

Evaluation of Sentinel Lymph Node Biopsy in Papillary Carcinoma of Thyroid During Total Thyroidectomy

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ABSTRACT

Background: Lymph node metastases are very common in papillary thyroid carcinoma affecting the survival of patients. The appropriate management of cervical lymph nodes is very important. Therefore, this study evaluated the utility of sentinel lymph node biopsy (SLNB) using methylene blue in the central neck compartment. **Objective:** The aim of this study is to investigate the possibility of using the SLNB to predict micro metastasis in papillary carcinoma of thyroid to avoid the unnecessary central lymph node dissection.

Patients and Methods: This prospective observational study was conducted on 40 patients presented to Ain shams university hospitals with papillary carcinoma of thyroid from October 2022 and for 1.5 years. Those patients underwent SLNB from the central compartment using methylene blue with total thyroidectomy and central lymph node dissection.

Results: There were 40 PTC patients enrolled in this study 23 were females and 17 were males. The age of patients ranged from 25 to 59 with mean age 41.9. The tumor size ranged from 0.5 cm to 5 cm. Out of 40 patients 19 patients were negative for both sentinel and non-sentinel lymph nodes while 4 patients were negative only for sentinel lymph nodes. 21 patients had positive non-sentinel lymph nodes (had actual disease) from which only 17 had positive sentinel lymph nodes. So, the sensitivity, specificity, negative predictive value and positive predictive value were 81%, 100%, 72.7%, 100%, 82.61% respectively.

Conclusion: From this study we concluded that sentinel lymph node biopsy using methylene blue test is technically feasible and safe method, which can reveal occult metastasis among PTC patients with CNO stage who may get benefit from selective neck dissection. However, it had disadvantages since the sensitivity of the methylene blue test is only around 80% so this test can miss patients with occult metastasis.

Key words: papillary carcinoma of thyroid (PTC), sentinel lymph node biopsy (SLNB), methylene blue test

INTRODUCTION

The primary route by which papillary thyroid cancer (PTC) spreads is through the lymphatic system to the neck lymph nodes. The effect of routine central lymph node dissection on prognosis and survival in PTC patients without evidence of lymph node metastases is yet unknown (1).

Although the pathway of the spread of PTC is not always predictable, it

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primarily spreads to the local draining LN. The lymphatic fluid is drained via the intra-thyroid capillaries into the lymphatic channels connected to the capsule, where it may potentially cross-communicate with the opposing lobe and isthmus. Roughly 90% of patients have involvement in the central neck compartment, and the prevalence of micro metastases (<2 mm) may approach 80%. The second most affected region is the lateral compartment LN (2). Thirdly, the supraclavicular nodes (10–52%) constitute the location of involvement. Involvement of the mediastinal LN is less common (2–15%). Up to 20% of individuals have lateral skip metastases, while 25% of patients have contralateral LN involvement (2).

Patients with PTC may undergo neck dissection, ultrasonography, or clinical examination for lymph node (LN) staging (3).

There is around 30% false-negative rate in the identification of neck LN metastases using clinical evaluation and radiographic approaches (4–6).

Imaging is a more reliable method of detecting metastases in cervical lymph nodes than clinical palpation (4). The preferred imaging modality at the moment for assessing cervical LN metastases in thyroid cancer patients before surgery is ultrasound (7). But, the thyroid gland, multifocal nodules, clavicle, and sternum conceal metastases in the central neck compartment, which results in low ultrasonography sensitivity (52–84%), in contrast to metastases in the lateral neck compartment, which can be identified by ultrasonography with higher sensitivity and specificity (8,9).

Dissection of the neck is one method of staging LNs. There are disadvantages of adding neck dissection to thyroidectomy in PTC, it may result in longer operative time under anesthesia, higher rates of morbidity, and more hospital stays (8).

Although central neck dissection is indicated based on clinical criteria and the pathology of the tumor biopsy, it may not be essential in many cases. Modified radical central compartment dissection in those patients is still debatable as the standard of care for manipulating occult cervical LN metastases because of the higher risk of hypocalcemia and recurrent laryngeal nerve damage (10,11).

For LN staging, histopathology is the only reliable technique. Sentinel lymph node biopsy has become to be a dependable technique for staging patients whose tumors metastasize through the lymphatic system, therefore identifying latent lymph node metastases. The first few lymph nodes that a tumor drains into are known as the sentinel lymph nodes (12).

