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Research

Challenging the 4 cm Rule: Nodule Size Does not Predict the Risk of Occult Malignancy in Cytologically Benign Thyroid Nodules

4 cm Kuralının Sorgulanması: Sitolojik Olarak Benign Tiroid Nodüllerinde Nodül Boyutu Gizli Malignite Riskinin Belirleyicisi Değildir

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ABSTRACT

Objective: Accurate differentiation between benign and malignant lesions remains a primary challenge in thyroid nodule management. This study evaluated the impact of nodule size on malignancy rates and on the incidence of occult malignancy among lesions that were preoperatively classified as benign, specifically questioning the reliability of the 4 cm threshold.

Methods: Between 2016 and 2019, 477 patients with preoperative benign cytology who underwent surgery were retrospectively analyzed. Patients were stratified into macro-nodules (≥4 cm, n=161) and smaller lesions (<4 cm, n=316). Multivariate logistic regression was used to identify independent predictors of malignancy, and a post-hoc power analysis was performed to evaluate the diagnostic strength of the findings.

Results: The overall malignancy rate was 11.5% (n=55/477). Malignancy rates were nearly identical between the groups: 11.8% [95% confidence interval (CI): 7.7-17.7%] for the ≥4 cm group and 11.4% (95% CI: 8.3-15.4%) for the <4 cm group (p=1.000). In the multivariate analysis, within the limits of the current regression model adjusted for age and sex, nodule size ≥4 cm did not emerge as a significant predictor of malignancy (odds ratio: 1.04, 95% CI: 0.58-1.86, p=0.885). A post hoc power analysis confirmed that the observed difference was clinically negligible (Cohen's h=-0.013). No significant differences were observed among histological subtypes, including papillary and follicular carcinomas, with respect to size (p>0.05).

Conclusion: Nodule size is an insufficient independent criterion for predicting malignancy specifically among surgically treated patients with benign cytology. Based on our findings in this surgically selected cohort, clinical decision-making should not rely solely on size thresholds. Instead, management should favor an integrated strategy that incorporates sonographic risk features and multidisciplinary evaluation to optimize patient outcomes and reduce unnecessary surgeries.

Keywords: Fine-needle aspiration biopsy, occult malignancy, thyroid cancer, thyroid nodule

ÖZ

Amaç: Tiroid nodülü yönetiminde benign ve malign lezyonların doğru şekilde ayırt edilmesi temel bir zorluk olmaya devam etmektedir. Bu çalışma, preoperatif olarak benign sitolojiye sahip lezyonlarda nodül boyutunun malignite oranları ve gizli malignite insidansı üzerindeki etkisini değerlendirmiş; özellikle 4 cm eşiğinin güvenilirliğini sorgulamıştır.

Gereç ve Yöntem: 2016-2019 yılları arasında, preoperatif sitolojisi benign olup cerrahi geçiren 477 hasta retrospektif olarak analiz edildi. Hastalar makro-nodüller (≥4 cm, n=161) ve daha küçük lezyonlar (<4 cm, n=316) olarak iki gruba ayrıldı. Malignitenin bağımsız öngördürücülerini belirlemek için çok değişkenli lojistik regresyon analizi kullanıldı ve bulguların tanısal gücünü değerlendirmek için post-hoc güç analizi yapıldı.

Bulgular: Genel malignite oranı %11,5 olarak saptandı. Gruplar arasındaki malignite oranları neredeyse aynıydı: ≥4 cm grubu için %11,8 [%95 güven aralığı (GA): %7,7-17,7] ve <4 cm grubu için %11,4 (%95 GA: %8,3-15,4) (p=1,000). Çok değişkenli analizde, ≥4 cm nodül boyutunun malignite için anlamlı bir belirleyici olmadığı görüldü (olasılık oranı: 1,04, %95 GA: 0,58-1,86, p=0,885). Post-hoc güç analizi, gözlemlenen farkın klinik olarak ihmal edilebilir olduğunu doğruladı (Cohen's h=-0,013). Papiller ve foliküler karsinomlar dahil olmak üzere histolojik alt tiplerde boyuta göre anlamlı bir fark saptanmadı (p>0,05).

