



# Malignancy risk in Bethesda class IV thyroid nodules in an iodine deficient region

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**Background:** According to the latest guidelines, in patients with high-risk nodules with indeterminate cytology, diagnostic lobectomy should be the preferable surgical approach in the absence of factors that suggest a total thyroidectomy.

**Methods:** This retrospective observational study has as its main aim the evaluation of the cases that underwent surgery, for Bethesda class IV nodules in our iodocarent geographical area. Particular attention was paid to carcinoma incidence, preoperative nodule size, histological characteristics of the neoplasm, surgical approach and eventual need of radiometabolic treatment. A total of 320 patients were included that underwent surgery for Bethesda IV nodules, between January 2010 and December 2020, at the General Surgical Clinic of the University Hospital of Parma, Italy.

**Results:** A total of 230 total thyroidectomies (71.9%) and 90 lobectomies (28.1%) were performed. Our data showed a strong impact of the 2015 ATA Guidelines on the surgical approach choice, with a progressive propensity towards a conservative approach and an increase of lobectomies from 7.2% to 41.5% after the new guidelines introduction. However, in our sample the percentage of lobectomies remains below 50%; this data is certainly influenced by the number of cases of multinodular pathology, often bilateral, in our geographical area. The nodules malignancy rate resulted 28.8%. Our data showed that increasing size correlated with an increasing malignancy rate ( $P < 0.01$ ), and follicular carcinomas were found to be larger than papillary carcinomas ( $P < 0.001$ ). A statistically significant correlation also emerged between nodule size increase and local/lymphovascular invasion ( $P < 0.05$ ). On the other hand, there was no statistically significant correlation between nodule size and multifocality, and between nodule size and presence of lymph node metastases. Out of the patients where it was possible to find this data, 66% underwent radioiodiomietabolic treatment: 59% with papillary carcinoma, and 85% with follicular carcinoma.

**Conclusions:** In patients with Bethesda IV thyroid nodules, diagnostic lobectomy should be the preferable surgical approach in absence of factors that suggest total thyroidectomy. In our opinion, total thyroidectomy remains the first choice in large nodules ( $\geq 4$  cm) as these nodules have a high malignancy rate, greater local/lymphovascular invasion and a consequent frequent indication for post-operative radiometabolic treatment.

**Keywords:** Indeterminate cytology; Bethesda system; thyroidectomy; lobectomy

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## Introduction

Thyroid cancer is the most frequent neoplasm of the endocrine system and accounts for approximately 3.8% of all neoplasms (1).

It is well established that iodine is essential for thyroid homeostasis. In addition to the known effects on glandular function, chronic iodine deficiency can favor the development of goiter or an increase in the incidence and prevalence of benign nodularities (2). The relationship with thyroid cancer remains controversial and the different studies that have investigated this correlation are not in agreement. A study has shown an increased risk of developing thyroid carcinoma in populations living in iodine-deficient areas, with a higher prevalence of follicular carcinoma (3).

American Thyroid Association (ATA) and most European guidelines consider cytological examination by needle aspiration the gold standard for the evaluation and management of thyroid nodular pathology (1,4,5).

For thyroid nodules cytological evaluation, the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) is one of the most used classifications. The BSRTC defines six diagnostic categories with increasing suspicious characteristics for malignancy: nondiagnostic (Class I), benign (Class II), atypia of indeterminate meaning/follicular lesion of indeterminate meaning (Class III), follicular neoplasm/Oxifilics neoplasm (Class IV), suspicious for malignancy (Class V), malignant (Class VI) (6).

The lesions included in Bethesda class IV are characterized by high cellularity, poor or absent colloid and absolute prevalence of microfollicular/trabecular structures, with characteristics suggestive of “follicular neoplasia”. Lesions with some nuclear alterations suggestive of papillary carcinoma but too mild or focal to include them in the category V are also included in this category.