Sentinel lymph node biopsy has emerged as a

groundbreaking idea in tumor staging. It is the gold standard for staging a number of malignancies, including breast cancer and malignant melanoma (13), and it has also been recommended for vulva, oropharyngeal, and penile cancers (14).

In patients with clinically negative nodal disease, sentinel lymph node biopsy is an alternative to elective lymph node dissection. This idea has been explored in a few studies involving patients with differentiated thyroid carcinoma (DTC) using methylene blue and radiotracers with dynamic lymphoscintigraphy (15,16).

Aim of Work

This study aimed to investigate the possibility of using the Sentinel lymph node biopsy to predict micro metastasis in papillary carcinoma of thyroid in order to avoid the morbidity associated with routine and unnecessary central lymph node dissection.

PATIENTS AND METHODS

Inclusion Criteria

We conducted a prospective study on patients diagnosed with papillary thyroid cancer by fine needle aspiration, regardless of age, sex, tumor size, multifocality, or bilaterality, and without suspicion of lymph node metastases by clinical and ultrasonography, who were presented to Ain Shams University Hospitals between October 2022 and March 2024.

Exclusion Criteria

1. Prior neck surgery;
2. Prior thyroid cancer;
3. Prior neck radiotherapy;
4. Pregnancy;
5. Palpable or US-detected lymph node involvement.
6. Other types of thyroid malignancies.

Sample size: 40 patients

Study tool: preoperative:

All participants were subjected to following:

1. Full medical history.
2. Complete physical examination.
3. Laboratory investigations including:
 - CBC;
 - PT, PTT, INR;
 - Liver and kidney function tests and virology;
 - Thyroid function test (T.S.H, free T3 & free T4);

- Thyroglobulin.
- Radiological investigations:
- Neck ultrasonography;
 - F.N.A from thyroid nodule;
 - Routine vocal cord assessment.

Study Procedure (intraoperative)

A transverse incision of the low collar bone has been made, and it has been followed by a longitudinal incision in the linea alba cervicalis and the separation of a skin flap. The ipsilateral jugular vein and the thyroid gland were both fully visible after the thyroid capsule was opened without causing any damage to it. Then, using a 1-mL syringe and a 27-gauge needle, 0.5 mL of 2% methylene blue was very slowly and gently administered into the tumor. Intra-tumoral injections have been performed at 3, 6, 9, and 12 o'clock. SLNs were characterized as lymph nodes that were blue-stained in less than three to four minutes. Following a frozen section examination, a complete thyroidectomy was carried out. The first node nearest the afferent stained lymphatic channel was designated as SLN in the absence of any stained nodes (*fig. 1, 2, 3*).

After that a prophylactic ipsilateral central neck dissection has been performed. The remaining unstained lymph nodes in the central compartment (non-Sentinel Lymph nodes) will be sent for routine histopathology. In bilateral nodules (5 patients) the procedure was done on both sides.

Postoperative

All patients were followed up for drain, serum calcium level. The routine histopathology results for the remaining central lymph nodes (non-sentinel) were compared to the results of the frozen section of the sentinel lymph nodes.

Statistical Methods

Data were gathered, tallied, and statistically examined. The statistical program for social science, version 21, SPSS, was used to analyse the data in the following ways: The features of the patient and the tumour were examined using descriptive statistics. Quantitative variables were described using percentages and numbers. The SLN's positive and negative predictive values, sensitivity, specificity, and accuracy were computed.