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ÖZ

Sonuç: Benign sitolojiye sahip hastalarda nodül boyutu, malignite öngörüsünde yetersiz bir bağımsız kriterdir. Cerrahi olarak seçilmiş bu kohorttaki bulgularımıza dayanarak, klinik karar verme sürecinde yalnızca boyut eşiklerine güvenilmemelidir. Bunun yerine, hasta sonuçlarını optimize etmek ve gereksiz ameliyatları azaltmak için ultrasonografik risk özelliklerini ve multidisipliner değerlendirmeyi içeren entegre bir strateji tercih edilmelidir.

Anahtar Kelimeler: İnce iğne aspirasyon biyopsisi, gizli malignite, tiroid kanseri, tiroid nodülü

INTRODUCTION

Thyroid nodules are frequently encountered in clinical practice, and determining whether these nodules are benign or malignant is of great importance. The American Thyroid Association (ATA) guidelines recommend ultrasound-guided (US) biopsy for nodules >1 cm when suspicious features are identified on imaging (1). The biopsy results are classified into six categories based on the Bethesda system: non-diagnostic, benign, atypia of undetermined significance (AUS), follicular neoplasm, suspicion of malignancy, and malignant pathology. The Bethesda reporting system estimates a minimal risk of occult malignancy, typically spanning from 0% to 3%, for thyroid lesions initially diagnosed with benign cytopathology (2). These findings underscore that a benign cytological diagnosis does not entirely preclude the presence of malignancy, thereby mandating a rigorous and individualized clinical assessment.

Existing literature provides conflicting evidence as to whether a diameter exceeding 4 cm is an independent risk factor for thyroid carcinoma. While some authors suggest that increasing size correlates with a higher risk of malignancy, others maintain that size alone is a poor predictor of oncological outcomes. On the other hand, there is evidence suggesting that the sensitivity of fine needle aspiration biopsy (FNAB) may be compromised in the setting of macro-nodular disease, leading to disproportionately higher rates of missed malignancies compared to smaller nodules (3). Furthermore, certain clinical perspectives recommend immediate surgical intervention for large-volume nodules, regardless of their cytological status (4). This "size-based" surgical philosophy, however, remains a subject of intense debate, as it may lead to over-treatment of inherently benign lesions. Such discrepancies in the literature complicate the surgical decision-making and clinical triage for patients presenting with significantly enlarged nodules.

The primary objective of this research was to evaluate the correlation between thyroid nodule dimensions and clinical outcomes, specifically focusing on the comparative analysis of malignancy incidence and the rates of malignancies detected postoperatively between nodules ≥4 cm and those <4 cm. Using a large cohort of nodules that were benign preoperatively, this study aims to provide a robust framework for managing these nodules and optimizing clinical decision-making for surgery.

METHODS

A total of 1090 patients who underwent thyroid surgery at our clinic between January 2016 and December 2019 were retrospectively reviewed. The inclusion criteria comprised patients aged ≥18 years with preoperative benign thyroid cytology who subsequently underwent thyroidectomy at our institution. We excluded patients under the age of 18, patients without available preoperative biopsy results, and patients diagnosed with diffuse goiter or with an absence of nodules. Additionally, any cytological findings other than benign—including AUS, follicular neoplasms, suspicion of malignancy, and overt malignancy—as well as cases with missing clinical data were removed from the study cohort. The patient selection process is detailed in the study flow diagram (Figure 1). As a result, 477 patients were included in the study.

