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Efficacy of neck ultrasound in the detection of cervical lymph node metastasis from thyroid carcinoma

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ABSTRACT

Background: In patients with proven thyroid carcinoma, neck metastases are often occult on routine physical examination. Both the central and lateral neck compartments can harbor non palpable, occult metastases. our study was done to assess the diagnostic accuracy of preoperative neck ultrasound (US) in the detection of both central and lateral cervical lymph node metastases from thyroid carcinoma so that it can help in tailoring the surgical treatment plan. *Patients and methods*: The study was conducted at the General Surgery Department of Ain shams University Hospital from December 2017 through December 2019. It included 40 patients who had proved thyroid carcinoma by preoperative histopathology. Preoperative Neck ultrasound was done for all patients to detect suspicious Lymph Nodes. Total thyroidectomy with central neck dissection+/- Lateral neck dissection according to ultrasound results was done. The accuracy of US was assessed according to whether the removed lymph nodes had histologically confirmed malignancy or not. *Results*: The sensitivity and specificity of US in predicting thyroid carcinoma metastasis in the central neck were 13.3% and 90%, respectively. The sensitivity and specificity of US in predicting metastasis in the lateral neck were 90.9% and 85.7%, respectively. Also ultrasound detected occult non palpable lateral neck metastasis in 47.5% of patients. *Conclusion*: Preoperative neck US is a valuable tool in assessing patients with thyroid cancers. The highly sensitive and specific nature of US in predicting cervical lymph node metastasis in the lateral neck can provide reliable information to assist in surgical management.

Keywords: Thyroid carcinoma, Neck dissection, Neck Ultrasound, Lymph nodes

1. INTRODUCTION

Palpable nodules in the thyroid were found in (4%-7%) of patients, and those nodules were malignant in (9% - 13%) in adult patients with no risk factors for thyroid carcinoma. Also cervical lymph nodes were found in (20% - 50%) of patients with 90% micro-metastasis (Ogilvie et al., 2016). Neck ultrasound (US) is very helpful in identifying malignant cervical lymph nodes in (20% - 30%) of patients, leading to changing the surgical management plan in 20% of cases. Preoperative neck ultrasound is very important for both determining the prognosis as well as tailoring surgical treatment strategies for thyroid carcinoma cases (Stulak et al., 2006). In the 2015 American Thyroid Association Guidelines for Thyroid Nodules, Preoperative neck ultrasound for central and lateral neck lymph nodes is crucial for all patients scheduled for thyroidectomy, either due to carcinoma or suspicious cases (Haugen et al., 2015).

Sonographic features suggestive of abnormal metastatic lymph nodes include enlargement, loss of the fatty hilum, a rounded rather than oval shape, hyper echogenicity, cystic change, calcifications, and peripheral vascularity. No single sonographic feature is adequately sensitive for detection of lymph nodes with metastatic thyroid cancer (Leboulleux et al., 2007). Central neck dissection (therapeutic) with total thyroidectomy is the standard procedure for cases with clinically suspicious central or lateral neck lymph nodes to provide disease free survival, while lateral neck dissection is indicated in patients with biopsy proven lateral cervical metastatic lymph nodes (Kouvaraki et al., 2013).

It has become obvious that preoperative neck US has a crucial role in tailoring the surgical treatment strategy in cases of thyroid carcinoma (Nam-Goong et al., 2014).

Aim

Our aim is to measure the accuracy of preoperative neck ultrasound (US) in the detection of both central and lateral neck lymph nodes, so that it can help in tailoring the surgical treatment plan in thyroid carcinoma.

Patients and methods

This was a prospective clinical study that was conducted at Ain Shams University Hospitals in Egypt, and included forty (40) patients who had proven thyroid carcinoma by preoperative histopathology during the period between December 2017 and December 2019. All cases were operated by or under supervision of consultant surgeons at Endocrine surgery unit at Ain Shams University. An informed consent was taken from all the patients who accepted to participate.

Inclusion Criteria

- Any patient with thyroid carcinoma (differentiated, medullary, anaplastic) diagnosed by preoperative histopathology regardless age, sex, size of tumor, multifocality or bilaterality.
- Patients who were diagnosed as recent thyroid carcinoma after total or hemi thyroidectomy and were candidate for neck dissection.