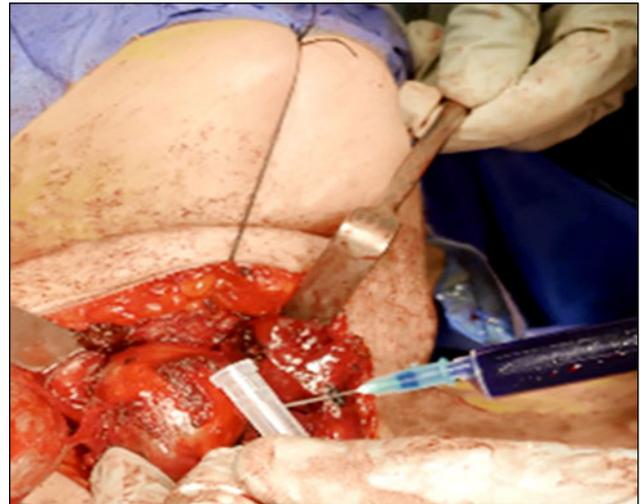


Figure 1 - Injection of methylene blue intra tumoral

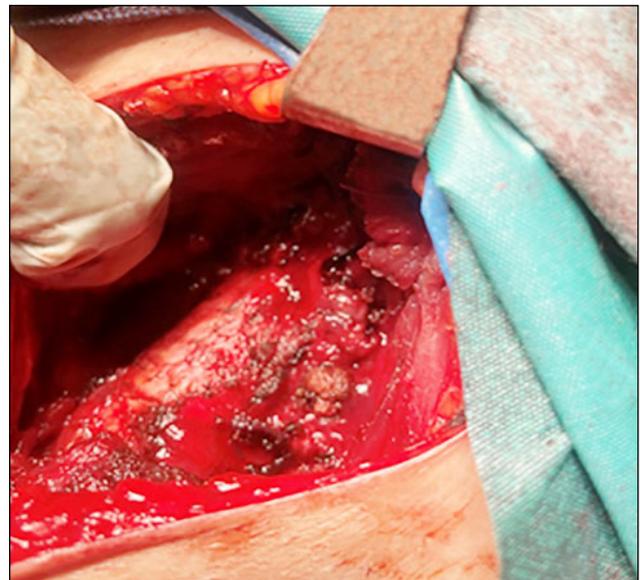


Figure 2 - Identification of Stained LNS

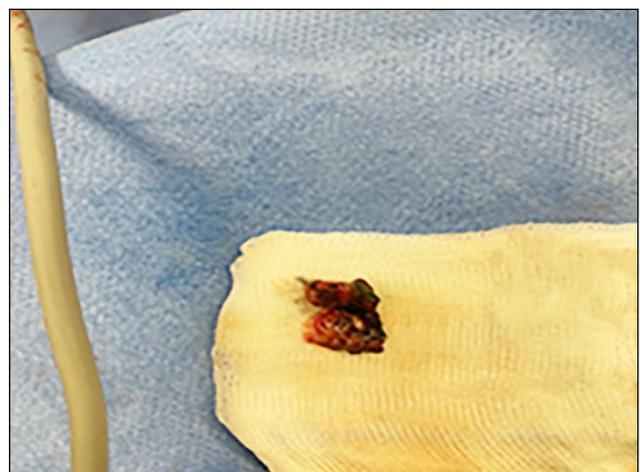


Figure 3 - Stained sentinel lymphnode

RESULTS

The characteristics of patients and comorbidities are described in *table 1* and *table 2*. The study was conducted on 40 patients who were presented to Ain shams university hospitals with papillary carcinoma of thyroid with clinically and radiologically negative lymph nodes. Out of 40 patients 23 were females while 17 patients were males. The patients age ranged from 25-59 with mean age 41.9.

Out of 40 patients 7 patients were hypertensive, 5 patients were diabetic, one patient was hepatitis C virus positive, while 27 patients did not have known comorbidities.

The tumor size and site are listed in *table 3*. The tumor size in the 40 patients ranged from 0.5 – 5 cm with median 3 cm. 13 patients had the tumor in the right lobe, 22 patients had the tumor in the left lobe while it was bi-lobar in 5 patients.

Out of 40 patients 19 patients were negative for both sentinel and non-sentinel lymphnodes while 4 patients were negative only for sentinel lymphnodes. 21 patients had positive non-sentinel lymphnodes (had actual disease) from which only 17 had positive sentinel lymphnodes as described in *tables 4a, 4b* and *fig. 4*.

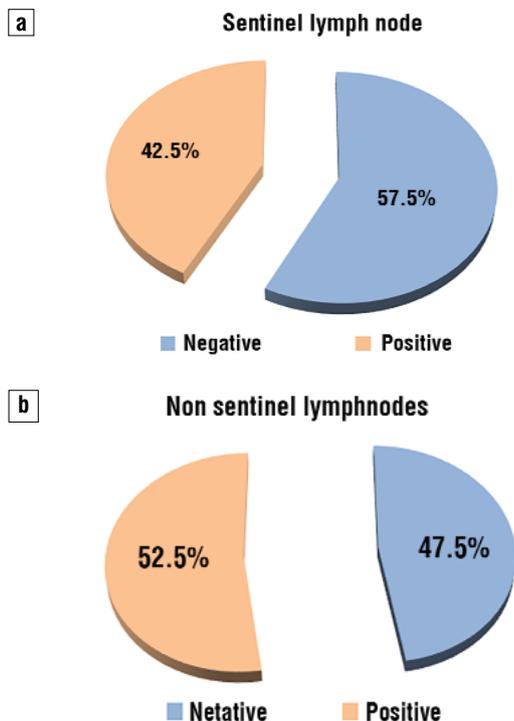


Figure 4 - Characteristics of sentinel (a) and non-sentinel (b) lymph nodes of the studied patients