The 2015 ATA guidelines suggest the following surgical management for nodules with indeterminate cytology:

- ❖ In patients with solitary indeterminate nodule candidate for surgery, thyroid lobectomy is the initial recommended surgical approach. This approach can be modified according to clinical or ultrasound nodule characteristics, patient’s preferences, or molecular test outcomes.
- ❖ In patients with cytologically indeterminate nodules suspicious for malignancy, with a positive finding for specific mutations for carcinoma, with suspicious ultrasound patterns, with size greater than 4 cm, or in patients with familial thyroid cancer or a history of radiation exposure, total thyroidectomy should be preferred.
- ❖ In patients with bilateral nodules, with important comorbidities or in case the patient prefers to undergo total thyroidectomy, to avoid the possibility of further surgery on the contralateral lobe, total thyroidectomy is indicated (4).

Total thyroidectomy is a more riskful procedure than thyroid lobectomy and has a higher complication rate. A recent meta-analysis describes a higher relative risk (RR) of major complications: recurrent laryngeal nerve injury (transient RR =1.7, permanent RR =1.9), hypocalcemia (transient RR =10.7, permanent RR =3.2) and haemorrhage/hematoma (RR =2.6) (7).

According to most guidelines the possible risks and benefits of the various surgical procedures must be exposed to the patient to decide the best therapeutic option (1,4).

The main aim of our study is the evaluation of the cases that underwent surgery for Bethesda class IV nodules in an iodocare geographical area, such as the province of Parma, with particular attention to: carcinoma incidence, preoperative nodule size, histological characteristics of the neoplasm, surgical approach and eventual need of radiometabolic treatment. We present this article in accordance with the STROBE reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/gS-22-491/rc>).

### Highlight box

#### Key findings

- Increasing size correlated with an increasing malignancy rate ( $P < 0.01$ ), and follicular carcinomas were found to be larger than papillary carcinomas ( $P < 0.001$ ).

#### What is known and what is new?

- In patients with Bethesda IV thyroid nodules, diagnostic lobectomy should be the preferable surgical approach in absence of factors that suggest total thyroidectomy. In our opinion, total thyroidectomy remains the first choice in large nodules ( $\geq 4$  cm) as these nodules have a high malignancy rate, greater local/lymphovascular invasion and a consequent frequent indication for post-operative radiometabolic treatment.

#### What is the implication, and what should change now?

- An accurate preoperative study is essential to decide, in accordance with the patient, the best surgical approach.

## Methods

This retrospective observational study has as its main aim the evaluation of the cases that underwent surgery, for Bethesda class IV nodules in our iodocarent geographical area. Particular attention was paid to: carcinoma incidence, preoperative nodule size, histological characteristics of the neoplasm, surgical approach and eventual need of radiometabolic treatment.

We analyzed data of patients that underwent thyroid surgery for nodules with high-risk indeterminate cytology, Bethesda class IV, in the period between January 2010 and December 2020 at the Operative Unit of the General Surgical Clinic of the University Hospital of Parma, Italy.

Exclusion criteria were: preoperative evidence of malignancy; missing essential clinical data; residence in a non-iodine-deficient region.

We analyzed the following variables: age; gender; date of surgery (pre/post introduction of ATA 2015 guidelines); type of surgery (lobectomy *vs.* total thyroidectomy); possible need for thyroid totalization surgery; cytological diagnosis: Bethesda class IV (TIR 3B cases according to SIAPEC-IAP, Italian Society for Anatomic Pathology joint with the Italian Division of the International Academy of Pathology, have been reclassified as class IV according to Bethesda System 2017); nodule size found during preoperative investigations; multinodularity; presence of bilateral nodules; postoperative histological report; postoperative size of the nodules that resulted carcinoma; histopathological characteristics (local or vascular invasion, multifocality, lymph node metastasis); eventual execution of radioiodiomatabolic therapy.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of University Hospital of Parma (No. 84/2022/OSS\*/AOUPR), and informed consent was taken from all individual participants.