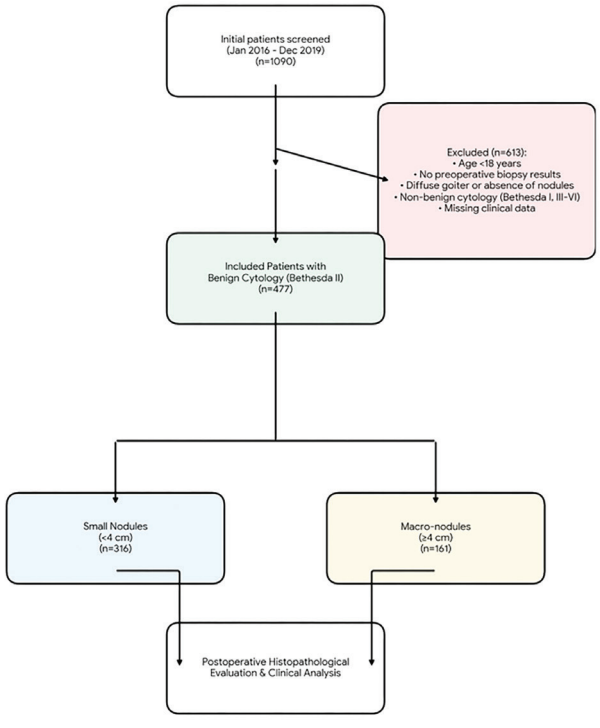

Figure 1. Flowchart of the patient selection process

The study population was categorized into two distinct cohorts according to a nodule diameter threshold of 4 cm: those with macro-nodules (≥4 cm) and those with smaller lesions (<4 cm). The patients' parameters, including gender, age, nodule size, postoperative pathology results, and histological subtypes, were retrospectively analyzed.

US-FNAB was systematically targeted at either the most sonographically suspicious lesion or the dominant nodule. The biopsy results were evaluated according to the Bethesda classification, and the cytological diagnosis was determined (2).

Surgical intervention was recommended based on several clinical criteria. For the macro-nodule group (≥4 cm), the primary indications were size-related concerns, including local compressive symptoms (dysphagia, neck pressure), potential for substernal extension, and the inherent risk of sampling failure in large lesions. For nodules <4 cm, surgery was indicated due to suspicious sonographic features (e.g., irregular margins, microcalcifications), rapid growth during follow-up, patient preference (anxiety regarding malignancy risk), or planned treatment for concomitant hyperthyroidism. Our institutional clinical approach followed the current evidence-based framework of the ATA guidelines (1).

This study was conducted after approval was obtained from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Research and Training Hospital Non-Interventional Clinical Research Ethics Committee (approval no: 2025-03-18, date: 05.02.2025).

Statistical Analysis

Statistical analyses were performed using Jamovi (version 2.3; the Jamovi project, 2022). Normality of continuous variables was assessed using the Shapiro-Wilk test and visual inspection of Q-Q plots. Quantitative outcomes were reported as mean ± standard deviation or median (minimum-maximum) as appropriate. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate. To identify independent predictors of malignancy, a multivariate logistic regression model was constructed, including age, gender, and nodule size as covariates. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to estimate the strength of associations. Furthermore, post hoc power analysis and effect-size estimation (Cohen's h) were performed to evaluate the diagnostic strength of comparisons of the primary outcomes. Statistical significance for all comparative analyses was predefined at a threshold of $p<0.05$.

RESULTS

The study included 477 cases, of whom 21.8% (n=104) were male and 78.2% (n=373) were female. The study cohort exhibited an age range of 18 to 80 years, with a calculated mean age of 47.6±13.1 years.

The overall malignancy rate in the study population was 11.5% (n=55/477). The malignancy rate was 11.4% (95% CI: 8.3-15.4%) in the <4 cm group and 11.8% (95% CI: 7.7-17.7%) in the ≥4 cm group. The overlapping CIs further support the absence of a statistically significant difference between the two cohorts (p=1.000) (Tables 1 and 2; Figure 2). In the multivariate logistic regression analysis, within the limits of the current regression model adjusted for age and sex, nodule size ≥4 cm did not emerge as a significant predictor of malignancy (OR: 1.04, 95% CI: 0.58-1.86, p=0.885) after adjusting for age and gender. A post-hoc power analysis was performed using the observed effect size (Cohen's h=-0.013). The analysis indicated that, given the nearly identical

Table 1. Comparative analysis of demographic data and clinical characteristics between the study cohorts