Table 1 - Age and gender distribution among the studied patients

		Total no. = 40
Gender	Male	17 (42.5%)
	Female	23 (57.5%)
Age	Mean ± SD	41.9 ± 9.97
	Range	25 – 59

Table 2 - Comorbidities distribution among the studied patients

Co-morbidities	Total no. = 40
NO known co-morbidities	27 (67.5%)
Hypertension	7 (17.5%)
Diabetes	5 (12.5%)
HCV	1 (2.5%)

Table 3 - Tumor size and site of the studied patients

		Total no. = 40
Tumor size	Median (IQR)	3 (1.75 – 3.5)
	Range	0.5 – 5
Site	RT Lobar	13 (32.5%)
	LT Lobar	22 (55.0%)
	BI-Lobar	5 (12.5%)

The diagnostic accuracy of sentinel lymph nodes is described in *table 5a & 5b* that shows sensitivity, specificity, positive predictive value, negative predictive value of 81%, 100%, 100%, 82.61% respectively.

Post-operative complications were described in *table 6* that shows that Two patients had experienced dye sensitivity which has been managed conservatively with steroids while only one patient had experienced temporary paralysis of unilateral vocal cord. Three

Table 4a - Characteristics of Sentinel and non-sentinel lymph nodes of the studied patients

Total number of cases positive SNL & NSLN: (total cases with Actual LN disease present)	21/40
Total number of cases –ve SNL&NSLN: (total cases actual LN disease absent)	19/40
Number of cases negative SNL & negative NSLN (true –ve)	19
Number of cases negative SNL & positive NSLN (false –ve)	4
Number of cases positive SNL & negative NSLN (false +ve)	0

Table 4b - Characteristics of Sentinel and non-sentinel lymph nodes of the studied patients

		Total no. = 40
Sentinel lymph node	Negative	23 (57.5%)
	Positive	17 (42.5%)
Non sentinel lymph nodes	Negative	19 (47.5%)
	Positive	21 (52.5%)

Table 5a - Diagnostic accuracy of sentinel lymph nodes on non-sentinel lymph nodes

		Non sentinel lymph nodes		Sensitivity	Specificity	PPV	NPV	Accuracy
		Negative	Positive					
		No. =19	No. = 21					
Sentinel lymph node	Negative	19 (100.0%)	4 (19.0%)	81.0%	100.0%	100.0%	82.61%	87.8%
	Positive	0 (0.0%)	17 (81.0%)					

Table 5b - Diagnostic accuracy of sentinel lymph nodes

	Value
Sensitivity	81 %
Specificity	100 %
Positive predictive value	100 %
Negative predictive value	82.61 %
Accuracy	87.8 %

Table 6: Complication distribution and time taken for surgery of the studied patients

		Total no. = 40
Dye sensitivity	Positive	2 (5.0%)
	Negative	38 (95.0%)
RLn palsy	Positive	1 (2.5%)
	Negative	39 (97.5%)
Hypo-parathyroidism	Positive	3 (7.5%)
	Negative	37 (92.5%)
Time taken for surgery	Mean ± SD	110.18 ± 11.49
	Range	90 – 140

patients had developed temporary symptomatic hypocalcemia and no post operative bleeding had occurred Average time taken for surgery was recorded which was 110.18 mins.

DISCUSSION

Cervical lymph node metastases are typical in PTC patients, which accounts for 60-80% of all thyroid malignant tumors detected in clinics. According to reports, the rate of metastases varies between 15 and 50 percent, and occult cervical lymph node metastases varies between 40 and 70 percent (17).

The researches indicates that cervical lymph node metastatic occurrences indicate a more advanced stage of the disease and a loss of valuable treatment time. Therefore, in order to increase the survival in those patients, those studies suggest prophylactic modified radical central neck dissection (17).

As of yet, no dependable or practical clinical technique exists to distinguish between occult lymph node metastases in CNO patients. For CNO instances, sentinel lymph node biopsy has been suggested as an alternate method of diagnosis and care (17).