### Statistical analysis

Data analysis was performed with the Jamovi v. Statistical package. 2.0 [The jamovi project (2021). Jamovi. (Version 2.0) (Computer Software). Retrieved from <https://www.jamovi.org>].

For the descriptive analysis of the continuous variables, main position, dispersion, and shape indices were calculated, including mean, median, mode, trimmed mean at 5%, variance, standard deviation, interquartile difference, minimum, maximum. Where relevant, standard errors and

related 95% confidence intervals have also been reported. Qualitative characters were reported in frequency tables and expressed as absolute frequencies, relative frequencies, and percentages. Fisher's exact test and Pearson's Chi-square test were used for categorical variables. Cramer's V Index was used to evaluate the association between the variables. Other analyzes were performed considering nodule size as a continuous variable. We used Student's *t*-test, Welch's test, Mann-Whitney's *U*-test, analysis of variance (ANOVA), and Kruskal-Wallis test. We used Fisher, Pearson's Chi-Square test and binary logistic regression to evaluate the association between preoperative nodule size and malignancy rate, and to evaluate the association between nodule size and local/lymphovascular invasion, multifocality or presence of lymph node metastases. For both continuous and categorical mutable variables, P values lower than 5% ( $P < 0.05$ ) were considered statistically significant.

## Results

In this study we included 320 patients. In our sample we found 244 females (76%) and 76 males (24%), with an average age of  $53.1 \pm 13.8$  years (range, 19–83 years). Considering 55 years as age cut off, 152 patients (47.5%) were older than 55 years and 168 patients (52.5%) were younger.

Preoperative study localized nodules in the right thyroid lobe in 165 cases (51.6%), in the left one in 136 cases (42.5%), in the isthmus in 14 cases (4.4%), bilaterally in 5 cases (1.5%).

Mean preoperative nodules size was 19.1 mm, with a maximum of 80 mm and a minimum of 6 mm. In 59 cases (18.4%) we found nodules smaller or equal to 1 cm, while in 22 cases (6.9%) we found nodules larger or equal to 4 cm. 239 nodules (74.7%) resulted to be between 1 and 4 cm (*Figure 1*).

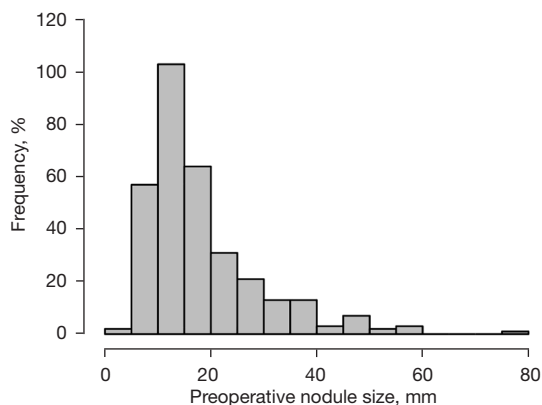
For the treatment of these nodules, 230 total thyroidectomies were performed (71.9%), 188 with the traditional technique and 42 with minimally invasive video-assisted thyroidectomy (MIVAT), and 90 hemithyroidectomies (28.1%), 52 with the traditional technique and 38 with minimally invasive video-assisted thyroidectomy (MIVAT). In 15 of the patients who underwent lobectomy (16.6% of all lobectomies performed) a totalization of thyroidectomy was required. From this analysis it emerged that in general a more demolitive surgical approach was preferred over a conservative one.

We analyzed the impact of guideline changes on the

surgical approach, evaluating separately surgeries performed before and after 2015, the year of publication of the latest ATA guidelines.

From 2010 to 2015, 125 surgical procedures were performed: 116 (92.8%) total thyroidectomies and 9 lobectomies (7.2%). From 2016 to 2020, 195 surgical procedures were performed: 114 (58.5%) total thyroidectomies and 81 lobectomies (41.5%). From our data analysis, we found an increased rate of lobectomies in the period after 2015, with a statistically significant difference ( $P < 0.001$ ) (Table 1).