		Nodule ≥4 cm, n (%)	Nodule <4 cm, n (%)	p-value
Sex	Male	37 (7.8)	67 (14)	[b]0.65
	Female	124 (26)	249 (52.2)	
Age	Mean±SD	48.1±12	47.2±14	[a]0.48
	Median (min-max)	48 (23-80)	47.5 (18-80)	
Nodule size	Mean±SD	50.2±10.1	25.1±9.4	[c]<0.001*
	Median (min-max)	47 (40-94)	26 (3.5-39)	
Postoperative pathology	Benign	142 (88.2)	280 (88.6)	[d]1.00
	Malign	19 (11.8)	36 (11.4)	
Histological diagnosis	Benign	142 (88.2)	280 (88.6)	[d]0.89
	Papillary microcarcinoma	6 (3.7)	13 (4.1)	
	Papillary carcinoma	11 (6.8)	21 (6.6)	
	Follicular carcinoma	2 (1.2)	2 (0.6)	

SD: Standard deviation, [a]: Student-t test, [b]: Pearson chi-square test, [c]: Mann-Whitney U test, [d]: Fisher's exact test, *p<0.05

malignancy rates between the two groups, the study was not powered to detect such a negligible difference, thereby reinforcing the conclusion that nodule size alone does not clinically alter malignancy risk in this cohort. Similarly, no significant correlation was observed between nodule dimensions and specific histological subtypes, including papillary and follicular carcinomas (p>0.05) (Table 3).

Histopathological examination of the 55 malignant cases identified 32 cases of papillary thyroid carcinoma, 19 cases of papillary microcarcinoma, and 4 cases of follicular carcinoma (Table 1 and Figure 3). Histopathological examination identified 55 malignant cases. Of these, 19 (34.5%) were classified as incidental papillary thyroid microcarcinomas (iPTMCs), defined as tumors ≤10 mm in diameter that were not the primary target of the preoperative FNAB. After excluding these incidental cases, the clinical malignancy rate attributable to the targeted nodules was 7.5% (n=36/477).

Table 2. Comparison of malignancy rates with 95% CIS

Variable	<4 cm (n=316)	≥4 cm (n=161)	p-value
Malignancy rate, n (%)	36 (11.4%)	19 (11.8%)	1.000[d]
95% CI*	8.3%-15.4%	7.7%-17.7%	-

CI: Confidence interval, [d]: Fisher's exact test, *Calculated using the Wilson score method

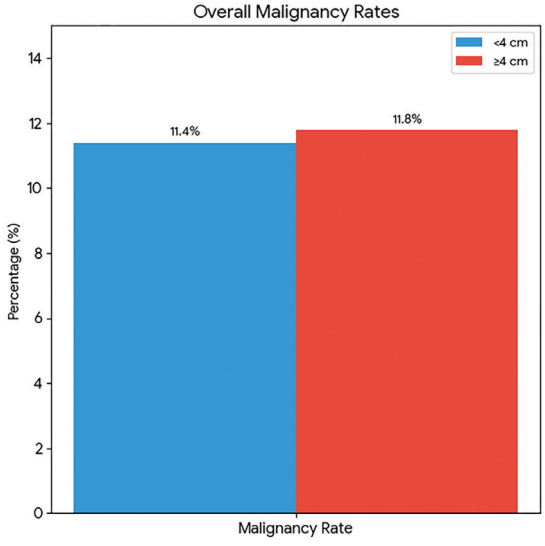

Figure 2. Comparison of overall malignancy rates between thyroid nodules <4 cm and ≥4 cm

Table 3. Multivariate logistic regression analysis of risk factors for malignancy

Variables	OR	95% CI	p-value
Age (>45 years)	1.12	0.85-1.48	0.420
Gender (male)	1.08	0.72-1.62	0.710
Nodule size (≥4 cm)	1.04	0.58-1.86	0.885

OR: Odds ratio, CI: Confidence interval

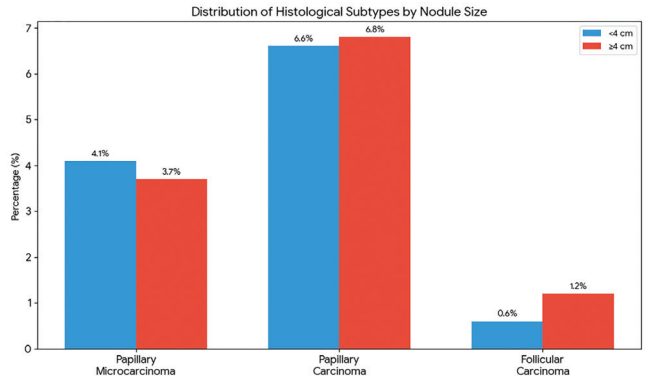

Figure 3. Distribution of histological malignancy subtypes stratified by nodule size

No statistically significant differences were identified between the study groups with respect to clinical parameters such as age, sex, and postoperative histological classifications (p>0.05).

