Preoperative neck ultrasound in clinical node negative differentiated thyroid cancer

Laura Y. Wang, MBBS, MS*, Frank L. Palmer, BA*, Dorothy Thomas, BS*, Ashok R. Shaha, MD*, Jatin P. Shah, MD*, Snehal G. Patel, MD*, R. Michael Tuttle, MD†, Ian Ganly, MD, PhD*

*Department of Surgery, Head and Neck Service, †Department of Medicine, Endocrinology Service, Memorial Sloan Kettering Cancer Center, 1275 York Ave, NY, NY, 10065, USA

Background: The impact of preoperative neck ultrasound (US) on management of the lateral neck in patients with differentiated thyroid cancer (DTC) is unclear. The objective of this study was to assess the impact of preoperative neck US on the rate of lateral neck dissection in clinical N0 neck and initial Response to Therapy .

Methods: An Institutional Review Board approved retrospective review of 890 patients that had thyroid surgery for DTC between 2009 and 2010 was performed at our institution. Patients with palpable neck disease, distant metastases, less than total thyroidectomy, no postoperative thyroglobulin (Tg) determinations, and positive Tg antibodies were excluded leaving 465 patients available for analysis. Patients were divided into those who had a preoperative neck US to evaluate lateral neck nodes (n=234) and those that did not (n=231). Patient and tumor characteristics were compared using the Chi square test. The primary endpoint was Response to Therapy, defined by postoperative US and Tg levels.

Results: There were no significant differences in age, histology, T stage, postoperative RAI dose, AJCC stage, ATA risk category or duration of follow up between the 2 groups. Patients with preoperative neck US were more likely to have lateral neck dissection (LND) compared to patients without preoperative neck US (n=31 (13.2%) vs. n=2 (0.9%); $p<0.001$). Preoperative neck US resulted in better RTT ($p= 0.005$); more likely to be no evidence of disease (NED), less likely to have biochemical or structural incomplete response or return for delayed neck dissection. Preoperative US group also resulted in fewer recurrences; 10 patients from the no preoperative US group returned to operating room compared to 2 patients (4.3% vs. 0.9%, $p= 0.018$) that had a preoperative neck US.

Conclusion: Preoperative neck US detects more lateral neck disease, leading to an increase in LND with subsequent improvement in Response to Therapy and fewer return to OR for regional recurrence management.

Differentiated thyroid cancer (DTC) is increasing in prevalence. In patients over 45 years of age, metastasis to the regional lymphatic system is a potent indicator of the biological behavior and the distant metastatic potential of the disease. As such, adequate evaluation of the lateral neck is essential for better determining the nuances of an individual's disease progression. Furthermore, a comprehensive understanding of preoperative disease status is important because it can be informative for selecting appropriate therapeutic interventions.

The American Thyroid Association (ATA) recommends the routine use of US to assess the lateral neck for metastatic lymph nodes in patients with DTC (1). This is based upon evidence from several studies that have found that patients with US detectable neck metastasis have a significantly worse outcome than those with no metastases

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received March 10, 2014. Accepted June 27, 2014.

Abbreviations:

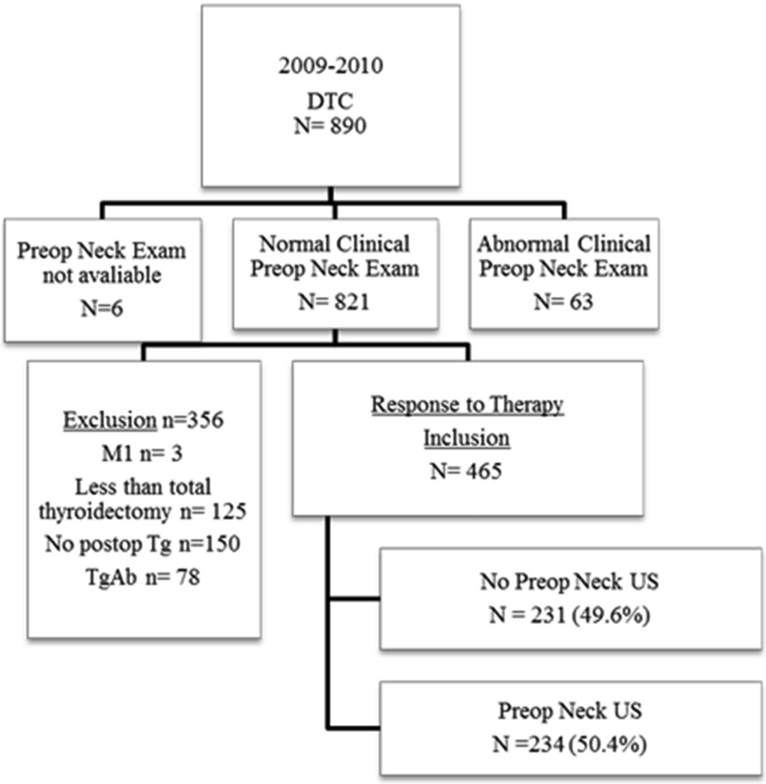


Figure 1. Inclusion Criteria

(2) or microscopic metastases detected only on histopathology (3). Others have demonstrated that US increases the detection of nodal disease compared to physical examination alone (4). Although these studies may demonstrate the usefulness of preoperative neck US in the diagnosis of lymph node metastasis, it is still controversial, if and how much preoperative neck US can improve prognosis.

At our institution, we have traditionally assessed the lateral neck by clinical examination alone and have recently transitioned to a practice of preoperative US assessment. Early adopters within our institution practice preoperative US assessment of the neck while later adopters relied on clinical assessment of the neck over the study period. This unique period of transition provided patients of similar clinical features, similar surgical techniques, radioactive iodine (RAI) use and follow up methods. This graduated change in practice therefore gave us an ideal opportunity to investigate the utility and impact on outcome of preoperative neck US by directly comparing patients who receive a preoperative neck US and those who do not. Our objective was to determine the impact of preoperative neck US on the patient's initial Response to Therapy, postoperative use of RAI and need for additional neck surgery.

Patients and Methods

Following Institutional Review Board approval, 890 consecutive surgical patients with DTC, operated on within our institution between January first 2009 and December 31st 2010, were reviewed from our hospital database. Patients were excluded if they had surgery outside of MSKCC, had clinically palpable neck disease or missing neck examination findings. The primary endpoints was Response to Therapy. Response to Therapy was developed to determine patients' likelihood of disease recurrence based on response to treatment as measured by serum thyroglobulin levels and regional imaging studies. To allow for this, patients with less than total thyroidectomy, distant metastases at presentation, no follow up thyroglobulin (Tg) or Tg antibody were also excluded. This left 465 patients for analysis (**Figure 1**).

Patient, tumor and treatment characteristics were recorded. Patient characteristics included age and gender. Tumor characteristics recorded included tumor histology, primary tumor size, presence of extrathyroid extension or vascular invasion, number and site of lymph nodes resected. All patients had total thyroidectomy. At our institution, we do not carry out prophylactic central neck dissection (CND) or lateral neck dissection (LND) in patients with a clinically N0 neck. Assessment of the lateral neck is performed by palpation at preoperative clinical visit or by preoperative US. Assessment of the central compartment for all patients is intraoperative palpation of the central compartment lymph nodes at the time of thyroidectomy. If no palpable nodes were present in the central compartment, then elective CND is not performed. If nodes are palpable and confirmed to have cancer on frozen section, then a central compartment neck dissection is carried out. N0 stage was defined if nodes were removed and found to be benign on pathology (pN0) or if no nodes were suspicious on palpation during surgery and therefore not removed (Nx). We have recently published our data on management of the clinically negative neck (5) reporting that N0/Nx have similar outcomes. Others have also demonstrated that Nx have very low incidence of recurrent/persistent disease, comparable to N0 groups.

Postoperative treatment details recorded were use of

RAI I^{131}. Postoperative thyroid stimulating hormone (TSH) suppression is practiced for all patients, aiming for a level of between 0.1–0.5 mcUnits/ml. All patients had follow up with Tg and postoperative ultrasound. Survival outcome was classified using the AJCC staging system and recurrence risk classified using the ATA risk group stratification.

The primary end point was initial Response to Therapy. Response to Therapy was defined as no evidence of disease (NED), biochemical persistent disease or structural persistent disease, as per previously published risk of recurrence stratification (6). Patients were considered to be NED if they had a suppressed serum Tg < 1 ng/mL, no detectable Tg antibodies, and no structural evidence of disease on ultrasound assessment. Patients with persistent disease were further classified as having either biochemical evidence of disease (elevated Tg values alone without structural correlate) or structural evidence of disease (elevated Tg values with structural correlate on ultrasound)

The presence of local or regional structural disease recurrence following treatment was based on cytological or histopathological confirmation of structurally identifiable disease. The median follow-up for the entire patient cohort was 29 months (range 1–52 months).

