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Clinical significance of sentinel lymph node biopsy in differentiated thyroid cancer

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***Abstract*---**Differentiated thyroid cancers are the most common endocrine malignancy and include three main entities: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and Hürthle cell carcinoma (HCC). Papillary thyroid cancer (PTC) is the most common histologic subtype. Was to review different sentinel lymph node biopsy (SLNB) techniques in patients with differentiated thyroid cancer. We also will compare the detection rates and sensitivity of the different detection methods in these patients and assessment of feasibility and side effects of the different techniques. This study was a cross sectional study, Surgical Oncology Department of National Cancer Institute, Cairo University and Damietta Cancer Center, Ministry of Health and Population. Radionuclide technique (lymphoscintigraphy and gamma probe scanning) was successful in 94.6 % (35/37) of the patients as shown in table 4 and relation between SLN and identification by gamma probe. In the 37 patients, the intraoperative frozen biopsy indicated that 22 patients were experiencing SLN metastases, while post-operative routine pathological examination was able to diagnose three additional patients with lymph node metastases. Double techniques of sentinel lymph node biopsy are feasible with minimal side effects and may assist to a paradigm shift in the aims of treatment of differentiated

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thyroid cancer, from a focus on survival to a focus of disease-free status as a valid endpoint to evaluate the effectiveness of therapy.

***Keywords*---**thyroid, malignancy, sentinel lymph node, biopsy, differentiated, papillary thyroid carcinoma.

Introduction

Differentiated thyroid cancers are the most common endocrine malignancy and includes three main entities: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and Hürthle cell carcinoma (HCC) (1). Papillary thyroid cancer (PTC) is the most common histologic subtype, accounting for 80% of cases (2). The main diagnostic features of PTC are its nuclear changes, which include subtle irregularities in the nuclear contour and size, deep nuclear grooves, and pseudo inclusions resulting from cytoplasmic invaginations (3). FTC is diagnosed microscopically through the identification of capsular or vascular invasion. This feature differentiates FTC from follicular adenoma. Therefore, a diagnosis of FTC cannot be confidently made with fine-needle aspiration (FNA) or frozen section. FTC is considered a more aggressive well differentiated thyroid cancer when compared to PTC (4).

The sentinel lymph node is defined as the first lymph node draining a regional lymphatic basin from a primary tumor. If the sentinel lymph node is found to be positive for metastasis, there may have had metastatic spread to the remainder of the lymphatic basin. An accurate SLNB technique is of particular relevance for patients who are found to be SLN negative, in which case the lymphatic basin is considered to be disease-free (5). A SLN technique involving frozen section evaluation allows for a surgeon to assess the necessity for a (Central compartment neck dissection) CCND at the time of the initial surgery and to avoid a potentially more difficult reoperation of the central neck (5). It remains controversial whether the presence of lymph node metastases, either overt or occult, has an impact on prognosis. Traditionally, it has been suggested that the presence of regional metastases has no effect on survival (1).

Patients and Methods

This study was a cross sectional study, Surgical Oncology Department of National Cancer Institute, Cairo University and Damietta Cancer Center, Ministry of Health and Population. Study population and Sample size estimation: All cases fulfilling the inclusion criteria within a year starting at February 2015 till February 2017. Inclusion Criteria: Patients undergoing thyroid resection with pre-operative pathological diagnosis of differentiated thyroid cancer with clinically and radiologically N0 neck nodes.

Exclusion criteria

Medullary and anaplastic thyroid cancer, benign thyroid disease, history of previous thyroid surgery, pregnancy or active breastfeeding, clinically evident regional lymph node and presence of distant metastasis.

Study design

This study is non-randomized, prospective study, non-comparative study with the purpose of determining rate of SLN detection by histopathological examination, anatomical distribution of SLNs, where every participant will have a sentinel node.

Methods of SLN

Radioactive technique using Technetium-99m-labeled dextran after lymph scintigraphic imaging and colorimetric method using Patent blue dye.

