

## Research Article

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## Predictive Factors of Lymph Node Involvement in Differentiated Thyroid Cancers

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### ABSTRACT

**Introduction:** Thyroid cancer is the most common type of endocrine malignancy. The objective of our study was to determine the pre and intraoperative predictive factors of lymph node involvement in differentiated thyroid cancers.

**Material and methods:** This is a prospective observational and single-center study over a period of 48 months involving a total of 101 patients diagnosed with papillary thyroid carcinoma without evidence of pre- and intraoperative lymph node metastases (cN0). All patients underwent total thyroidectomy with bilateral prophylactic central dissection performed immediately.

**Results:** The average age of the male patients was 44.11 years (standard deviation of 14.56), with no significant difference with that of the female sex 46.29 (standard deviation = 15.41). Nodal invasion (pN1a) is found in 22.77% of whom 17/23 are under 55 years old (73.91%) against 6/23 (26.08%) of patients whose age is  $\geq 55$  years. Lymph node invasion ipsilateral to the CPT is found in 9.90% on the left and 10.89% on the right. Bilateral central invasion is found in 2/23 patients, i.e. (1.98%), the number of metastatic nodes varied from 1 to 11 nodes. Extracapsular extension and angioinvasion were significant risk factors for lymph node involvement with p values respectively ( $p=0.04$  and  $p=0.050$ ).

**Conclusion:** Adequate understanding and application of prognostic factors is currently our best approach to optimize individual decision-making in patients. In our study a primary tumor size  $>2.0$  cm, extracapsular spread and angioinvasion were significantly correlated risk factors for lymph node metastasis with a number of metastatic nodes qualifying these patients as an intermediate risk group for recurrence according to ATA guidelines. These patients will benefit from prophylactic central dissection even in the absence of clinically evident central compartment lymphoganglion metastasis.

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### Introduction

Differentiated thyroid carcinoma (DTC) generally has an excellent prognosis, with adult survival rates of 92 - 98% at 10 years of follow-up [1]. However, it frequently tends to metastasize and often precociously to regional lymph nodes in the central compartment, 5 - 20% of patients develop local or regional recurrence requiring further treatment and 10 - 15% develop distant metastases [1].

In practice it remains difficult to identify which patients have a central lymph node metastasis (CLMN) before the initial surgery because, contrary to the lateral compartment, the lymph node evaluation of the central compartment by ultrasound remains difficult due to the presence of the gland thyroid above especially if it is enlarged, nodular or inflamed and in particular in patients with a short and/or kyphotic neck [2].

Surgical resection remains the mainstay of treatment for PTC. whether prophylactic central dissection should be performed in

all cases of CPT, even if no lymph nodes are clinically detectable (cN0), is still a matter of discussion [3–5]. This is mainly due to the unique characteristics of CPT, including the large difference between a high rate of occult lymph node metastasis up to 50-70%[6]at initial presentation, but only a small proportion 5-10% of these metastases progress to clinically significant disease, and having a limited or non-existent impact on long-term results, and also because it is associated with a significant surgical risk and potential sequelae [6].

The objective of our study was to determine the pre and intraoperative predictive factors of lymph node involvement in differentiated thyroid cancers.

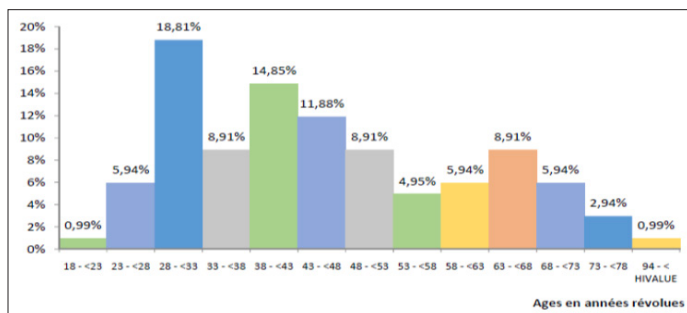
### Material and methods

We conducted a monocentric, observational study with prospective collection of results, patients operated for low-risk CPT papillary thyroid carcinoma (T1N0, T2N0) without clinically or sonographically detectable adenopathy (cN0) over a period of 48 months at the general surgery department B, of the central army hospital Dr Mohamed Seghir Nekkache. All the patients

were treated by total thyroidectomy with bilateral “prophylactic” dissection of levels VI and VII of the central compartment performed immediately.