Patient, tumor and treatment variables were compared within groups using Pearson's chi squared test. A p value less than 0.05 was considered significant. Statistical analysis was carried out using JMP statistical package (SAS Institute Inc. SAS Campus Drive, Cary, NC 27513) and SPSS (IBM Company Headquarters, 233 S. Wacker Drive, 11th Floor, Chicago, Illinois 60606).

Results

The median age of the cohort was 48.7 years (range 14–84 years) and 337 were female (72.4%). Two hundred and thirty four patients (50.4%) had a preoperative ultrasound evaluation of cervical neck lymph nodes and 231 patients (49.6%) did not. Patient demographics stratified by preoperative neck US status are shown in Table 1. There were no significant differences in age, histology, T stage, postoperative RAI dose, AJCC stage, ATA risk category or duration of follow up between the 2 groups. The N1a and N1b patients were more likely to have T3T4 tumors as one would expect. There was no difference in the histologic subtypes between patients who were N0/Nx, N1a and N1b.

Rate of neck dissection

Management of the neck stratified by preoperative US is shown in **Figure 2**. Patients with and without preoperative neck US did not differ in the rate of CND (15.8% ((18+19)/234) vs. 15.6% (36/231) respectively). In contrast, the use of preoperative neck US significantly impacted on the operative management of the lateral neck. Patients with a preoperative neck US were more likely to have a LND compared to those without (13.2% ((12+19)/234) vs. 0.9% (2/231), $P < .001$).

A detailed flowchart showing the management of the lateral neck is shown in **Figure 3**. Of the 234 patients who had preoperative neck US, 48 patients had abnormal lateral compartment nodes detected. Of these, 31 patients underwent LND. Of the 17 patients that did not have LND: 8 patients had benign fine needle biopsy, 6 patients had the 'abnormal' lymph node sampled intraoperatively and found to be benign on frozen section, 1 patient had known Hodgkin's lymphoma, 1 had metastatic prostate cancer and 1 patient had a preoperative decision for RAI over neck dissection. No patient with a normal preoperative lateral neck on US had LND. Of the 31 patients who had lateral ND, preoperative FNA was performed in 17 patients; 16 of which were malignant, 1 was benign. The remaining 14 patients did not have a preoperative FNA as the findings on US were deemed suspicious enough to warrant ND. Nine of these 14 patients had lateral neck metastases on final histopathological evaluation.

Nodal Disease and Quality of Neck Dissection

The quality of neck dissection (defined by the mean number of nodes resected per neck dissection) was similar in both groups. The mean number of side adjusted positive nodal disease in the central and lateral compartments did not differ in patients with and without a preoperative neck ultrasound ($P = .637$, $P = .988$ respectively). Twenty-seven patients had false negative preoperative US. Most these (n = 25) were in level 6 of the central neck (N1a), 1 was in level 7 of the central neck (N1b) and 1 patient had a borderline lateral LN sampled intraoperatively .

RAI therapy

Patients without a preoperative neck US were more likely to receive postoperative RAI therapy compared to patients who had a preoperative neck US ($P = .004$). In patients that received RAI, the mean RAI administered activity did not differ between the two groups ($P = .713$).

Response to initial therapy

Response to Therapy was significantly better in patients with a preoperative neck US (Table 1). Two hundred and twenty six patients (96.6%) with a preoperative neck US were classified as NED within 18 months compared to 205 patients (88.7%) without a preoperative neck US ($P = .005$). Biochemical and structural persistence were also