Exclusion Criteria

- Patients with follicular carcinoma without suspicious lymph nodes preoperatively (either by pathology or radiology)
- Micro papillary thyroid carcinoma
- Patients with high risk of anesthesia (ASA IV or V) not candidate for surgery
- Patient refusal

All patients will be subjected to the following Preoperative assessment

- Full clinical history; personal history, present history, past history.
- Full clinical examination, general and local examination.
- Routine preoperative investigations including, complete blood count, random blood sugar, liver function test, kidney function test, coagulation profile, serum electrolytes, Thyroid profile and thyroglobulin level as base line.
- Neck Ultrasonography, by senior radiology staff using superficial probe with a frequency ranging from 7-12 MHz for both palpable and impalpable cervical lymph nodes.

Our aim here is to detect suspicious thyroid nodules and suspicious lymph nodes in both central and lateral compartments.

FNAC from the thyroid nodules

- Thyroid scan and Thyroid anti-bodies if indicated
- Electrocardiography, Echocardiography, pulmonary function test, if indicated
- Preoperative co-morbid factors such as hypertension, Diabetes mellitus, toxic state or electrolyte disturbance will be controlled when possible before surgery

Data collection

Data will be collected from patient records, medical files, and interviews.

Operative strategy

According to the results of preoperative ultrasound and clinical examination

- Patients with suspicious lymph nodes were subjected for total thyroidectomy with therapeutic central and selective lateral neck dissection.
- Patients with no suspicious lymph nodes were subjected for total thyroidectomy with prophylactic central neck dissection and biopsy of any palpable lymph nodes for intraoperative frozen section assessment and if the palpable lateral compartment lymph nodes were positive for malignancy by frozen and selective lateral neck dissection were done.

Outcome measures

histopathological examination of the surgical specimen's was done to confirm the presence or absence of malignancy in the removed lymph nodes. All specimens were evaluated by faculty members of the Department of Pathology and Laboratory Medicine at our university. Comparing these pathology results to preoperative ultrasound results, the results were presented as true and false positive, and true and false negative for both central and lateral compartment LNs separately. Also tumor characteristics as tumor size, histological type, multicentricity and extra thyroid extension were reported. Also operative complications (nerve injury and vascular injury) and post-operative complications (hypocalcemia, hoarseness) were reported (figure 1- 3).

Follow up

In the hospital patients were followed for vital signs, signs of hypocalcemia, hoarseness, choking and drain. In the OPC follow up for complications and recurrence for a period of one year with clinical examinations, ultrasound, and thyroid scan when needed.

Statistical analysis

Data were collected tabulated and statically analyzed. Analysis of data was done using SPSS (statistical program for social science version 21) as follows: Descriptive statistics (mean, standard deviation, range) was done for patient and primary tumor characteristics and continuous variables. The sensitivity and specificity for both central and lateral neck ultrasounds were calculated, also positive predictive value (PPV), and negative predictive value (NPV) were calculated. Also ROC curve was used for both compartments.

Furthermore, Pearson correlation was done to correlate between preoperative diagnostic modalities and post-operative pathology. P-value ≤ 0.05 was considered significant.

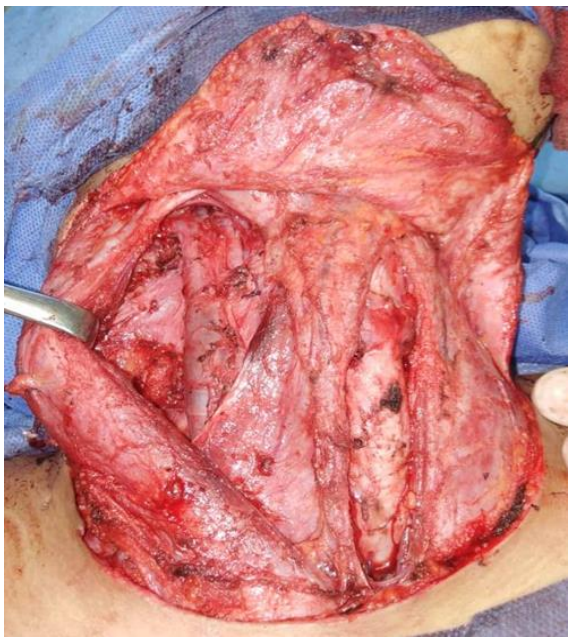

Figure 1 sternomastoid muscle retracted laterally with flap elevated.