Technique

Following consent for SLN procedure. Two to twenty four hours prior to surgery, 0.4 ml (74 MBq) of 99Tmc-DX will be injected into the primary thyroid tumor. Patent blue 0.5% (0.25 ml/cm) was be injected at four points (1-2 mm) around the tumor, with careful intent to maintain the thyroid gland in the original anatomical position; two to four minutes later the affected side's lobe and isthmus were be removed and sent for frozen section analysis The gamma probe will be used to detect radiopharmaceutical hot spots around the thyroid and in levels II-VII of bilateral neck. Lymph nodes with maximum spot count will be excised and collected. Lymph nodes in which more than 10 times background gamma count will be detected will be determined to be SLN, and will be used for subsequent comparisons with the results of preoperative lymph scintigraphic imaging. Ipsilateral Selective neck dissections (levels II-V) of the neck will be performed on those with positive SLNs by frozen-section analysis. Cervical lymph node dissection specimens were sent for routine pathological examination.

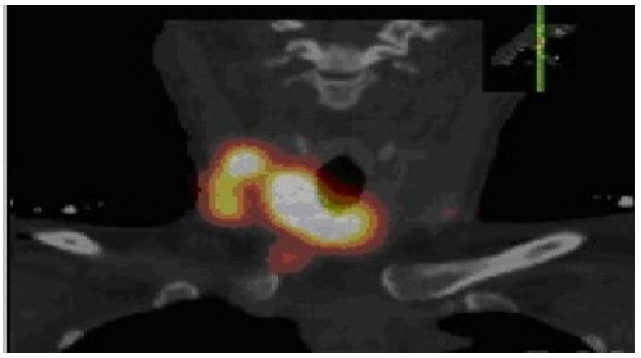

Figure 1. Lymphoscintigraphy acquired at 1 h after 99Tmc-DX injections.
The SPECT image with invasive PTC located in the right lobe shows three SLNs.
Three SLNs are seen in the right lateral compartment (level III and IV)

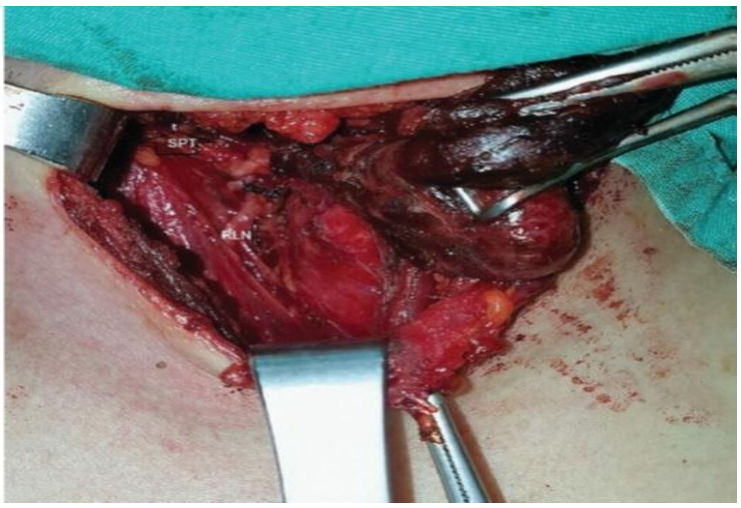

Figure 2. Retraction of the thyroid gland superiorly to allow removal of peri-recurrent nerve nodes and peritracheal lymph nodes. RLN recurrent laryngeal nerve, SPT superior parathyroid gland

STATISTICAL METHODS: Statistical analysis was done using IBM SPSS® Statistics version 26 (IBM® Corp., Armonk, NY, USA). Numerical data were expressed as mean, standard deviation and range. Qualitative data were expressed as frequency and percentage. Pearson's Chi-square test or Fisher's exact test was used to examine the relation between qualitative variables. Evaluation of the sentinel lymph node positivity was done by calculating sensitivity, specificity, positive predictive values (PPV), negative predictive value (NPV) and diagnostic accuracy (DA) against gold standard (results of pathology of lymphadenectomy). All tests were two-tailed. A p-value < 0.05 was considered significant.

