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The role of Sentinel Lymph Nodes Biopsy Using Blue Dye in the Management of Differentiated Thyroid Carcinoma

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Abstract

Around 1.7 percent of human malignancy is caused by thyroid cancer. In terms of patient health and survival, the disease and its management have a higher mortality and morbidity rates than is desirable. To determine if sentinel lymph node biopsy is effective and feasible for treating the differentiated thyroid cancer with negative nodes clinically and to avoid needless lymph nodes dissection among cases of differentiated thyroid cancer (DTC) as their original lymph nodes did not show any spread. We did this prospective research at Al-Azhar University Hospitals in Egypt, and twenty differentiated thyroid cancer patients were included. Total thyroidectomy with sentinel lymph node biopsy and central neck dissection was done. SNB using methylene blue dye was used exclusively in the early stages of DTC, and afterwards CND was conducted. Sentinel LNs were identified in 17/20 patients. 13 SLN were positive for metastasis and 4/20 (20%) were negative for metastasis. Non sentinel LNs were extracted via central dissection. compartment 14/20 was found positive for metastasis and 6/20 were found negative. Detection rate was 85%. False negative rate was 25% (1/4), sensitivity was 93% (13/14) and specificity was 100% (3/3), accuracy 94 %, PPV was 100% (13/13), while NPV was 75% (3/4). SLN biopsy was capable of discovering hidden lymph node metastases in DTC patients without US or gross clinical lymph node affection and could be utilized to identify those who require a dissection of the central neck. The blue dye approach is also safe and feasible, however, it limits the utility of SLNB in the management of clinically node negative DTC due to its poor detection rate and a significant FNR..

Keywords: Thyroid carcinoma, Blue dye, Sentinel lymph nodes biopsy.

1. Introduction

The most prevalent primary endocrine malignancy and is increasing in its incidence is differentiated thyroid carcinoma (DTC), which constitutes about 90 percent of malignancy of thyroid gland. 30 to 80 percent of papillary thyroid cancer (PTC) patients and around 90 percent of children and adolescents with PTC had metastasis to regional lymph nodes. Metastasis occurs to central (paratracheal, pretracheal; level VI), to upper mediastinal; level VII, and laterally to

jugulocarotid and supraclavicular; level II, III, IV, V. Another type rarely metastasize to lymph nodes is follicular thyroid carcinoma, which usually spreads to other organs such as the bone or lungs via blood stream [1].

However, lymph node metastasis (LNM) has recently been recognized as a poor prognostic factor for cancer-specific outcomes. The individuals with PTC have a favorable prognosis despite the high occurrence of lymph node metastasis. A number of debates have raged for decades about whether or not LNM have a substantial role in patients' overall survival [2].

There is no doubt that LNM has a positive impact on the recurrence of disease. Locoregional recurrence is considerably increased by LNM. Even after apparently successful surgery, recurrence or persistent disease in the neck is a substantial cause of morbidity and considered a serious challenge for surgeons. It is estimated that 10 to 30 percent of DTC patients suffer from local recurrence after their initial surgery, increasing their overall morbidity, regardless of the greatest efforts of therapy. Lymph nodes are the most frequently affected by relapses, according to numerous research. As a result, surgery is the most important therapeutic option for DTC patients. Primary thyroid carcinoma is treated with total or near-total thyroidectomy, depending on the extent of the cancer. If clinically suspected or histologically or cytologically verified lymph node metastases, central or lateral neck dissection is recommended. [3].

Dissection of radiologically undetectable (clinically N0, cN0) occult LNM is still debatable, taking into account the fact that routine neck dissections frequently reveal histologic evidence of micro-deposits. As a result of such debate about surgical approaches and lymph node management and in a trial to balance between the benefits of routine prophylactic lymph node dissection in decreasing the recurrence rate and the risk of increasing morbidity associated with the procedure, the idea of sentinel lymph nodes (SLN) has evolved in the management of DTC patients. First lymph nodes to drain primary tumors are known as sentinel lymph nodes (SLNs), and as a result, they provide information on the condition of the rest of the lymph nodes [4].