DISCUSSION

The present investigation indicates that the incidence of postoperative malignancy does not differ significantly between thyroid nodules exceeding 4 cm and smaller nodules in patients with a preoperative benign cytological diagnosis. However, relatively high malignancy rates of 11.8% and 11.4% were observed in the two groups, respectively.

According to the ATA guidelines, no additional diagnostic methods or treatments are required for nodules with benign cytology. While prior investigations have reported malignancy incidences as low as 3.2% in benign cytology, our findings demonstrate a notably higher rate of 11.8% (5). This elevated rate likely points to technical challenges, including sampling errors—particularly in large or multinodular goiters, where the most suspicious focus may be missed—and the inherent diagnostic limitations of cytopathological interpretation. Furthermore, interobserver variability among cytopathologists may contribute to the higher-than-expected incidence of malignancy in lesions initially classified as benign. The inclusion of iPTMCs in our analysis is another key contributor to our reported malignancy rate. While these microlesions might not have been targeted by the initial FNAB, they represent a significant finding in the surgical specimens of patients with macronodular disease. Additionally, the standardized surgical indications used in our clinic help to contextualize the selection of certain

benign nodules for resection. Our findings highlight that the potential for malignancy should not be overlooked in the management of nodules with benign cytology. Future studies incorporating molecular testing or more stringent repeat-biopsy protocols could help mitigate these diagnostic errors.

Our institutional data revealed that the incidence of malignancy identified postoperatively in patients with benign cytology was 11.8% in the ≥4 cm cohort, which was comparable to the 11.4% observed in nodules below this size threshold. The literature reports occult malignancy rates in thyroid cytopathology that range from 3% to 24% (6-10). In multinodular glands, malignancy may arise from a non-biopsied nodule rather than the one targeted by FNAB. Therefore, these rates may reflect incidental malignancies or sampling limitations associated with multinodular disease rather than a technical failure of the cytopathological analysis. However, our study demonstrated that nodule size does not significantly influence the risk of a missed malignancy. Our findings demonstrate that a 4 cm diameter threshold does not reliably predict malignancy in preoperatively benign nodules. Although the literature documents a broad spectrum of false-negative outcomes, ranging 3% to 24%, our observed rate of 11.8% (95% CI: 7.3-17.9) underscores the limitations of US-FNAB for large nodules. This relatively high rate emphasizes that surgical decisions should not rely on size alone, but rather on a composite assessment of sonographic risk features and clinical judgment.

The debate continues regarding whether large nodule size is a risk factor for malignancy. Some studies have found that larger nodules increase the risk of malignancy (11). On the other hand, several reports in the literature fail to demonstrate a meaningful statistical relationship between increasing nodule size and the likelihood of a malignant diagnosis (12,13). According to our institutional results, nodule diameter was not a decisive predictor of thyroid carcinoma in patients preoperatively diagnosed with benign cytology. In the multivariate analysis, within the limits of the current regression model adjusted for age and sex, nodule size ≥4 cm was not a significant predictor of malignancy. We recognize that a more comprehensive model including sonographic risk features (such as microcalcifications, irregular margins, and hypoechoic appearance) and clinical risk factors (e.g., family history or radiation exposure), would provide a more nuanced understanding of the risk of malignancy. While our analysis focused on challenging the independent reliability of nodule size, sonographic characteristics remain the cornerstone of thyroid nodule triage. This finding is statistically supported by our post-hoc power analysis (Cohen's h=-0.013), which confirmed that the observed difference was clinically negligible. Consequently, our data reinforce the premise that nodule size alone is insufficient as an independent predictor for surgical intervention in the specific population referred for thyroidectomy. This observation might be influenced by our specific focus on patients who were preoperatively classified in the benign Bethesda category. While these results may not be directly applicable to all conservatively managed thyroid nodules in the general population, they provide critical evidence for the surgical management of macronodules.