Table 1. Comparison of Patients with and without Preoperative Neck US

		No Preop US		Preop US		
		n	(%) or Mean +/-SD	n	(%) or Mean +/-SD	*p value*
Age	<45yo	100	43.3	83	35.5	*0.084*
	≥45 yo	131	56.7	151	64.5	
Gender	Female	181	78.4	156	66.7	***0.005***
	Male	50	21.6	78	33.3	
Histology	Papillary	215	93.1	224	95.7	*0.096*
	Follicular	9	3.9	2	0.9	
	Hurthle Cell	7	3.0	8	3.4	
T Stage	T1	114	49.4	117	50.0	*0.536*
	T2	31	13.4	41	17.5	
	T3	70	30.3	60	25.6	
	T4	16	6.9	16	6.9	
N Stage	pN0/Nx	168	72.7	171	73.1	***0.000***
	pN1a	59	25.5	34	14.5	
	pN1b	4	1.7	29	12.4	
Neck Dissection	CND only	34	14.7	18	7.7	***0.000***
	LND only	0	0.0	12	5.1	
	CND and LND	2	0.9	19	8.1	
	No ND	195	84.4	185	79.1	
Side Adjusted LNs removed	Mean Positive LNs/CND	36	3.8+/-3.4	38	4.2+/-4.2	*0.637*
	Mean Total LN/CND	36	9.9+/-5.0	38	10.8+/-6.8	*0.526*
	Mean Positive LNs/LND	2	2.5+/-3.5	31	2.5+/-2.4	*0.988*
	Mean Total LN/LND	2	32.0+/-21.2	31	25.8+/-16.4	*0.752*
RAI Therapy	Yes	99	42.9	70	29.9	***0.004***
	No	132	57.1	164	70.1	
RAI Dose (mCi)	Mean +/- SD	98	121+/-41	69	119+/-34	*0.713*
AJCC Stage	I	153	66.2	153	65.4	*0.227*
	II	15	6.5	17	7.3	
	III	49	21.2	39	16.7	
	IV	14	6.1	25	10.7	
ATA Risk Category	Low	94	40.7	113	48.3	*0.240*
	Intermediate	121	52.4	105	44.9	
	High	16	6.9	16	6.9	
Lowest Tg (within 6 months postop)	(mean+/-SD)	231	0.602 +/-2.64	234	0.094 +/-0.334	***0.004***
Response to Therapy	NED	205	88.7	226	96.6	***0.005***
	Biochemical incomplete	13	5.6	4	1.7	
	Structural incomplete	13	5.6	4	1.7	
Neck Dissection for persistent or recurrent disease	Yes	10	4.3	2	0.9	***0.018***
	No	221	95.7	232	99.1	
FU (months)	Mean +/- SD	231	31+/-13	234	30+/-13	*0.352*
	Range		004–57		007–54	

lower in the group with preoperative US (1.7% vs. 5.6%, 1.7 vs. 5.6% respectively).

Neck Dissection for Recurrent or Persistent disease

In addition to better Response to Therapy, patients who had preoperative US were significantly less likely to have a subsequent lateral neck dissection for recurrent or persistent disease. **Figure 4** shows details of 12 patients who required neck dissection. Ten patients from the no preoperative US group returned to operating room compared to 2 patients (4.3% vs. 0.9%, $P = .018$) that had a preoperative neck US. Overall median follow up for this group was 38 months. No patient with a normal preop-

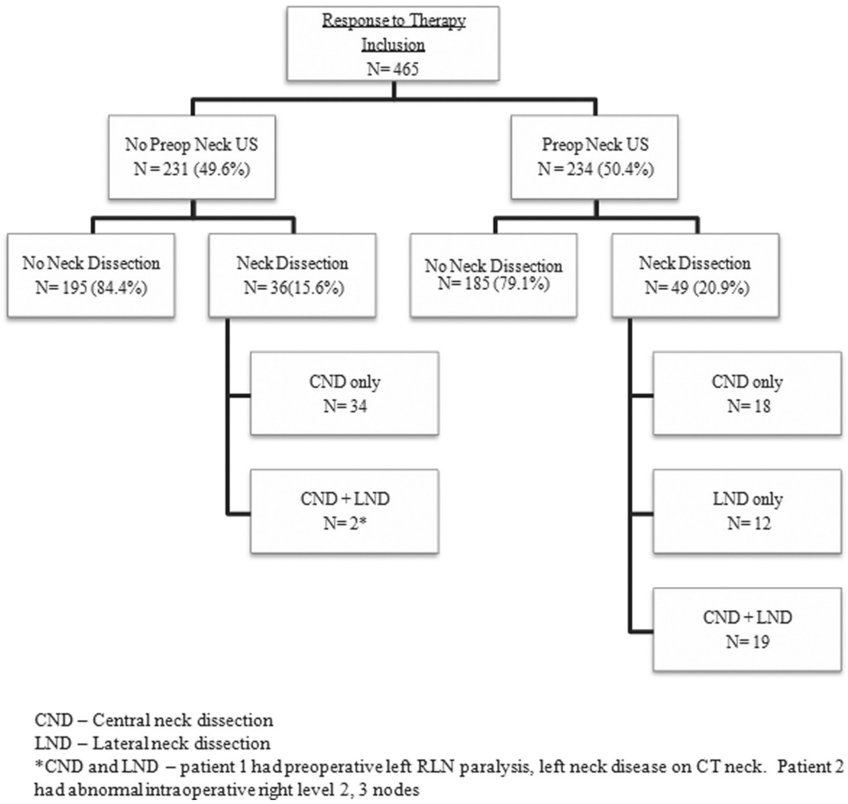


Figure 2. Surgical Neck Management in patients with and without Preoperative Neck US

erative neck US required a neck dissection following treatment for recurrent or persistent disease.