We assessed the presence or absence of bilateral nodules emerged during preoperative study. Bilateral nodules were found in 127 patients (39.7%), while in 193 patients (60.3%) there weren't bilateral nodules. We therefore analyzed the type of surgical procedure in patients with or without bilateral nodules. In patient with bilateral nodules, 113 total thyroidectomies (89%) and 14 lobectomies (11%) were performed; in the absence of bilateral nodules, 117 total thyroidectomies (60.6%) and 76 lobectomies (39.4%) were performed. We found a statistically significant correlation between the presence or absence of bilateral nodules and the type of surgical procedure performed, with a significant



**Figure 1** Preoperative nodules size distribution (overview of the nodule size of the patients treated).

increase of hemithyroidectomies in absence of bilateral thyroid nodules ( $P < 0.001$ ). Also in this case, we evaluated the surgical procedures performed before and after 2015, year of publication of the latest ATA guidelines. From 2010 to 2015, in presence of bilateral nodules, 52 total thyroidectomies (100%) and 0 lobectomies (0%) were performed; in the absence of bilateral nodules, on the other hand, 64 total thyroidectomies (87.7%) and 9 lobectomies (12.3%) were performed.

From 2016 to 2020, in presence of bilateral nodules, 61 total thyroidectomies (81.3%) and 14 lobectomies (18.7%) were performed; while in absence of bilateral nodules, 53 total thyroidectomies (44.2%) and 67 lobectomies (55.8%) were performed. Also in this case we found an increase of lobectomies in the period after 2015, with a statistically significant difference ( $P < 0.001$ ) (Table 2).

The presence of single or multiple nodularities was also evaluated, regardless of bilateralism. Multiple nodularities emerged in 182 cases (56.9%), single nodularities in 138 cases (43.1%).

The postoperative histological diagnoses were divided into six groups (Table 3).

The malignancy rate of the nodules classified as Bethesda class IV was 28.8%. In 3.4% of all cases, we found a neoplasm in a nodule different from the one subjected to fine needle aspiration. Out of the 71 papillary carcinomas, 9 (12.6%) were found to have local and/or lymphovascular invasion, while out of the 21 follicular carcinomas, 17 (80.9%) were found to have local and/or lymphovascular invasion. Out of the 71 papillary carcinomas, 22 (30.9%) were multifocal, while out of the 21 follicular carcinomas, 2 (9.5%) were multifocal.

Follicular carcinomas were found to have more aggressive features than papillary carcinomas but resulted less frequently multifocal.

The average preoperative size, obtained after ultrasonography, of the nodules that resulted carcinoma on histological examination were compared with the postoperative size emerged from the anatomopathological

**Table 1** Surgical procedures performed before and after 2015

Surgeries before or after 2015	Total thyroidectomy, n (%)	Lobectomy, n (%)	Total
Before 2015	116 (92.8)	9 (7.2)	125
After 2015	114 (58.5)	81 (41.5)	195
Total	230 (71.9)	90 (28.1)	320

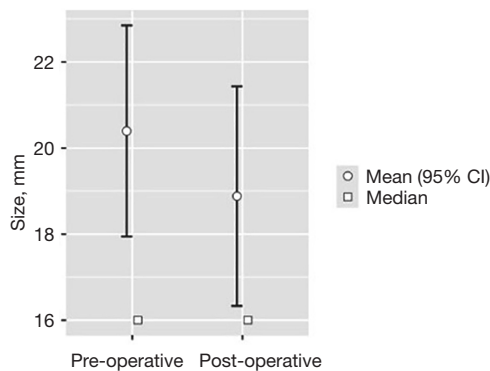
**Table 2** Surgical procedures performed before and after 2015, in the presence or not of bilateral nodularities