As long as the lymphatics from a tumor site drain in a specific way, the sentinel node will be the first lymph node to encounter micro-deposits from the tumor's site and will serve as a good indicator [5].

For neoplasms that disseminates across the lymphatic system, Sentinel lymph node biopsy (SLNB) has gained general acceptance as a reliable procedure for identification of LN micrometastasis and in turn aids in patient staging. The sentinel lymph node biopsy has emerged as a ground-breaking method in staging of malignancies. Sentinel lymph node biopsy is considered the gold standard for cancer staging and can be performed in a range of cancers, including breast cancer and malignant melanoma, as well as penis, vulva oropharyngeal, and thyroid cancers. It has been proposed that sentinel lymph node biopsy can be used as an alternative to elective lymph node dissection in patients who have clinically negative nodal disease, and this concept has been tested in some studies in patients with DTC. The technique can be done using blue dye, radiotracers or combined technique. Inspite the higher incidence of LNM in DTC, it is uncertain whether it has any significant prognostic implications [6].

PTC has been the subject of numerous research, all of which have found SLNB to be feasible, safe, but its efficacy and therapeutic use remain debatable [4].

Several centers have reported on the feasibility of sentinel node biopsy to assist node dissection in a subset of patients who have undergone surgery. It is possible to perform a sentinel node biopsy using radioisotopes, blue dye or a mix of radioisotopes and blue dye [7]. The aim of this study was to determine if sentinel

lymph node biopsy is effective and feasible in patients with clinically negative nodal affection and to avoid needless lymph nodes dissection among cases of differentiated thyroid cancer (DTC) as their regional lymph nodes did not show any spread.

2. Patients and Methods

This study was prospective research at Al-Azhar University Hospitals in Egypt, and twenty differentiated thyroid cancer patients were included. The patients were subjected to sentinel lymph node biopsy with a total thyroidectomy and central neck dissection (CND) during the period between 1st of July 2016 and 1st of May 2021.
The Al-Azhar University academic and ethical committees gave their clearance for the study, which was conducted in Egypt. Every patient signed an informed written consent for the operation before to having it performed.

2.1 Inclusion criteria:

T1 & T2 DTC regardless of age, sex, and no clinical LNs or distant metastases.

2.2 Exclusion criteria:

Preoperative evidence of cervical lymph node metastases during physical examination and ultrasound, patients with big tumours (T3 and T4) and those with local invasion, as well as other thyroid malignancies (and follicular carcinoma), history of surgery for neck or head for nonthyroidal neck.

2.3 During this research, all patients underwent a preoperative evaluation through:

1- Information gleaned from the patient's medical history, physical examination, diagnosis and staging**.**

2- Laboratory: Coagulation profile, complete liver function, Complete blood picture, Serum creatinine, serum electrolytes, thyroid function test (T.S.H, free T3 & free T4), and tumour markers (thyroglubin).

3- Neck us**.**

4- F.N.A from thyroid nodule to confirm thyroid carcinoma **.**

5- Routine vocal cord assessment**.**

6- Consent from patients detailing the risks and benefits of the surgery, both in writing and orally.

2.4 Patient preparation:

Personal Control of any coexisting medical disease, and prophylactic antibiotic with induction of anesthesia.

2.5 Surgical procedure:

Patient is placed in supine position with arms tucked at the sides. A soft roll is placed beneath the shoulders and a head ring is used to stabilize the head, head of the bed at approximately 30 degrees, the anterior surface of the neck is prepped and draped. Transverse curvilinear collar incision was made approximately fingerbreadth above the sternal notch, along a normal skin crease, and skin raised in a subplatysmal plane from sternal notch inferiorly reaching thyroid cartilage level superiorly and the sternocleidomastoid muscles laterally. Before mobilizing the thyroid gland, 0.3 ml of methylene blue dye, 1 percent, was injected peritumorally into four sites at the three, six, nine, and twelve o'clock positions or 0.5 ml of methylene blue dye, 1 percent was injected into the thyroid nodule using a tuberculin syringe after retraction of the strap muscles with least dissection to avoid any lymphatic disruption and before mobilizing the gland. The blue dye propagated throughout the ipsilateral

thyroid lobe and into the central compartment in a matter of seconds to minutes. Blue-stained lymph nodes were discovered by following the stained lymphatic path and these nodes were assigned as SLNs. All of these SLNs were meticulously collected and delivered to the pathology lab for standard pathology testing. Central neck dissection (CND) (level VI) as well as a total thyroidectomy were then conducted. Non-SLNs are the lymph nodes in the central compartment that have not been stained.