Discussion

Occult metastases in patients with DTC are common occurring in 20%–90% of patients (7, 8). Despite this high frequency, occult central or lateral metastases have no effect on outcome and are largely thought to be indolent disease (3). However, lateral compartment location and macrometastases (nodes > 1cm in size) are thought to confer worse prognosis, especially in older patients (9, 10). This is reflected in the AJCC staging system where patients over 45 years of age are stage III if they have central neck disease and stage IV if they have lateral neck disease. It is therefore important to carefully assess the lateral neck by clinical examination supplemented with imaging in patients with DTC.

In the assessment of neck nodes, it has been shown that preoperative neck ultrasound has improved sensitivity compared to preoperative physical examination for the diagnosis of nodal disease. Kouvaraki et al demonstrated that preoperative neck US detected LN metastases in neck compartments believed to be uninvolved by physical examination in 21% of patients undergoing primary thyroid surgery (11) and the detection of preoperative US cervical lymph nodes potentially alters the surgical management in up to 30% of patients (11, 12). Furthermore, diagnosis of positive regional lymph nodes has been associated with poorer outcomes, particularly in older patients (2, 3). As a result of these studies, the ATA recommends preoperative neck US to assess the lateral neck compartment lymph nodes for all patients undergoing thyroidectomy for thyroid cancer (1). However, it should be noted that the use of US in the assessment of the central neck lymph nodes is much less sensitive (13). In the present study, the overall sensitivity and specificity of US assessment of both lateral and central neck nodes was 57% and 88% respectively. The reduced sensitivity was largely due to the failure to detect positive nodes in the central neck. Twenty-seven patients had false negative preoperative US. Most these (n = 25) were in level 6 of the central neck (N1a), 1 was in level 7 of the central neck (N1b) and 1 patient had a borderline lateral LN sampled intraoperatively (N1b). This further illustrates the limitations of preop US in assessing the central compartment neck nodes.

Sonographic features suggestive of abnormal metastatic lymph nodes include loss of the fatty hilus, a rounded rather than oval shape, hypoechogenicity, cystic change, calcifications, and peripheral vascularity. However, no single feature is adequately sensitive for detection of lymph nodes with metastatic thyroid cancer (14, 15). US has been shown to be superior to other imaging modalities such as computer tomography (CT), magnetic resonance imaging (MRI), (MRI) and positron emission tomography (PET) for the detection of cervical lymph node metastases where sensitivities range between 30%–40% (16). US examination also has the additional benefit of being easily combined with fine needle aspirate biopsy (FNAB). US with FNAB is a more accurate method for assessment of neck node status. A Dutch study of 120 patients found the specificity of combined US and FNAB results was significantly higher than US alone; 92.9% compared with 60.0% (17). Our institution increasingly utilizes FNAB cytological confirmation of sonographically suspicious cervical lymph nodes to guide the extent of neck dissection. While the utility of US in regional LN diagnosis has