Results

Thirty-seven patients (8 males and 29 females) with papillary thyroid carcinoma meeting selection criteria as shown in table 8, were underwent sentinel lymph node biopsy using radioactive technique using Technetium-99m-labeled dextran after lymph scintigraphic imaging and colorimetric method using patent blue dye with mean age 41.4 years with range (19-51) years as shown in table 1.

Table 1
Patients description by Age

	Frequency	Percent	Mean
less than 45	21	56.8	41.41
45 and more than	16	43.2	
Total	37	100.0	

All patients 100% have preoperative pathology, 32 papillary thyroid carcinoma and 5 suspicious of papillary thyroid carcinoma, benign and follicular neoplasm

cases excluded due to need to paraffin examination to detect capsular or vascular invasion which is not feasible at frozen section examination. All patients 100% two to twenty four hours prior to surgery, 0.4 ml (74 MBq) of $^{99}Tm_c$-DX were injected into the primary thyroid tumor by ultra-sound guidance. Two to twenty four hours later, all patients were underwent low collar incision were made in the anterior neck. The thyroid surface was exposed and the location of the primary tumor was identified.

Patent blue 0.5% (0.25 ml/cm) was injected at four points (1-2 mm) around the tumor, with careful intent to maintain the thyroid gland in the original anatomical position; two to four minutes later the affected side's lobe and isthmus were removed and sent for frozen section analysis. From dye injection till visualization of dye colored node (SLN) or the lymph node with the maximum count by gamma probe, or more than 10 times more than the background count is considered the SLN. The detection rate was calculated as the number of patient with at least one detected cervical lymph node divided by the total number of patients who underwent SLN mapping. SLN was detected in 37/37 with detection rate 100%. The blue dye technique was able to identify SLN in 86.5 % (32/37) of patients, as shown in table 2 and relation between sentinel lymph node and identification by patent blue dye is shown in table 3.

Table 2
Sentinel lymph node identification by patent blue dye

		identification by dye		Total
		No	Yes	
Male	Count	0	8	8
	% within sex	0.0%	100.0%	100.0%
	% within identification by dye	0.0%	25.0%	21.6%
Female	Count	5	24	29
	% within sex	17.2%	82.8%	100.0%
	% within identification by dye	100.0%	75.0%	78.4%
Total	Count	5	32	37
	% within sex	13.5%	86.5%	100.0%

Table 3
Relation between SLN and identification by patent blue dye

	No.	Chi-Square	df	Sig.
No	5	19.703	1	0.001
Yes	32			
Total	37			

Radionuclide technique (lymphoscintigraphy and gamma probe scanning) was successful in 94.6 % (35/37) of the patients as shown in table 4 and relation between SLN and identification by gamma probe is shown table 5.

Table 4
Identification of SLN by gamma probe

		Identification by gamma probe		Total
		No	Yes	
Male	Count	0	8	8
	% within sex	0.0%	100.0%	100.0%
	% within Identification by gamma probe	0.0%	22.9%	21.6%
Female	Count	2	27	29
	% within sex	6.9%	93.1%	100.0%
	% within Identification by gamma probe	100.0%	77.1%	78.4%
Total	Count	2	35	37
	% within sex	5.4%	94.6%	100.0%

Table 5
Relation between SLN and identification by gamma probe

	No.	Chi-Square	df	Sig.
No	2	29.432	1	0.001
Yes	35			
Total	37			

In the 37 patients, the intraoperative frozen biopsy indicated that 22 patients were experiencing SLN metastases, while post-operative routine pathological examination was able to diagnose three additional patients with lymph node metastases that was shown in table 6. These three patients represent the three false-negative SLNs stained with H&E. Table 6