The literature recommends direct surgical removal for large thyroid nodules (4). However, other studies have shown that nodule size alone is not a decisive factor in surgical decision-making (14,15). In our cohort, we observed that the false-negative rate remained high regardless of size, suggesting that the "size-rule" for surgery may lead to overtreatment of benign disease without significantly improving detection of malignancy. While nodule diameter is an insufficient independent predictor of the need for surgery, clinicians must remain cognizant of the elevated potential for false negatives, which warrants a highly individualized, cautious follow-up protocol. The reliability of cytology, especially in large nodules, should be questioned, and results should be supported by repeat biopsies. In the surgical decision-making process, nodule size alone is not sufficient; clinical and pathological factors must also be considered. This approach can prevent unnecessary surgeries while enabling early detection of the risk of malignancy.

Adherence to the ATA guidelines, the use of the Bethesda classification, and procedures performed by specialized professionals enhance the study's alignment with international standards. Compliance with international standards increases the reliability of our data and the scientific value of the study. With these strengths, our study can contribute to clinical practice and serve as a foundation for future research.

Study Limitations

We must acknowledge the presence of a significant selection bias inherent in our study design, as our cohort consists exclusively of surgically treated patients. In our clinical practice, nodules ≥4 cm were often operated on based on size alone, whereas smaller nodules (<4 cm) typically required additional indications for surgery, such as compressive symptoms or suspicious sonographic features. This discrepancy in surgical indications, known as indication bias, means that our findings primarily apply to patients already selected for surgical intervention and may

not be generalizable to the broader population of patients with benign thyroid nodules managed conservatively. Additionally, interpretations of these findings are constrained by the study's single-institution scope and retrospective methodology, which may limit the broader applicability of the data across regions with differing iodine status. Additionally, the more selective approach to surgical decision-making for benign nodules <4 cm may have introduced bias in this group. Specifically, smaller nodules were more likely to be operated on because of suspicious sonographic features or clinical symptoms. In contrast, macro-nodules (≥4 cm) were often sent for surgery based on size alone, which indicates a common selection bias in surgical series. This difference in surgical indications reflects the "real-world" clinical challenge where size often matters more than cytological findings in macro-nodular disease. Additionally, the high rate of occult malignancy may result from technical difficulties in sampling large-volume lesions or from differences in interpretation among cytopathologists. A significant limitation of our study is the lack of direct lesion-to-lesion correlation between the specific nodule biopsied and the final histopathological focus of malignancy. In multinodular cases, the detected cancer might represent an incidental finding in a non-targeted nodule, which precludes the calculation of a true lesion-specific false-negative rate for FNAB. Despite these limitations, our study offers a significant dataset that questions the use of size as a standalone reason for surgery.

CONCLUSION

The present investigation found that, in a surgical cohort, nodule dimensions are not independent predictors of either malignancy risk or the likelihood of postoperative detection of malignancy in cytologically benign cases.. However, we found the incidence of detected malignancies was relatively high. This finding highlights that nodule size alone is not a sufficient criterion for decisions regarding thyroid surgery. Based on our findings within this surgically selected cohort, clinical decision-making should avoid relying solely on size thresholds. Instead, management should favor an integrated strategy incorporating sonographic risk features and multidisciplinary evaluation to optimize patient outcomes and reduce unnecessary surgeries.

ETHICS

Ethics Committee Approval: This study was conducted after approval was obtained from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Research and Training Hospital Non-Interventional Clinical Research Ethics Committee (approval no: 2025-03-18, date: 05.02.2025).

Informed Consent: Due to its retrospective nature, informed consent was waived.

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FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: B.A., F.C., S.B., A.G., D.G., Concept: B.A., H.A., S.B., A.G., D.G., Design: B.A., H.A., F.C., A.G., D.G., Data Collection or Processing: B.A., S.B., Analysis or Interpretation: B.A., S.B., D.G., Literature Search: B.A., F.C., Writing: B.A., H.A., F.C., S.B., A.G., D.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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