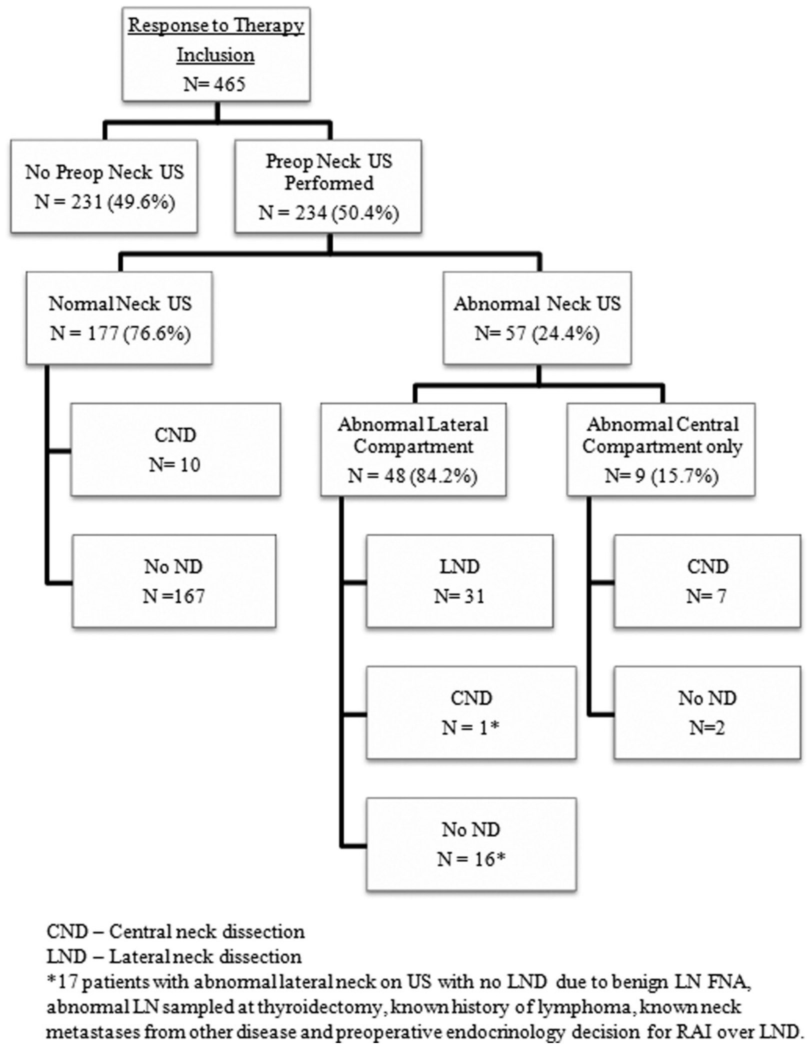


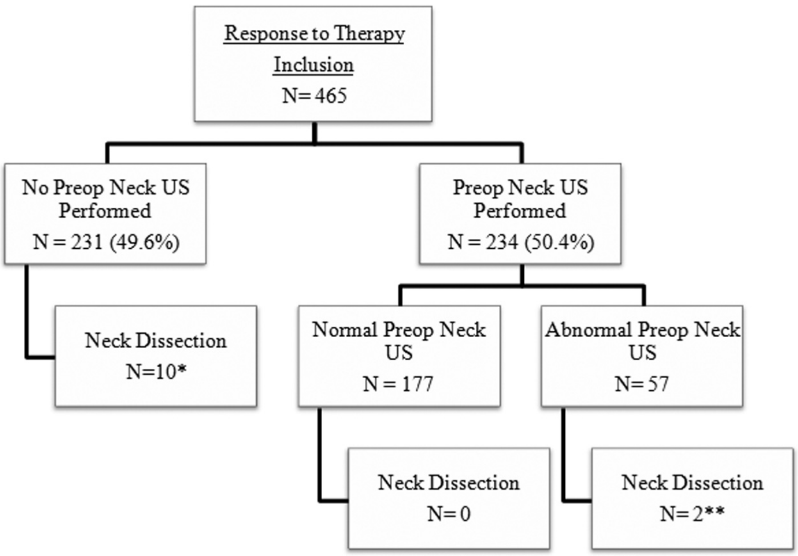
Figure 3. Lateral Neck Management based on Preoperative Neck US result

been established, how preoperative neck US changes prognosis is still unclear.

At our institution, we have traditionally assessed the lateral neck by clinical examination and have only recently employed US assessment in selected patients. In the years 2009 to 2010 approximately 50% of our patients did not have preoperative lateral neck node assessment prior to surgery. This therefore gave us an ideal and unique opportunity to investigate the ATA recommendations with regards to the utility and efficacy of preoperative neck US. By directly comparing patients who had and those that did not have preoperative neck US we were able to directly compare response to therapy between groups and also directly compare subsequent later neck dissection rates for persistent or recurrent neck disease. This study also gave us an opportunity to compare the therapeutic outcome, with reference to disease specific and recurrence free survival, as well as the frequency of neck dissection in each group.