**Results**

The average age of the male patients was 44.11 years (standard deviation of 14.56), with no significant difference with that of the female sex 46.29 (standard deviation = 15.41), the sex ratio was 0.35 (Graph. No. 1).



**Graph No 1:** Distribution of patients by age

The size of the CPT ≤ 2cm is found in 71.28% of patients with a clear predominance for microcarcinomas ≤ 1 cm (T1a) i.e. a frequency of 46.53% (95% CI [36.55-56.73]). A non-negligible frequency is recorded of 28.71% for tumors classified as T2 (95% CI [20.15-38.57]). Tumors were considered multifocal if 2 foci were found in one or two lobes. In the case of the multifocal tumor, the largest dimension was used for statistical analysis. At histology, the tumor was multifocal in 24.74% of patients (95% CI [16.70-34.33]) and bilateral in 18.81% (95% CI [11.72-27.81]) (Board. No. 1). Classic PTC is found in 93.06% of cases (95% CI [88.10-98.02]), in 6.93% of cases, aggressive cells were found (95% CI [1, 98-11.88]).

**Board No 1: Nodal involvement: Multivariate analysis of preoperative factors**

Associated factor	Adjusted RR	95% CI	Pvalue
Gender Male / Female	2.50	0.61-10.32	0.20
Tumor size T1b/T1a T2/T1a	3.53 7.2019	0.56-22.2266 1.35-38.26	0.18 0.0177
Histological type Classic CPT aggressive type	0.86	0.08-9.73	0.90
Multifocality	6.68	0.75-59.56	0.09
Bilaterality	0.76	0.07-8.21	0.82
Extracapsular extension	6.16	0.97-39.12	0.043
Angioinvasion	4.94	0.94-26.02	0.0500

A positive lymph node invasion (pN1a) is found in 22.77% (95% CI [15.02-32.18]) of which 17/23 are under 55 years old (73.91%) against 6/23 i.e. (26.08%) patients whose age is ≥ 55 years. lymph node invasion ipsilateral to the CPT is found in 9.90% on the left (95% CI [4.08-15.72]) and 10.89% on the right (95% CI [6.34-19.46]). Bilateral central invasion is found in 2/23 patients (1.98%).

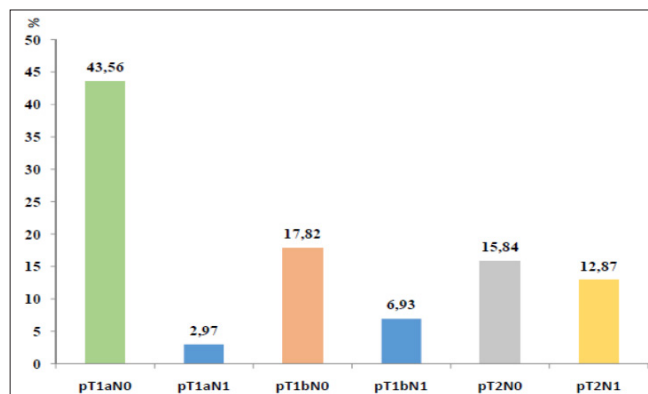
The number of metastatic nodes varied from 1 to 11. 5/23 patients or 21.74% had more than 5 metastatic nodes which immediately classified them at intermediate risk in the ATA (American Thyroid

Association) classification. In this sample, 1/23 patient (4.35%) (95% CI [0.11-21.95]) had one node with extranodal extension and 1 other patient had 2 nodes with extranodal extension (Table 2).

