailed biochemical data regarding the severity of hyperthyroidism in the TMNG group. While all patients were rendered clinically euthyroid before surgery, we did not analyze whether the initial presentation was overt or subclinical hyperthyroidism. Since the degree of thyrotoxicosis and the duration of the disease may influence glandular vascularity and hemostatic mechanisms, the absence of these biochemical details limits our ability to correlate the severity of hyperthyroidism with specific surgical outcomes, such as the numerically higher bleeding rate observed in the TMNG group. Furthermore, a significant limitation of our study is the lack of standardized categorical data regarding the exact incidence of transient and permanent hypocalcemia. While postoperative mean calcium levels were monitored and reported, the retrospective design prevented a precise retrospective distinction between biochemical hypocalcemia and clinically symptomatic cases requiring long-term supplementation. This lack of granular data limits the clinical interpretation of parathyroid function outcomes and should be considered when evaluating the comparative morbidity between MNG and TMNG groups.

Another limitation is that the surgeries were performed by four different surgeons. However, each surgeon met the criteria for being a high-volume, experienced endocrine surgeon (>100 thyroidectomies/year), which helps mitigate this limitation. Furthermore, our study is limited by a relatively short minimum follow-up duration of six months, which is insufficient for evaluating long-term oncologic outcomes. Consequently, data regarding completion thyroidectomy, radioactive iodine (RAI) ablation therapy, or long-term recurrence rates in patients with incidental malignancy were not systematically analyzed. While our primary focus was on immediate perioperative complications and initial histopathological findings, the lack of longitudinal oncologic data represents a limitation in assessing the definitive prognosis of these incidental cancers. Additionally, the slight imbalance in the extent of surgery between groups constitutes a potential limitation. While total thyroidectomy was the standard for TMNG, the performance of hemithyroidectomy in a small subset of MNG patients may have influenced the overall complication profile of that group. Although the vast majority of our cohort received standardized total resections, this procedural variation must be acknowledged as a potential confounding factor in the comparative analysis of postoperative outcomes. The lack of statistical significance in malignancy rates ($p=0.09$) should be interpreted with caution. Our post-hoc power analysis (power = 43.2%) indicates that the study may be underpowered to detect a clinically meaningful difference of 8%. Therefore, the lower malignancy rate observed in the TMNG group suggests a potential trend that warrants further investigation in larger, prospective multicenter trials.

Conclusion

In conclusion, our findings suggest that hyperthyroidism may not substantially increase the risk of major surgical complications in patients undergoing thyroidectomy for multinodular goiter, provided that standardized techniques are employed by experienced surgeons. However, the six-fold increase in the odds ratio for postoperative bleeding in the TMNG group (OR: 6.26) indicates a clinical trend that necessitates heightened perioperative vigilance. While no statistically significant difference in incidental malignancy rates was observed, our study highlights that the lower prevalence in the TMNG group (8.6% vs. 16.3%) is likely influenced by smaller nodule diameters enhancing the accuracy of preoperative FNAB, rather than a protective effect of the hyperthyroid state alone. Due to the retrospective nature and the limited statistical power (43.2%) of our study, these conclusions should be considered

hypothesis-generating. Ultimately, the persistent risk of incidental malignancy in both groups emphasizes the importance of thorough histopathological examination and cautious patient counseling regardless of thyroid functional status.

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Conflict of interest statement

Authors declare no conflict of interest for this article.

Ethics Committee Approval

The study was approved by the Ethics Committee for Clinical Research of Bakırköy Dr. Sadi Konuk Training and Research Hospital with protocol code 2024\178 on 24.06.2024.

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