In our cohort, suspicious cervical LNs were identified in 24.4% of patients with normal clinical neck exams on preoperative US, a finding consistent with the literature; preoperative US identifies suspicious cervical lymph nodes in 20%–31% of cases (2, 18, 19). One of the major findings of our study was that patients with a preoperative neck US had a higher rate of lateral neck dissection (13.2% vs. 0.9%, *P* $< .001$) and a significantly better Response to Therapy than patients without preoperative US (*P = .005)*. In addition, patients who had preoperative neck US were less likely to return to the OR for recurrent or persistent disease (0.9% vs. 4.3%, *P = .018*). Another important finding from our study was that those who did not have a preoperative neck US were more likely to receive postoperative RAI (42.9 vs. 29.9%, *P = .004*). Patients without a preoperative lateral neck node assessment by US were more likely to have an elevated Tg following total thyroidectomy and this likely led to the initiation of adjuvant RAI. This is supported by the finding that patients with a preoperative neck US have a significantly lower postoperative Tg value (0.094 ug/ml +/- 0.334) compared to patients without preoperative US (0.602 ug/ml +/- 2.64) (*P = .004*). These 3 observations (improved Response to Therapy, reduced rate of subsequent neck dissection for persistent or recurrent neck disease and reduced RAI usage) support the recommendation that preoperative assessment of the lateral neck detects impalpable lateral neck disease thereby identifying select patients who will benefit from subsequent lateral neck dissection.

These results therefore provide some justification for the use of preoperative ultrasound. However, one could also argue that the use of preoperative ultrasound results in many patients being overtreated with some patients having lateral neck dissections unnecessarily. While preoperative US decreases return to OR for persistent or recurrent disease, it is not clear if early detection and surgical intervention results in improved survival. When we compare the DSS of our preoperative US cohort vs the no preoperative US cohort, the 3 year DSS are identical at 100% for both groups. Longer follow up of both groups



*10 patients requiring neck dissections did not have preoperative neck US
**2 had abnormal preoperative neck US
1 patient had abnormal LNs on preoperative US that were sampled intraoperative but no formal neck dissection was carried out.
1 patient had right central and lateral neck dissection at first operation but required return to OR despite this

Figure 4. Lateral neck dissection for recurrent or persistent disease

is required to better define the impact of this improved Response to Therapy on survival. It is possible that early detection results in no improvement in survival compared to a management strategy of only carrying out a lateral neck dissection when nodes become clinically palpable. In addition, early detection by preoperative US may result in some patients having a neck dissection unnecessarily. For example, in our study, neck dissection was performed initially in 13.2% of preoperative US patients (31/234). In the no preoperative US cohort, 2 patients required neck dissection initially but a further 10 required a neck dissection later on making an overall neck dissection rate of 5.2% (12/231). This suggests that over 50% of the preoperative US patients may have underwent LND for potentially indolent disease.

Therefore one can argue that both management strategies (1. preoperative US and early detection of nodes with early LND and 2. no preoperative US with salvage LND when clinically palpable nodes become apparent) are equally effective in terms of survival. The early detection strategy has the potential advantage in terms of patient counseling; as these patients can be reassured after the first Tg blood measurement and postoperative US assessment that they have a negligible risk of recurrence and can thus have less intense follow up. The same cannot be said for the late detection strategy (no preoperative US cohort) as we do not know which of these patients will recur and therefore all patients in this cohort require long term follow up. The benefit of the late detection strategy means that all LND will be performed for clinically detectable disease, rather than for subclinicial disease.

In conclusion, our study demonstrates that the use of preoperative neck node assessment by US facilitates a more complete surgical resection to the regional lymph nodes in patients with DTC. This results in improved Response to Therapy, reduces adjuvant RAI treatments and reduces regional recurrence rates. Such a policy is beneficial for patient counseling, limits subsequent follow up tests and allows for early patient discharge. However, although this policy results in improved Response to Therapy, it remains unclear if there is any impact on survival.

Acknowledgments

Address all correspondence and requests for reprints to: Dr Ian Ganly, Department of Head and Neck Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, NY, 10065, USA. Telephone: **212–639–7604,** Fax: **212–396 –5560 Email:** ganlyi@mskcc.org.

Disclosure Summary: Authors have no disclosures to declare.
This work was supported by.