Surgeries before-after 2015	Bilateral nodules	Total thyroidectomy, n (%)	Lobectomy, n (%)	Total
Before 2015	No	64 (87.7)	9 (12.3)	73
	Yes	52 (100.0)	0 (0.0)	52
After 2015	No	53 (44.2)	67 (55.8)	120
	Yes	61 (81.3)	14 (18.7)	75
Total	No	117 (60.6)	76 (39.4)	193
	Yes	113 (89.0)	14 (11.0)	127

**Table 3** Postoperative histological diagnoses

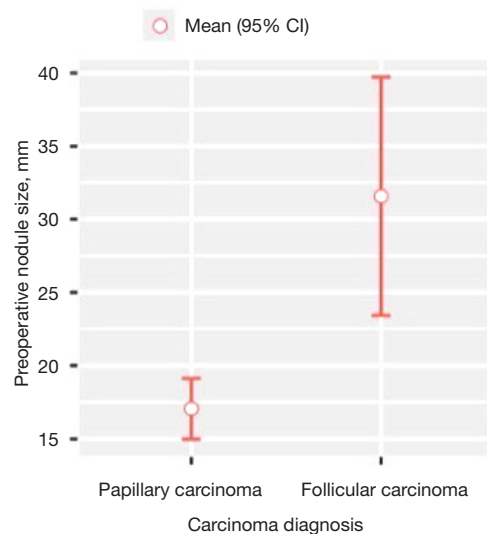
Preoperative diagnosis	N (%)
Benign neoplasm	191 (59.7)
Papillary carcinoma	71 (22.2)
Follicular carcinoma	21 (6.6)
Incidental microcarcinoma	20 (6.3)
NIFTP	6 (1.8)

NIFTP, non-invasive follicular thyroid neoplasm with papillarylike nuclear features.



**Figure 2** Comparison between pre- and post-operative size of thyroid carcinomas. CI, confidence interval.

analysis. The mean preoperative size of the carcinomas was 20.4 mm, while the postoperative one resulted 18.9 mm (Figure 2). We searched a possible correlation between the preoperative size of malignant nodules and the histotype (papillary carcinoma vs. follicular carcinoma). In our sample, follicular carcinomas were found to have an average larger size than papillary carcinomas (31.6 vs. 17.1 mm), with a statistically significant difference ( $P < 0.001$ ) (Figure 3). The size criterion was also related to the incidence of carcinoma.



**Figure 3** Correlation between preoperative size and diagnosis of papillary and follicular carcinoma lymph node metastases. CI, confidence interval.

Considering the 59 nodules smaller/equal to 1 cm, in 14 cases (23.7%) a diagnosis of carcinoma was made. Among the 239 cases larger than 1 cm but less than 4 cm, 69 (28.9%) resulted carcinomas.

Analyzing the 22 nodules larger/equal to 4 cm, the diagnosis of carcinoma was made in 9 cases (40.9%) (Table 4).

Nodule size was considered as a continuous variable, and it was found that with increasing size there was an increased malignancy rate ( $P < 0.01$ ).

Among the nodules that resulted malignant on post-operative histological examination, we analyzed the anatomopathological malignancy features, searching for a correlation between nodule size and neoplastic aggressiveness. We assessed local/vascular invasion, multifocality and presence of lymph node metastasis.



Our analysis revealed a statistically significant correlation between increased nodule size and local/lymphovascular invasion ( $P < 0.05$ ). On the other hand, no statistically significant correlation between nodule size and multifocality was found (Figure 4).

After postoperative histological examination, lymph node metastases were found in two patients, but our data did not show a statistically significant correlation between preoperative size and incidence of lymph node metastases. This finding may have been influenced by the small number of patients with lymph node metastases (Figure 5).

Considering 55 years as a cut-off, we found that patients younger/equal to 55 have a higher risk of cancer than those older than 55 ( $P = 0.004$ ). In the younger group, a malignancy rate of 35% (60 out of 168) was found, significantly higher than the older group, which showed a rate of 21% (32 out of 152 patients). On the other hand, in our study sex did not seem to influence the malignancy risk.