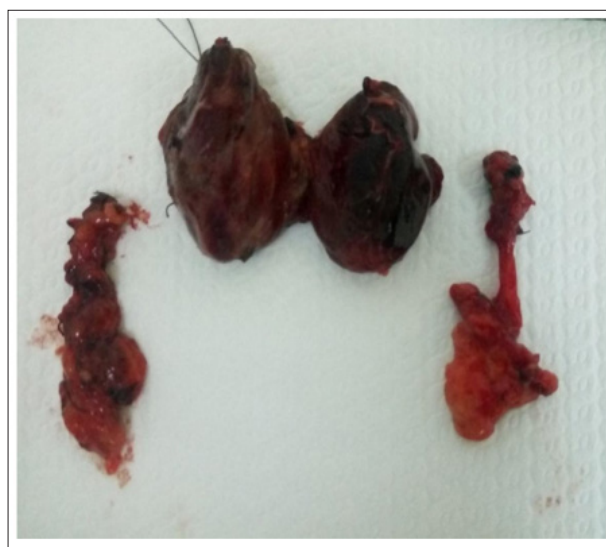
**Table 2: Distribution of patients according to the number of lymph nodes invaded**

Number of GG invaded	n	%	interval of confidence a 95%
1	5	21,74	20,46-30,40
2	6	26,09	21,46-39,40
3	1	4,35	0,37-8,33
4	3	13,04	3,20-14,20
5	3	13,04	3,20-14,20
6	1	4,35	0,37-8,33
7	1	4,35	0,37-8,33
11	3	13,04	3,20-14,20
Total	23	100,00	

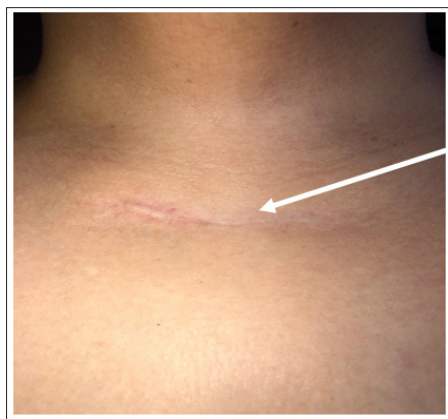
All tumors with positive node involvement (N1) are classified according to the 8th edition pTNM classification. The highest frequency, 12.87% (95% CI [7.04-21.00]), is recorded for large pT2N1 tumors, especially for patients under 55 years of age, 15.07% of whose tumors are classified as pT2N1 (Graph. No. 2).



**Graph No 2:** Distribution of patients according to pTNM classification



**Figure:** Wire Oriented Total Thyroidectomy Piece at the level of the upper right pole with cleaning bilateral center. CHB/HCA



**Figure:** Cervicotomy scar

## Discussion

It is widely accepted that cervical lymph node metastases are a major cause of local recurrence of CPT and may also influence patient survival.[7,8]. Nixon et al. in their study showed that reoperation for recurrent PTC was relatively difficult and could significantly increase surgical complications that would affect patients' quality of life.[8]. Thus, the treatment of the cervical lymph nodes during the initial surgery is very important for the prognosis of the patients. Central compartment assessment and management is therefore primarily aimed at reducing central cervical recurrence, and therefore decreasing the need for reoperation to an absolute minimum. We believe that adequate discovery, understanding and application of prognostic factors is currently our best approach to optimizing decision making in patients.

In our series we show that 23/101 or 22.77% of the patients (cN0), had positive metastases which classified them (pN1a) in the TNM/AJCC classification, namely that all the patients had benefited from a high resolution cervical ultrasound in preoperative which had not identified the presence of lymph nodes in the central compartment, and that the number of metastatic lymph nodes in the prophylactic central dissection varied from 1 to 11 lymph nodes, a significant number but not found on ultrasound, which confirms the data literature on the unreliability of ultrasound in detecting central compartment lymph nodes.

In a large multicenter thyroid cancer cohort from six Korean hospitals, which included 8058 CPT patients who underwent initial surgery, the authors concluded that the patient age threshold of 55 years also significantly differentiates the risk of disease-specific mortality[9]. In the same cohort other risk factors were also independent risk factors for disease-specific mortality such as male gender, larger tumor size (>2 cm), presence of extrathyroidal extension (ETE). Based on these studies, the TNM/AJCC Staging System Revised 8th Edition increased the patient age threshold from 45 to 55 [10].

Larger tumor size has consistently been reported to be related to an increased incidence of lymph ganglion metastases. Several authors have shown that CLNMs were positively related to tumor size, the larger the size the greater the risk of CLNM increases but the discrepancies were to determine the predictive tumor size threshold of CLNMs for CPT  $\leq 4$ cm [7,11-13]. Ahn et al. showed that tumor size  $\geq 1$  cm was the risk factor for CLNM, these results were supported by authors Liu et al. who conducted a large retrospective analysis investigating the clinicopathological

data of 966 patients with CPT in China, concluding that 1cm and greater was the threshold of tumor size predictive of lymph ganglion metastases [7,13].