Figure 2 Thyroid gland and central compartment lymph nodes as one block

Figure 3 Lateral compartment Lymph nodes as one block

3. RESULTS

In this study we had a total of 40 patients. They included 21(52.5%) females and 19(47.5%) males, and the median age was 45 and ranging from 20 to 68 years, mean (43.27 ± 14.42). 4 patients (10%) had total thyroidectomy and central neck dissection only, while 33 patients (82.5%) had both central and lateral neck dissection plus total thyroidectomy, only 3 patients (7.5%) had completion neck dissection after previous total thyroidectomy (both central and lateral ND). Of all patients only 11 patients (27.5%) had clinically palpable lateral neck lymph nodes (Table 1).

Table 1 patient characteristics

Characteristic	**No (%)**
Sex , F /M	21(52.5%)/19(47.5%)
Age , mean ± SD [range], yr.	43.27 ± 14.42 [20-68]
Type of operation	
TT+CND+/-cherry picking	4 (10%)
TT+CND+LND	33 (82.5%)
completion Neck dissection	3 (7.5%)
Palpable Lns(cases)	11(27%)

TT= total thyroidectomy, CND =central neck dissection, LND = lateral neck dissection

Table 2 primary tumor characteristics

Characteristic	No (%)
tumor size , mean ± SD [range], cm	2.18 ± 1.17 [0.5-5]
Pathological type	
Papillary	37 (92.5%)
Follicular	1 (2.5%)
Medullary	2 (5%)
Multifocal(cases)	12(30%)
Extra thyroid extension(cases)	11(27.5%)

Primary Tumor characteristics including pathological type, size, multifocality and extra thyroidal extension evaluated by histopathological examination, showed that, 37 (92.5%) were papillary, 1 (2.5%) follicular and 2 (5%) medullary thyroid carcinoma, also tumor size ranges from 0.5 – 5 cm with mean 2.18 ± 1.17. the tumor was multifocal in 12(30%) cases, with Extra thyroid extension in 11 (27.5%) cases (Table 2).

Using cross tabulation results from Table 3 (which shows true and false positive and negative results for both central and lateral neck compartments) we could calculate sensitivity, specificity, positive predictive value, negative predictive value and accuracy for both compartments as shown in (table 4).

Table 3 Cross tabulation results of ultrasound and corresponding pathology

		Pathology +ve	**Pathology –ve**
US Central	*+ve(5)*	4	1
	-ve(35)	26	9
US Lateral	*+ve(31)*	30	1
	-ve(9)	3	6

Table 4 Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of ultrasound (95%CI)

	Sensitivity (CI)	**Specificity(CI)**	**PPV(CI)**	**NPV(CI)**	**Accuracy(CI)**
Central	13.3%(3.8-30.7)	90%(55.5-99.7)	80%(28.4-99.5)	25.7%(12.5-43.3)	32.5%(18.6-49.1)
Lateral	90.9%(75.7-98.1)	85.7%(42.1-99.6)	96.8%(83.3-99.9)	66.7%(29.9-92.5)	90%(76.3-97.2)

Table 5 correlation between preoperative (examination and ultrasound) and the final pathology of the corresponding compartment

		pathology		r	P	Sig (Correlation)
		positive	negative			
Clinically palpable LNs	Yes (11)	11	0	0.284	0.076	NS (Weak correlation)
	No (29)	22	7			
US central compartment	Positive(5)	4	1	0.044	0.789	NS (No correlation)
	Negative(35)	26	9			
US lateral compartment	Positive(31)	30	1	0.697	0.001	HS (Strong correlation)
	Negative(9)	*3*	*6*			

r= Pearson correlation coefficient, P= p value

From these results we found that the sensitivity and specificity of US in predicting thyroid carcinoma metastasis in the central neck were 13.3% and 90%, respectively. The sensitivity and specificity of US in predicting metastasis in the lateral neck were 90.9% and 85.7%, respectively Table .