Finally, we analyzed the number of patients that underwent radioimetic therapy after surgery. We found those data only on 53 patients, 39 diagnosed with papillary carcinoma and 14 diagnosed with follicular carcinoma. Out of the 39 patients with papillary carcinoma, 23 (59%) underwent radiometabolic treatment, while out of the 14

patients with follicular carcinoma, 12 (86%) underwent radiometabolic treatment. A total of 35 patients (66%) resulted to need this treatment (Table 5).

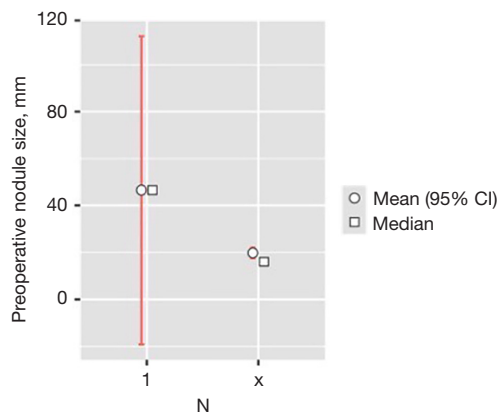
### Discussion

In the treatment of indeterminate thyroid nodules, increasing emphasis is being placed on appropriateness of care and avoidance of over-and under-treatment, since total thyroidectomy gives a complete diagnostic and therapeutic certainty in cases of thyroid carcinoma but an initial total thyroidectomy for benign disease might be considered excessive or unnecessary from an oncologic standpoint (8).

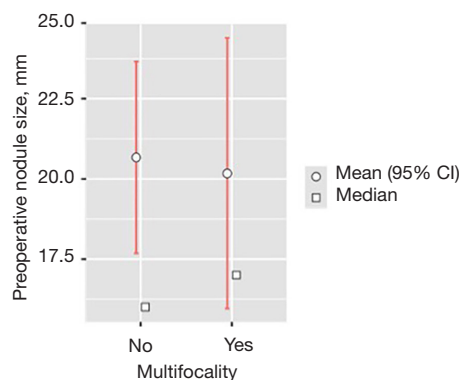
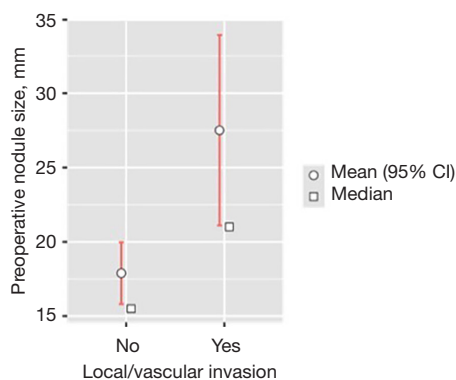
As confirmed by a recent review on the literature by Almquist (9), in patients with nodules with high-risk indeterminate cytology, diagnostic lobectomy should be the preferable surgical approach, in absence of factors that

**Table 4** Correlation between size and malignancy rate

Preoperative size	Carcinoma, n (%)		Total
	Yes	No	
≤1 cm	14 (23.7)	45 (76.3)	59
>1 to <4 cm	69 (28.9)	170 (71.1)	239
≥4 cm	9 (40.9)	13 (59.1)	22



**Figure 5** Correlation between preoperative size and lymph node metastases. CI, confidence interval; N, nodes.



**Figure 4** Correlation between preoperative size, local/vascular invasion and multifocality. CI, confidence interval.

**Table 5** Postoperative radiometabolic treatment

Postoperative diagnosis	Radiometabolic treatment, n [%]		Total
	Yes	No	
Papillary carcinoma	23 [59]	16 [41]	39
Follicular carcinoma	12 [86]	2 [14]	14
Total	35	18	53

suggest a total thyroidectomy. The 2015 American Thyroid Association guidelines include among these factors also the finding of positivity for specific mutations for carcinoma, the presence of an ultrasound pattern particularly suspicious for malignancy, size greater than 4 cm, the presence of bilateral nodules, a history of radiation exposure or the presence of familial thyroid cancer (4).