References

1. **Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM.** Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2009;19:1167–1214.
2. **Moreno M, Agarwal G, de Luna R, Siegel E, Sherman S, Edeiken-Monroe B, Clayman G.** Preoperative lateral neck ultrasonography as a long-term outcome predictor in papillary thyroid cancer. *Arch Otolaryngol Head Neck Surg*. 2011;137:157–162. doi: 110.1001/archoto. 2010.1254.
3. **Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K, Miyauchi A.** Ultrasonographically and anatomopathologically detectable node metastases in the lateral compartment as indicators of worse relapse-free survival in patients with papillary thyroid carcinoma. *World J Surg*. 2005;29:917–920.
4. **Kouvaraki M, Shapiro S, Fornage B, Edeiken-Monro B, Sherman S, Vassilopoulou-Sellin R, Lee J, Evans D.** Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. *Surgery*. 2003;134:946–954; discussion 954–945.
5. **Nixon I, Ganly I, Patel S, Morris L, Palmer F, Thomas D, Tuttle R, Shah J, Shaha A.** Observation of clinically negative central compartment lymph nodes in papillary thyroid carcinoma. *Surgery*. 2013; 154:1166–1172; discussion 1172–1163. doi: 1110.1016/j.surg. 2013.1104.1035.
6. **Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M,**

Brokhin M, Omry G, Fagin JA, Shaha A. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. *Thyroid*. 2010;20:1341–1349.

7. **Qubain S, Nakano S, Baba M, Takao S, Aikou T.** Distribution of lymph node micrometastasis in pN0 well-differentiated thyroid carcinoma. *Surgery*. 2002;131:249–256.
8. **Arturi F, Russo D, Giuffrida D, Ippolito A, Perrotti N, Vigneri R, Filetti S.** Early diagnosis by genetic analysis of differentiated thyroid cancer metastases in small lymph nodes. *J Clin Endocrinol Metab*. 1997;82:1638–1641.
9. **Hughes CJ, Shaha AR, Shah JP, Loree TR.** Impact of lymph node metastasis in differentiated carcinoma of the thyroid: a matched-pair analysis. *Head Neck*. 1996;18:127–132.
10. **Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A.** A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. *Surgery*. 2004;135:139–148.
11. **Kouvaraki MA, Shapiro SE, Fornage BD, Edeiken-Monro BS, Sherman SI, Vassilopoulou-Sellin R, Lee JE, Evans DB.** Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. *Surgery* 2003;134:946–954; discussion 954–945.
12. **Stulak JM, Grant CS, Farley DR, Thompson GB, van Heerden JA, Hay ID, Reading CC, Charboneau JW.** Value of preoperative ultrasonography in the surgical management of initial and reoperative papillary thyroid cancer. *Arch Surg* 2006;141:489–494; discussion 494–486.
13. **Lesnik D, Cunnane M, Zurakowski D, Acar G, Ecevit C, Mace A, Kamani D, Randolph G.** Papillary thyroid carcinoma nodal surgery directed by a preoperative radiographic map utilizing CT scan and ultrasound in all primary and reoperative patients. *Head Neck*. 2014;36:191–202. doi: 110.1002/hed. 23277. Epub 22013 Apr 23272.
14. **Leboulleux S, Girard E, Rose M, Travagli J, Sabbah N, Caillou B, Hartl D, Lassau N, Baudin E, Schlumberger M.** Ultrasound criteria of malignancy for cervical lymph nodes in patients followed up for differentiated thyroid cancer. *J Clin Endocrinol Metab*. 2007;92: 3590–3594. Epub 2007 Jul 3593.
15. **Kuna S, Bracic I, Tesic V, Kuna K, Herceg G, Dodig D.** Ultrasonographic differentiation of benign from malignant neck lymphadenopathy in thyroid cancer. *J Ultrasound Med*. 2006;25:1531–1537; quiz 1538–1540.
16. **Jeong H, Baek C, Son Y, Choi J, Kim H, Ko Y, Chung J, Baek H.** Integrated 18F-FDG PET/CT for the initial evaluation of cervical node level of patients with papillary thyroid carcinoma: comparison with ultrasound and contrast-enhanced CT. *Clin Endocrinol (Oxf)*. 2006;65:402–407.
17. **Baatenburg de Jong R, Rongen R, Lameris J, Harthoorn M, Verwoerd C, Knegt P.** Metastatic neck disease. Palpation vs ultrasound examination. *Arch Otolaryngol Head Neck Surg*. 1989;115:689–690.
18. **Solorzano C, Carneiro D, Ramirez M, Lee T, Irvin Gr.** Surgeon-performed ultrasound in the management of thyroid malignancy. *Am Surg*. 2004;70:576–580; discussion 580–572.
19. **Shimamoto K, Satake H, Sawaki A, Ishigaki T, Funahashi H, Imai T.** Preoperative staging of thyroid papillary carcinoma with ultrasonography. *Eur J Radiol*. 1998;29:4–10.