Table shows the correlation between preoperative examination of clinically palpable lateral LNs and also ultrasound results for both central and lateral compartments and the corresponding post-operative pathology, we found that there was a weak correlation (r= 0.284, p value= 0.076) for clinically palpable LNs with non-significant p value, and no or very weak correlation (r= 0.044, p value= 0.789) for central compartment ultrasound with non-significant P value, but in lateral compartment there was a strong positive correlation (r= 0.697, p value= 0.001) for US with the corresponding pathology with highly significant P value.

Using ROC curve (Figure 4 and 5) for the lateral and central compartment ultrasound respectively, we found that for the lateral compartment the AUC (area under the curve) was 0.883 with P value = 0.001 (less than 0.05) which is statistically highly significant (HS). For the central compartment the AUC was 0.517 with P value = 0.778 (more than 0.05) which is statistically non significant (NS).

The mean hospital stay was 2.40 ± 1.25 and the all cases stayed from 2 to 7 days. As Regarding overall post-operative complications, 8 cases were complicated (20%).1(2.5%) patient had unilateral RLN injury during CND, manifested by dyspnea and hoarseness of voice. 1(2.5%) patient had SAN nerve injury, as it was infiltrated by the malignant LNs and had to be excised. The same

patient had intraoperative vascular injury as the internal jugular vein was infiltrated by the malignant LNs and a segment of it had to be excised with the specimen. 3(7.5%) patients had transient hypocalcemia that resolved later on afterone month follow up. 3(7.5%) patients had post-operative hoarseness of voice. None of the cases developed wound infection or postoperative bleeding (Table 6).