From these guidelines, it also emerged that total thyroidectomy is no longer the recommended surgical procedure for all differentiated thyroid carcinomas larger than 1 cm, lobectomy can be a sufficient initial treatment in the case of: differentiated neoplasms smaller than 4 cm, minimally invasive follicular carcinomas, non-invasive follicular thyroid neoplasm with papillarylike nuclear features (NIFTP) of all sizes, and encapsulated and intrathyroidal papillary carcinomas with follicular variant (4,10). This therapeutic approach is supported by the fact that surgery extension does not appear to have a significant effect on survival or on recurrence rate (11,12) and by the fact that lobectomies have an almost halved complication rate compared to total thyroidectomies (11% *vs.* 20%) (13). Furthermore, a conservative resection allows the preservation of glandular functionality in about 80% of cases (14), and in the need of a thyroidectomy totalization, outcome and complication rates are similar to single step total thyroidectomies (15,16).

From the data of this retrospective study, a strong impact of the 2015 ATA Guidelines emerged on the choice of the surgical approach, with a progressive propensity towards a conservative approach for the treatment of thyroid nodules with indeterminate cytology (17). We found an increase of lobectomies, from 7.2% to 41.5%, after the introduction of the new guidelines. However, in our sample the percentage of lobectomies remains below 50%; this data is certainly influenced by the number of cases of multinodular pathology, often bilateral, in our geographical area. In fact, in the analyzed sample, preoperative ultrasound study found multiple nodularities in 56.9% of cases and bilateral

nodularity in 39.7%.

Several studies have shown that rates of goiter, nodular goiter, and papillary thyroid cancer are higher in iodine-insufficient areas than in those that have sufficient iodine (18).

Iodine deficiency has been shown to increase TSH levels determining hyperplasia and hypertrophy of follicular cells (2). Iodine deficiency surely contributes to the frequent finding of multinodular pathology in our patients and often influenced the surgical procedure choice in our sample.

Therapeutic attitude also changed in patients with preoperative findings of bilateral nodularity, in fact, we found 0% of lobectomies in presence of bilateral nodules in the period prior to 2015, and 18.7% in the subsequent period.

In our series, the malignancy rate of Bethesda class IV nodules, was 28.8% as the main literature data (6).

The average preoperative size of the nodules that resulted carcinoma after histological examination was 20.4 mm while postoperative size was 18.9 mm. In our series ultrasound was confirmed as a reliable tool for assessing thyroid nodule size (4,5,19-21).

Although some studies state that there is no correlation between size increase and diagnosis of differentiated carcinoma (22,23), our data showed that preoperative thyroid nodule size, considered as a continuous variable, is correlated with an increase malignancy rate ( $P < 0.01$ ).

In our study, we found a diagnosis of carcinoma in 23.7% of the nodules with a size less/equal to 1 cm, in 29.9% of the nodules larger than 1 cm but less than 4 cm and in 40.9% of the nodules larger than 1 cm or equal to 4 cm. Therefore, a significantly higher percentage of carcinoma diagnosis emerged in nodules larger than 4 cm, compared to the one smaller than 4 cm. This supports the indication to perform a total thyroidectomy in nodules larger than 4 cm, as recommended by ATA guidelines. This finding seems in contrast with a recent multicentric study published by our group (24) in which we analyzed 761 patients that underwent thyroid surgery with indeterminate cytology nodules in the period between January 2010 and December 2018 at the General Surgery Unit of the University Hospital of Parma and at the Endocrine Surgery Unit of the "Morgagni-Pierantoni" Hospital of Forlì. In this study we found that therapeutic or diagnostic lobectomy should be the treatment of choice for most thyroid nodules with indeterminate cytology, in the absence of other indications for total thyroidectomy, regardless of the nodule size. The different result could be related to the inclusion in the prior

study of Bethesda class III nodules that have an average lower malignancy rate than class IV nodules (25).