2.6 Postoperative care:

Total or ionized calcium are checked on the morning of postoperative day 1, as some reports have shown that nearly one-third of patients will have mild temporary hypocalcemia within the first 1 to 2 days after surgery. Calcium supplementation is administered based on how low the postoperative calcium level is and as needed for any numbness or tingling. Levothyroxine is prescribed and started 21 days after surgery, to allow TSH elevation before thyroid scanning. Laryngoscopy is indicated postoperatively if the patient complains of hoarseness or for any voice changes in order to assess for RLN or vocal cord damage. Serum thyroglobulin is followed postoperatively to detect persistent or metastatic disease. RAI remnant ablation is oftentimes recommended, especially if there is residual remnant tissue, nodal metastasis, extrathyroidal extension, or distant disease.

2.7 Statistical analysis:

Data were collected and statistically analyzed in the following ways: The characteristics of the patient and the tumor were studied using descriptive statistics. The quantitative variables were described using percentages and numbers. In this study, the SLN's accuracy and sensitivity were assessed, as well as its specificity, positive and negative predictive values and complications.

3. Results

The whole twenty patients who were recruited in the study, ranged in age from 26 to 76 years old, with 16 being women and 4 being men. Tumors ranged in size from 0.8 to 4cm and were all differentiated carcinomas; 8 patients had right lobe tumors 12 patients had left lobe tumors Table. 1.

Ten patients (50 percent) had ipsilateral paratracheal SLNs, three (15 percent) had pretracheal SLNs, three (5 percent) had prelaryngeal SLNs, and one (5 percent) had contralateral paratracheal SLNs, with no stained lymph nodes found in the lateral neck Table. 2.

Identification rate of SLN 85% and non SLN 100%. The LN pathological examination showed that SLNs found to be positive in 13 cases and negative in 4 cases, but in non SLNs were positive in 14 cases and negative in 6 cases Table. 3.

Cases with +ve SLNs & NSLNs were 13/20, on the other side Total number of cases –ve SNL & NSLN were 3/20, cases of true –ve, false –ve, false +ve were recorded as 3, 1, 0 respectively Table. 4. Detection rate was 85%. False negative rate was 25% (1/4), sensitivity was 93% (13/14) and specificity was 100% (3/3), accuracy 94%, Positive predictive value PPV was 100% (13/13), while Negative predictive value NPV was 75% (3/4) Table .5.

Postoperative complications were temporary symptomatic hypocalcemia developed in 1 of 20 patients (5%), and laboratory hypocalcemia developed in 2 patients (10 %); no permanent hypocalcemia. One patient (5%) had postoperative wound infection and one patient (5%) had postoperative temporary paralysis of the unilateral vocal cord, and no permanent paralysis or mortality was observed Table. 6.

Table (1): Characteristics and symptoms of the patient.

Patients Number	20
Age	26-76 years
Females	16
Males	4
Tumor size (cm)	0.8- 4 cm
Left Lobe Tumor	12
Right Lobe Tumor	8
Hospitalization (days)	2-5

Table (2): Central compartment SLN locations.

Site	SLN Detected [N (%)]
Paratracheal group on the ipsilateral side	10(50 %)
On the same side prelaryngeal	3(15 %)
On the same side pretracheal	3(15 %)
Paratracheal group on the contralateral side	1(5 %)
Total	17 (85 %)

Table (3): Characteristics of sentinel lymph node (SLN) and non-sentinel lymph node (NSLN).