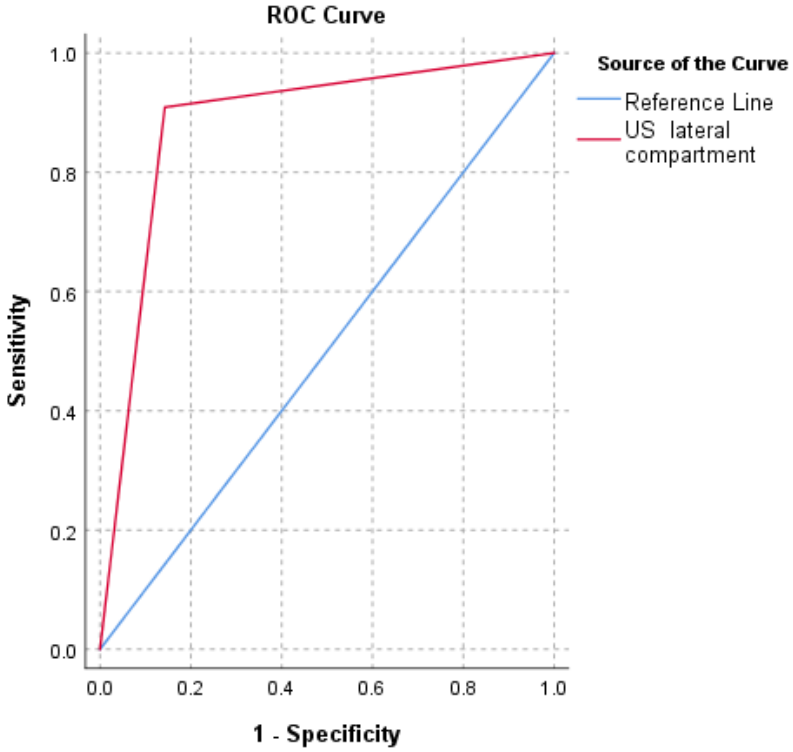

Figure 4 ROC curve of ultrasound of the lateral compartment

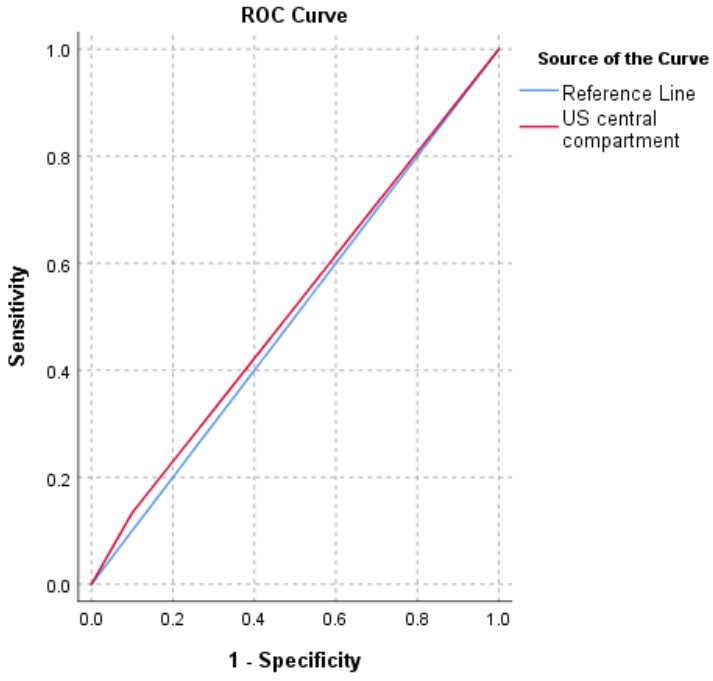

Figure 5 ROC curve of ultrasound of the central compartment

Table 6 complications

Complication	Number(%)
RLN injury	1(2.5%)
SAN injury	1 (2.5%)*
Transient hypocalcemia	3(7.5%)
Permanent hypocalcemia	0 (0%)
Hoarseness of voice	3 (7.5%)
Vascular injury	1 (2.5%)*

RLN = recurrent laryngeal nerve, SAN= spinal accessory nerve* The same patient

There was zero mortality in our cases and none of the cases developed recurrence during our follow up period of 12 months.

4. DISCUSSION

The prognosis of patients with thyroid carcinoma associated with cervical lymph node metastasis is poor compared to those without LN metastasis. Factors associated with persistent disease or recurrent papillary thyroid carcinoma are extra nodal invasion, lymph node metastasis, a tumor size >3 cm, extra-capsular extension, and the locations of metastatic lymph nodes with central compartment lymph nodes being the most frequently involved site. So, complete surgical removal of lymph nodes in the central compartment during thyroid cancer surgery is important to decrease recurrence and mortality (Lundgren et al., 2006). Cervical lymph node metastasis from thyroid cancer increases the chances for disease recurrence, but its effect on survival is minimal in low risk patients (Sato et al., 1998).

According to A study of (SEER) database, there are four parameters that lead to poor disease outcome, those parameters are metastatic lymph nodes, remote metastasis, old age (>45 years) and large tumor size. This study included more than 9000 patients (Podnos et al., 2005). Also 14 years' survival in PTC patients is different among patients with cervical lymph node metastasis positive or negative patients. It is 82% in node negative patients, and 79% in node positive patients, also another SEER study on follicular carcinoma showed decreased survival in patients with neck metastatic lymph nodes (Zaydfudim et al., 2008). So the only curative treatment for thyroid carcinoma is thyroidectomy with appropriate neck dissection to remove the gland and associated metastatic lymph nodes. Also radioactive iodine may be used for metastatic disease (Zaydfudim et al., 2008). We can't depend on routine physical examination to detect neck lymph nodes; as metastatic lymph nodes are often not detectable by clinical palpation. Also both neck compartments (central and lateral) may contain occult non-palpable metastasis. In recurrent cases anatomic changes add to this difficulty, so we should use other imaging modalities (Cooper et al., 2009). Again, according to the American thyroid association guidelines, ultrasound is used in both assessment of the neck lymph nodes as we as assessment of the contralateral lobe of the thyroid in all patients who were scheduled for thyroidectomy. Also it has become evident that ultrasound is superior to physical examination in both detecting lymph nodes and thyroid nodules (Cooper et al., 2009).