In our study, with respect to tumor size, we distinguished 3 groups based on the TNM/AJCC staging system. Multivariate analysis showed that larger tumor was associated with increased likelihood of CLNM, and primary tumor size >2.0 cm was a very significant independent risk factor ( $p=0.0205$ ) for central compartment lymph node metastases with an adjusted relative risk  $RR = 7.4121$  (95% CI [1.39-39.27] therefore greater than 1, which means that the tumor size > 2cm represents a degree of dependence seven times greater for patients with lymph node involvement positive for the risk factor that is a size greater than 2cm.

CPTs have certain clinicopathologic features that could exhibit aggressive behavior and lead to a poor prognosis. In some studies, patients who underwent pCND were generally more likely to have more risk factors, such as larger tumor size, extrathyroidal extension, multifocality, and bilaterality[5]. In our study, tumor size classified as T2 of the TNM classification was a very significant independent preoperative risk factor ( $p = 0.0205$ ). All the other predictive factors for the presence of lymph node micro metastases were postoperative, results obtained in histology including multifocality ( $p=0.00009$ ), bilaterality ( $p=0.0008$ ), angioinvasion ( $p=0.00002$ ) and extracapsular extension ( $p=0.0003$ ). These results are found in a randomized controlled trial by Viola et al.[3] where the authors randomized 98 patients, almost 50% of patients with CPT, had micro metastatic lymph nodes in the central compartment but none of the presurgical characteristics analyzed in their study, could predict their presence unlike our study where tumor size was a factor associated with the positivity of central dissection.

In analysis of the Surveillance, Epidemiology, and End Results (SEER) database determined that nodal metastasis was only associated with increased mortality in patients over 45 years of age[14]. However, a more recent study of patients from the SEER Database and the National Cancer Database (NCDB) of patients under the age of 45 found that an increasing number of lymph node metastases was associated with a decrease in overall survival up to 6 metastatic nodes, after which more metastatic nodes conferred no additional risk of mortality [15].

Among our 23 patients who present a positive lymph node invasion (pN1a), 17/23 or 73.91% are aged < 55 years and 21.74% had more than 5 positive lymph nodes, the number of which systematically qualified them for the group at intermediate risk of recurrence according to ATA guidelines[16]. Most of the patients had other risk factors which, in themselves, also placed them in the intermediate risk group. Its detection allowed for more accurate tumor staging and better selection of patients for radiation therapy, as these patients would have been inappropriately downgraded and may be undertreated if central prophylactic curage had not been performed. However, the presence of metastatic lymph nodes is only relevant in patients over 55 years of age because in younger patients the presence or absence of lymph node metastases does not alter the stage of the disease [16].

In our series, 73/101 were under 55 years old and therefore systematically classified as stage I, on the other hand the stage changed in 6/101 (5.94%) patients over 55 years old from stage I to stage II, with an impact on their clinical management. A logistic regression study on risk factors showed that tumor size T1b and T2 as well as multifocality were factors significantly associated

with the decision-making for treatment with iratherapy with values respectively  $p=0$ ,  $0001$ ,  $p=0.0003$  and  $p=0.0210$ .

However, in the revised ATA 2015 guidelines, the presence of extranodal extension (ENE) was not included as an independent factor, but the presence of more than 3 lymph nodes with ENE was considered a high-risk feature, with a risk of recurrence / persistence of 40% allowing the patient to be classified at a higher stage[16]. In our series, 4.35% of patients had one node with ENE and one patient (4.35%) had 2 nodes with ENE. These data did not influence the ATA risk classification.

### Conclusion

Adequate understanding and application of prognostic factors is currently our best approach to optimize individual decision-making in patients. In our study a primary tumor size > 2.0 cm, extracapsular spread and angioinvasion were significantly correlated risk factors for lymph node metastasis with a number of metastatic nodes qualifying these patients as an intermediate risk group for recurrence according to ATA guidelines. These patients will benefit from prophylactic central dissection even in the absence of clinically evident central compartment lymph ganglion metastasis.

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