	SLN	Non SLN
	No & Percentage	No & Percentage
Identification rate of SLN	17/20 (85 %)	20/20 (100%)
LN metastasis found positive	13/20	14/20
LN metastasis found negative	4/20	6/20

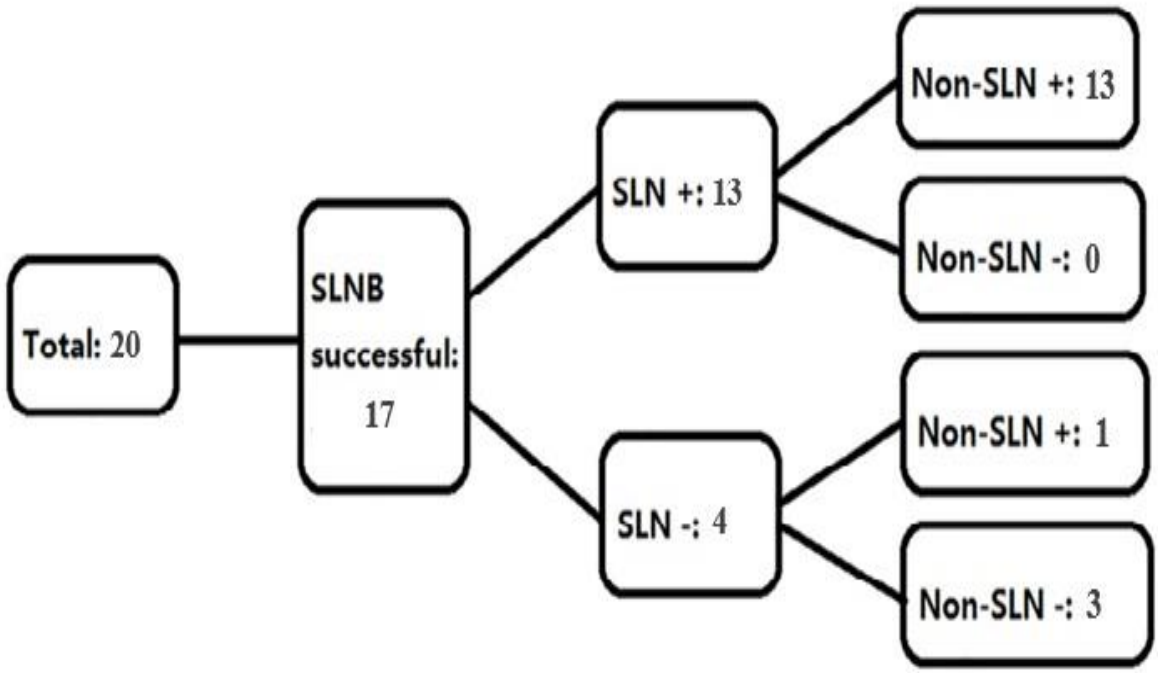

Figure (1): Overview of SLNB. SLNB = sentinel lymph node biopsy; SLN = sentinel lymph node; non-SLN = non-sentinel lymph node.

Table (4): Characteristics of sentinel lymph node (SLN) and non-sentinel lymph node (NSLN).

Total number of cases +ve SNL & NSLN	**13/20**
Number of cases –ve SNL & -ve NSLN (true –ve)	**3**
Number of cases –ve SNL & +ve NSLN (false –ve)	**1**
Number of cases +ve SNL & -ve NSLN (false +ve)	**0**

Table (5): Accuracy of the SLN.

	No	**Percentage**
Sensitivity	13/14	92.8 %
Specificity	3/3	100 %
Negative predictive value (NPV)	3/4	75 %
Positive predictive value (PPV)	13/13	100 %
Accuracy	16/17	94.1 %

Table (6): Complications of SLNB in DTC.

Complications	**Number of patients (%)**
Blue dye	0 (0%)
Hypocalcemia Temporary laboratory (asymptomatic) Temporary symptomatic	2 (10%) 1 (5%)
RLN paralysis Temporary paralysis: Permanent paralysis:	 1 (5%) 0 (0%)
Wound infection	1 (5%)
Mortality	0 (0%)

4. Discussion

In this research, SNB was carried out followed by total thyroidectomy and CND in the early stages of DTC using methylene blue dye. Sentinel LNs were identified in 17/20 patients. 13 SLN were positive for metastasis and 4 were negative for metastasis. Non sentinel LNs were extracted via the central compartment dissection, 14/20 was found positive for metastasis and 6/20 were found negative.