Ultrasound is not used only to detect non palpable lymph nodes, but also it can be used to provide more characters for palpable lymph nodes and to detect suspicious features in these nodes. US is comparable to CT (Computed tomography) and MRI in thyroid malignancy, but also it is more accurate in detecting lymph node metastasis (Hwang et al., 2009). Our study was a prospective study that was conducted in Ain Shams University Hospitals in Egypt, and included forty (40) patients who had confirmed thyroid carcinoma. All patients underwent preoperative Neck ultrasound by senior radiology staff using superficial probe with a frequency ranging from 7-12 MHz to detect lymph nodes in both central and lateral neck compartments then F.N.A form thyroid nodule and palpable ultrasound negative lymph nodes was done. This was followed by total thyroidectomy with central neck dissection +/- lateral neck dissection or completion neck dissection according to results of preoperative ultrasound. Pathologic confirmation of thyroid cancer in LNs was made only after cytological and/or histological examination of neck specimens obtained by surgical excision.

Comparing our study results to a study done by Ahn et al., we found that our results were comparable in both central and lateral compartments. Considering the central compartment, the sensitivity and specificity in this study was 55% and 69%, respectively while it was 13.3% and 90% respectively in our study. Comparing lateral compartment results, we found that in Ahn et al., study, the sensitivity and specificity was 65% and 82% respectively while in our study it was 90.9% and 85.7% respectively. The difference in the sensitivity of neck US may be influenced by the differences in patients and tumor characteristics (Ahn et al., 2008). Ultrasound can be very helpful when it is done by experienced qualified doctors, as it provides images and information about thyroid carcinoma and associated neck metastasis also it can be used to aid FNA to provide accurate specimens. Also it can be used for post-operative

follow up for recurrence. On the other hand, US can be time consuming and misleading in some cases as it needs long learning curve and practice to gain good knowledge, so it is operator dependent. Beside the long learning curve and practice, good knowledge to the anatomy of the neck is required, also follow up exams should be done by the same person.

There are some limitations to US in visualizing air filled structures as in the retropharyngeal region and in the mediastinal region, which may harbor low central compartment (level VI) lymph nodes (Ahnet al., 2008). The false negative results in our study were (65% in the central neck and 7.5% in the lateral neck); these results can be justified by the presence of small micro metastasis and difficulty in assessing the central neck and mediastinal region by ultrasound. We had two limitations in our study, first the small sample size that limited sub group selection, second there was detection bias as the ultra-sonographer wasn't blinded to the patient's medical history or previous laboratory and imaging results. It was a standard practice in our study to remove the Para tracheal lymph nodes (central compartment, level VI) with thyroidectomy regardless of the findings on preoperative ultrasonography (excluding follicular carcinoma), but patients with no pre-operative evidence of neck metastasis were candidate for follow up only after thyroidectomy and central neck dissection.

In our study, sensitivity, specificity, negative predictive value, positive predictive value of ultrasound in detecting central LNs were 13.3%, 90%, 25.7%, 80% respectively, and for lateral LNs were 90.9%, 85.7%, 66.7%, and 96.8% respectively. Also the diagnostic accuracy for central and lateral compartments were 32.5% and 90% respectively.

5. CONCLUSION

Preoperative neck US for patients with thyroid cancer is more sensitive and specific in the evaluation of lateral cervical compartment lymph nodes versus central compartment lymph nodes. It is reasonable to consider a prophylactic central neck dissection for high-risk patients with thyroid cancer; even in the absence of clear US evidence for local metastatic disease due to the low sensitivity of neck US in evaluating lymph nodes in the central neck in the presence of the thyroid gland. Neck US also can detect clinically impalpable LNs, so we can't depend only on clinical examination to detect LN metastasis.

Abbreviations

US: Ultrasound
LNs: Lymph nodes
CND: Central neck dissection
LND: Lateral neck dissection
TT: Total thyroidectomy
RLN: Recurrent laryngeal nerve
SAN: Spinal accessory nerve

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Author Contributions

Details of contribution of each authors regards manuscript work & production.

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Conflict of Interest

The authors declare that there are no conflicts of interests.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study.

Ethical approval

The study was approved by the Medical Ethics Committee of Department of General Surgery, Faculty of Medicine, Ain shams University, Cairo, Egypt Code (No.IRB 00006379).

Data and materials availability

All data associated with this study are present in the paper.

Peer-review

External peer-review was done through double-blind method.

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