Table 6
Postoperative pathology

		postoperative pathology		Total
		Negative	Positive	
Male	Count	4	4	8
	% within sex	50.0%	50.0%	100.0%
	% within postoperative pathology	33.3%	16.0%	21.6%
Female	Count	8	21	29
	% within sex	27.6%	72.4%	100.0%
	% within postoperative pathology	66.7%	84.0%	78.4%
Total	Count	12	25	37
	% within sex	32.4%	67.6%	100.0%

Routine biopsy of 22 patients indicated SLN metastases in a total of 45 nodes, of which 20 were level VI (44.4 %), 12 were level IV (26.6 %), 10 were level III (22.2

%), two were level II (4.4 %) and one was at level VII (2.2 %). The SLNB accuracy was 94.6 %, the negative predictive value was 80 %, the positive predictive value was 100%, specificity was 100%, and sensitivity was 88 %. In the 25 total patients who were eventually diagnosed with metastasis, 22 were SLN-positive and non-SLN-negative, while the remaining three were SLN- negative and non-SLN-positive. Therefore, the combined identification showed the sensitivity of SLN was 88 %. Specificity was 100%, negative predictive value was 80 %, positive predictive value was 100%, and accuracy was 94.6 % as shown in table 7.

Table 7
Assessment of the combined techniques to identify SLNs and metastasis

Parameters of success	Number	Percentage
Identification rate	37/37	100
Sensitivity	22/25	88
Specificity	12/12	100
Negative predictive value	12/15	80
Positive predictive value	22/22	100
Accuracy	35/37	94.6

Discussion

Papillary thyroid carcinoma is a common thyroid malignant tumor, accounting for 60-80% of the total diagnosed malignant thyroid tumors. (7). In our study we examined 37 patients with papillary thyroid carcinoma, with mean age 41.4 years with range (19-51) years, and female to male ratio was 3.6:1. There is no controversy in performing therapeutic neck dissection on cervical lymph node positive PTC patients to reduce the chance of persistence and recurrence (8), however debate remains as to whether CND should be performed on cN0 PTC patients. Unfortunately, the therapeutic value of neck surgery on patients with apparent cN0 PTC remains unconfirmed. Studies have suggested that cervical lymph node metastases do not affect the survival rate of patients with papillary thyroid carcinoma, supporting the passive “wait and see “approach (9).

Kelemen PR et al., (10) first applied SLNB to the study of thyroid carcinoma; since then, several articles on the successful application of SLNB to PTC have appeared in the literature. The methods currently used for SLNB are most often blue dye and dye combined with radionuclide. Balasubramanian et al., (11) performed a retrospective meta-analysis of 24 thyroid carcinoma SLNB studies that appeared in the literature from January 1998 to November 2010. In these, 17 reports comprising a total of 832 cases of thyroid carcinoma used a single staining method to identify the SLN; the total SLN identification rate for this approach was determined to be 83.7%.

Papillary thyroid carcinoma represents a large group of well-differentiated thyroid carcinomas with several histologic variants including micro carcinomas, follicular variants, encapsulated variants, diffuse sclerosing variants, oxyphilic cell variants, and two more aggressive variants ; the tall cell variant and the columnar cell variant (12). The most common presentation of PTC is a young woman with

either a palpable neck mass in the thyroid or a palpable cervical lymph node. One of the features of PTC is its tendency for multifocality, ranging from 18% to 46%, depending on the series (13). Lymph node involvement is common, occurring in 30% of patients. Extra thyroidal extension occurs in 8% to 32% of cases (14). The most common site of extra thyroidal extension is the surrounding muscle (8%), followed by the recurrent laryngeal nerve (6%) and trachea (5%). Distant metastasis occurs in 1% to 25% of PTC patients, representing the lowest rate of all well-differentiated thyroid carcinomas (14). A study has found the survival rate of PTC at 1 year to be 97.5%, while the survival rate at 5 and 10 years is 92.8%, 89.5% respectively (15).