Our data agree with a meta-analysis published in 2016 by Hammad *et al.* (26) which states that nodules size correlates with the risk of carcinoma, although according to their analysis this isn't true for nodules larger than 6 cm which, on the contrary, are more frequently benign.

In agreement with most studies (27,28), also in our analysis follicular carcinomas were found to have a greater average size than papillary carcinomas (31.6 vs. 17.1 mm), with a statistically significant difference ( $P < 0.001$ ).

A statistically significant correlation also emerged between nodule size increase and local/lymphovascular invasion ( $P < 0.05$ ). This finding is in contrast with what was stated in a recent study by Valderrabano *et al.* (29), in fact in their study they didn't find a correlation between tumor size and aggressiveness. On the other hand, the lack of correlation between size and presence of multifocality, and between size and presence of lymph node metastases, emerged from our study, was in agreement with the aforementioned work.

In our sample, in line with scientific literature (28,29), a statistically significant correlation was highlighted between age minor than 55 years and increased malignancy rate (30), while the absence of correlation between female sex and higher malignancy rate, emerged from our study, resulted in contrast to literature.

Out of the patients where it was possible to find this data, 66% underwent radiometabolic treatment: 59% of the patients with papillary carcinoma, and 85% of the patients with follicular carcinoma. This data should be analyzed considering that, in our sample, follicular carcinomas were found to have larger size and more aggressive characteristics than papillary carcinomas; in fact, local and/or lymphovascular invasion was found in 80% of cases, compared to 12.6% of papillary carcinomas. It may be that in our sample we found follicular carcinoma in more advanced stage because the more aggressive papillary cancers are not diagnosed as Bethesda class IV on fine needle aspiration but may rather be diagnosed in Bethesda class V or VI. Radioiodiomatabolic treatment was assessed only in 53 patients, so this data still has relative reliability.

In agreement with scientific literature in our series minimally invasive video-assisted thyroidectomy (MIVAT) resulted a feasible technique for the treatment of various patients with Bethesda class IV nodules (31-36).

It is now established that the type of surgical approach

must be discussed with the patient, considering both malignancy risk emerged from the preoperative study and patient's will.

This study has some limitations due to the retrospective nature of the study and to the fact that it is a single institution analysis, maybe a bigger sample of patients could enforce the reliability of the results.

## Conclusions

As confirmed by the latest guidelines, in patients with Bethesda class IV thyroid nodules, diagnostic lobectomy should be the preferable surgical approach, in the absence of factors that suggest a total thyroidectomy.

In an iodocarent geographical area, such as the province of Parma, the presence of cases of multinodular pathology, often bilateral, is frequent and influences the surgical approach.

Our analysis shows a statistically significant correlation between preoperative size of indeterminate nodules, Bethesda class IV, and increased malignancy rate, in particular for follicular carcinomas. Therefore, in our opinion, total thyroidectomy remains the first choice for the treatment of large nodules ( $\geq 4$  cm) as these nodules have a high malignancy rate, greater local/lymphovascular invasion and a consequent frequent indication for post-operative radiometabolic treatment.

An accurate preoperative study is essential to decide, in accordance with the patient, the best surgical approach.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://gs.amegroups.com/article/view/10.21037/gS-22-491/rc>

*Data Sharing Statement:* Available at <https://gs.amegroups.com/article/view/10.21037/gS-22-491/dss>

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*Conflicts of Interest:* All authors have completed the ICMJE



uniform disclosure form (available at <https://gs.amegroups.com/article/view/10.21037/gs-22-491/coif>). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of University Hospital of Parma (No. 84/2022/OSS\*/AOUPR), and informed consent was taken from all individual participants.

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