The first lymph node in the regional lymphatic basin that drains a primary tumor is known as the SLN. The first node that is closest to the afferent stained lymphatic vessel will be regarded as the SLN in the absence of any stained nodes. The pathologic state of the remaining lymph nodes should be reflected in the SLN if lymphatic drainage is to happen gradually (18).

Sentinel lymph node can be done using many techniques including blue dye, lymphoscintigraphy and intra operative gamma probe technique, combined blue dye and lymphoscintigraphy. The blue dye technique has numerous benefits. Such as It doesn't call for much in the way of time, energy, or money. Methylene blue, isosulfan blue, patent blue and indigo carmine are examples of the blue dyes that can be utilized. There have been incidents of anaphylaxis from using isosulfan blue, but patent blue appears to be less dangerous. However, the blue dye method has its drawbacks. The detection rate is lower, and the parathyroid gland, as well as nearby soft tissue, may falsely be stained positive. The detection rate of thyroid cancer using a blue dye approach was 15% lower than the detection rate using a radio-isotope technique, according to a meta-analysis of SLNB for the disease (18,19).

Forty individuals suffering from papillary thyroid cancer participated in our study. Malignant nodules varied in size from 0.5 to 5 cm. In 55% of the cases nodules were in the left lobe, in 32.5% were in the right lobe, while it was bilateral in 12.5% of cases.

We identified the sentinel lymph node (LN) in our patients by injecting methylene blue intratumorally. The first node that is closest to the afferent stained lymphatic vessel will be regarded as the SLN in the event that no stained nodes are found.

Sentinel lymph nodes were detected in all patients. The size ranged from 0.5-5 cm. 17/40 (42.5%) SLN were positive for metastasis and 23/40 (57.5%) were negative for metastasis. Non sentinel LNs were extracted via the

central compartment dissection. 21/40 were found positive for metastasis and 19/40 were found negative.

From our results SLN had sensitivity, specificity, negative predictive value, positive predictive value of 81%, 100%, 72.7%, 100%, 82.61% respectively.

By comparing our results to studies that have used methylene blue dye it was nearly similar to Ayman ET AL IN 2019 who had sensitivity, specificity, negative predictive value, positive predictive value and accuracy of 86.7%, 100%, 72.7%, 100%, 73.3% respectively and Le Van QUANG ET AL in 2018 who had Sensitivity, Specificity, positive and negative Predictive Values of 79.1%, 100%, 100%, 79.7% respectively (19,20).

By comparing our results to studies that used patent blue dye Tahan ET AL in 2024 who had a slightly better Sensitivity which was 83.6% in a study conducted on 30 patients but similar specificity (21).

By comparing our results to studies using lymphoscintigraphy and intra operative gamma probing by Amaia Expósito Rodríguez ET AL IN 2022 had Sensitivity, Specificity, positive and negative Predictive Values of 86%, 100%, 100%, 85.17% respectively on a study conducted on 53 patients who were presented with papillary carcinoma of thyroid with clinically and radiologically negative lymph nodes (22).

The sensitivity of lymphoscintigraphy is slightly better than the methylene blue method but the methylene blue method is cheaper and more available than other techniques and still have relatively good results.

From our study there were no statistically significant relation between the specificity and sensitivity of the sentinel lymph nodes and the gender, age, comorbidities and the size of the tumor.

In our study 3 out of 40 patients (7.5%) had experienced transient symptomatic hypocalcemia after surgery. Only one (2.5%) patient had experienced transient recurrent laryngeal nerve palsy, two patients (5%) had experienced dye sensitivity there were no bleeding or death problems. Postoperative complication rate, including recurrent laryngeal nerve injury, hypoparathyroidism, and postoperative hematoma, were not different from previous studies of thyroidectomy. Hence, the addition of SLNB using methylene blue dye to thyroidectomy looks feasible and safe.

CONCLUSION

Based on our findings SLN biopsy using methylene blue dye technique is a safe and technically feasible procedure with low cost. Nevertheless, there are disadvantages. The methylene blue test's sensitivity is

only about 80%, which means that patients with occult metastases may not be detected, which might have an impact on their prognosis and survival. So we advise conducting more researches on larger case series to assess SLN biopsy using methylene blue which is cheaper, feasible than other methods such as lymphoscintigraphy and intra operative gamma probing before adopting this method as the standard of care in the treatment.

Conflicts of Interest

There is no conflict of interest.

Funding

No funding research.

Ethics of Approval

The research was approved by the ethical committee in Ain Shams University.

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