Goran et al. [8] performed SNB in 111 patients using blue dye only. SLNs were detected in 111 with SDR 100%, sensitivity 57%, specificity 100 %, and accuracy 97%, false negative rate (FNR) was not applicable (NA).

Abd elwahab et al. [9], performed SNB in 25 patients using blue dye. Sentinel node was recognized in 21 cases (84%). However, no colored SN was found in any of the other four cases. (14%) with SDR 84%, FNR was 8%.

Ji et al. [4], performed SNB using blue dye in 114 cases. SLNs were detected in 84 patients with SDR 74 %, sensitivity 64 %, specificity 100 %, and accuracy NA %, FNR was 35%.

Hao et al. [10], recognized SN in 79 cases (79 %), sensitivity reached 80 % and specificity was 100 %, accuracy was 93 % and FNR was 9 %.

Anand et al. [11], had a 79 percent success probability of detection When it came to test parameters such as specificity, sensitivity and accuracy, they were all one hundred percent, with no false positives.

In our study, detection rate was 85%. false negative rate (FNR) was 25% (1/4), sensitivity was 93% (13/14) and specificity was 100% (3/3), accuracy 94 %, PPV was 100% (13/13), while NPV was 75% (3/4).

SNB approach has a learning curve, which could explain differences in detection rates

between studies. At the very least, 10 SNB assisted CNDs should be done before SNB is used for the first time in any study. [12]. The use of radioisotope-based approaches eliminates the drawbacks of using blue dye and increases the sensitivity of SLN detection. These findings are in line with those of prior meta-analyses in this field [13].

When compared to isotope only approaches, the combined method had a variable sentinel detection rate (0–66 percent). There is a possibility that this result reflects a sample of patients that is too small to be meaningfully compared to those of blue dye and radioisotope procedures. However, using blue dye, radioisotope, and combination approaches, non-visualization of the lymphatics and SLNs has been reported in locations that are generally unreachable via a collar incision [7, 14].

Despite this, SPECT/CT is more effective in locating non-visualized SLNs [36, 57, 73–75], [6, 8].

The false negative rate shows significant heterogeneity, which could be related to a variety of reasons. Firstly, the challenges in interpreting samples and the selection bias within the various nodes forwarded to the pathologist, especially after freezing sections [7, 15].

If the main neoplasm possesses CK19 + expression, the One Step Nucleic Acid Amplification provided conclusive evidence of CK19 +expression [16].

As a second point, an unidentified disease-bearing non-dominant nodule could be the site of an occult lymph node metastasis that is missed since no injection was done to this nodule. Also, the typical course of lymphatic drainage can be impeded by tumor-laden lymphatics in individuals with bulky metastatic LN [17, 18]. At last, another possibility is that trials with a limited sample size, where the bulk of SLN detection failures happened among the first recruited patients, could be affected by the learning curve effect [19, 20].

There are only a few brief trials looking into the protective effects of SNB on long-term illness and recurrence in the same region [20].

A transitory symptomatic hypocalcemia emerged in our study postoperatively in one out of the whole 20 patients (5 percent), and two people acquired laboratory hypocalcemia (10 percent); no one had a hypocalcemia that was persistent. One patient experienced transient paralysis of one vocal cord following surgery, but there was no evidence of long-term damage or death.

Complication rates following thyroidectomy were not different from prior trials, including postoperative hematoma, recurrent laryngeal nerve damage and hypoparathyroidism. Therefor it appears viable and safe to combine thyroidectomy with SLNB [21].

5. Conclusion

Our study implies that the use of SLN biopsy, can reveal subclinical hidden metastases in DTC patients without US lymph nodes or gross clinical involvement (cN0 stage), could be utilized to identify those who require a dissection of the central neck. The blue dye approach is also safe and feasible; however, it limits the utility of SLNB in the management of clinically node negative DTC due to its poor detection rate and a significant FNR. Although the significance of SLNB in thyroid cancer treatment is still unclear, more research on bigger patient populations is needed before it can be recommended for routine use in the treatment of malignancy of thyroid glands.

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