In our study, thirty-seven patients with papillary thyroid carcinoma meeting selection criteria were underwent sentinel lymph node biopsy using radioactive technique using Technetium-99m-labeled dextran after lymph scintigraphic imaging and colorimetric method using patent blue dye. The detection rate was calculated as the number of patient with at least one detected cervical lymph node divided by the total number of patients who underwent SLN mapping. The blue dye technique was able to identify SLN in 86.5 % (32/37) of patients. Radionuclide technique (lymphoscintigraphy and gamma probe scanning) was successful in 94.6 % (35/37) of the patients.

By using combined technique, SLN was detected in 37/37 with detection rate 100%. A total of 96 SLNs were identified in all 37 patients, 6 of sentinel lymph nodes were in level II (6.2 %), 31 in level III (32.3 %), 23 in level IV (23.9 %), 35 in level VI (36.4 %), and one in level VII (1%). In literature, the first site of metastasis from PTC is the central nodes and then the lateral lymph nodes of neck. In 35% of patients, occult metastasis in tracheoesophageal groove is also present (16). In our study, routine pathology of 22 patients indicated SLN metastases in a total of 45 nodes, of which 20 were level VI (44.4 %), 12 were level IV (26.6 %), 10 were level III (22.2 %), two were level II (4.4 %) and one was at level VII (2.2 %). In the 37 patients, the intraoperative frozen section examination revealed 22 patients were experiencing SLN metastases, while post-operative routine pathological examination was able to diagnose three additional patients with lymph node metastases.

In literature cervical lymph node metastases in patients with papillary thyroid carcinoma estimated between 15-50%, (7) and occult cervical lymph node metastases have been reported at 40-90% (17). The advantages of the blue dye technique are that there is no need for special equipment, the procedure is technically simple to perform, the reagent is low-cost, and there is no radioactive contamination. In particular, the technique facilitates the unaided visualization of the targeted tissues, which can be helpful when combined with the radionuclide technique for the r-probe to locate the “hot” lymph nodes. The disadvantages of the dye technique are that it requires a low collar incision of the thyroid gland which may not fully expose the SLNs outside the central compartment (level VI) which may lead to omissions of SLNs in the lateral neck area.

The authors noted that the vital blue dye technique has some disadvantages, such as risk of disruption of the lymphatic channels deriving from the thyroid

carcinoma, difficulty in disclosing those SLN lying outside the central compartment, and the fact that parathyroid glands can take up the blue dye as well. SLNB showed a high success rate for patients with PTC and was technically feasible. The identification of lymph node metastases in patients with cN0 PTC through SLNB will facilitate the decision to conduct regional lymph node dissection or not, and could significantly reduce surgical complications by avoiding over-treatment. Moreover, the technique will contribute to the improvement of prognosis for PTC patients. Whether the approach is able to significantly enhance the long-term survival rate of patients with PTC and reduce neck recurrence rate.

In our study, no recurrent laryngeal nerve affection, No postoperative complications such as bleeding, seroma or wound infection were experienced by any of the 37 treated individuals. Three patients experienced transient symptoms of numbness in the hands; the symptoms were relieved after consumption of calcium effervescent (500 mg Calcium and 400 IU vitamin D). No permanent hypocalcemia occurred. No patient experienced toxicity or allergic reactions due to injection of radionuclide tracer or patent blue dye. The identification of lymph node metastases in patients with cN0 PTC through SLNB facilitates the decision to conduct regional lymph node dissection or not, and could significantly reduce surgical complications by avoiding over-treatment.

Conclusion

Double techniques of sentinel lymph node biopsy are feasible with minimal side effects and may assist to a paradigm shift in the aims of treatment of differentiated thyroid cancer, from a focus on survival to a focus of disease-free status as a valid endpoint to evaluate the effectiveness of therapy.

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