Papillary thyroid carcinoma nodal surgery directed by a preoperative radiographic map utilizing CT scan and ultrasound in all primary and reoperative patients

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ABSTRACT: *Background.* To study the diagnostic accuracy of physical examination (PE), ultrasonography (US), contrastenhanced computed tomography (CT) and in preoperative detection of macroscopic nodal metastasis in primary/recurrent papillary thyroid carcinoma (PTC) patients to determine if the routine addition of CT would be beneficial in accurate preoperative lymph-node surgery planning.

Methods. In a tertiary center prospective study, 162 PTC patients underwent preoperative lymph-node evaluation by PE, US, and CT. Sensitivity, specificity, positive/negative predictive value (PPV/NPV) of each nodal detection technique were calculated in central/lateral cervical compartments. The gold standard for diagnostic-accuracy was surgical pathology.

Results. In patients undergoing primary (Group I)/revision (Group II) surgical treatment for PTC, combined US/CT yielded significantly higher sensitivity for macroscopic lymph-node detection in both lateral and central neck, most marked in Group I-central compartment.

Conclusions. Combined preoperative US/CT provides reliable, objective, preoperative macroscopic nodal metastasis map to design rational nodal surgery in primary/revision PTC patients. © 2013 Wiley Periodicals, Inc. *Head Neck* 00: 000–000, 2013

KEY WORDS: papillary thyroid cancer, neck dissection, macroscopic nodal metastasis, preoperative radiography, CT scan, ultrasonography

INTRODUCTION

Papillary thyroid carcinoma (PTC) is a disease characterized by lymph node metastasis with incidence rates, depending on the mode of detection and definition of node positivity, ranging from 12% to 80% of patients.[1–11] Much of this nodal positivity is microscopic nodal disease, which is clinically inapparent. Clinically apparent nodes are defined as nodes evident by (1) preoperative physical examination (ie, palpation), (2) preoperative radiographic evaluation, or (3) intraoperative detection by the surgeon and are present in 35% of patients presenting with PTC.[12–14]

Although small volume microscopic lymph nodes may be present in up to 80% of patients diagnosed with PTC, locoregional recurrence rates in treated patients range from 2% to 6% regardless of whether lymph node dissection is performed or radioactive iodine (RAI) is given.[11,15–27] Although this microscopic nodal disease is of little if any clinical significance, some surgeons perform routine prophylactic central neck dissection. For PTC, nodal surgery may instead be based on the detection and treatment of gross clinically apparent macroscopic disease. This study was undertaken to create and study a robust radiographic evaluation to achieve this goal of preoperative macroscopic nodal detection.

Clearly, in terms of prognostic importance, it is only macroscopic nodal disease (as opposed to microscopic) that counts in terms of increased risk of additional nodal recurrence and, therefore, it is only macroscopic nodal disease that warrants surgical treatment.[28]

Interpretation of the surgical literature is substantially hampered by the fact that pathologically positive necks have not been stratified in most studies as to macroscopic versus microscopic. This provides significant difficulty in these studies' clinical interpretation.

Nodal detection preoperative/postoperative imbalance

It is also widely known that up to one third of patients with PTC will recur after initial treatment and that nodes missed at initial surgery is a well-recognized source of recurrent disease, and is more accurately termed persistent disease.[29,30] Indeed, the 2009 American Thyroid Association (ATA) guidelines note "completeness of surgical

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resection is an important determinant of outcome…, residual metastatic lymph nodes represent the most common site of disease persistence/recurrence…, and adequate surgery is the most important variable influencing prognosis.''[31] Current standards of endocrine follow-up for detection of postoperative recurrences include serial high-resolution cervical ultrasonography, stimulated thyroglobulin (Tg) measurement, and I^{131} whole body scanning, sometimes combined with CT, MRI, and positron emission tomography (PET/CT).[5,32–39] These postoperative measures are significantly more sensitive in the detection of clinically significant nodal disease than nodal screening currently offered to patients preoperatively, which is typically a physical examination, ultrasonography, and perhaps intraoperative inspection of the central neck. Ultrasound sensitivity is poor in preoperative evaluation of the central neck (region 6) ranging from 10.5% to 27%.[8,40,41] Intraoperative palpation is also insufficient in detecting nodal disease, with studies suggesting that less than 50% of nodal metastases can be appreciated by experienced surgeons at the time of surgery.[2–4,42] Clearly, surgeons need an accurate preoperative radiographic map to improve preoperative nodal detection and avoid this preoperative/postoperative imbalance that currently characterizes PTC nodal management to reduce what can be sometimes morbid reoperations. In the absence of such a map, nodal surgery is often offered prophylactically, given the lack of sensitivity of ultrasonography and intraoperative palpation in the central neck. Ultrasonography is limited by its dependence upon technician skill and by its inability to overcome the shadowing effects of the lower cervical and upper thoracic anatomic structures including the thyroid gland itself, the laryngeal skeleton and trachea, the clavicular heads, and sternum. Axial contrast-enhanced CT imaging has long been successfully used by head and neck oncologic surgeons in the assessment of local and regional malignancies of the upper aerodigestive tract and cervical viscera. This imaging tool adds considerable information to that obtained by ultrasonography. In fact, we believe the detection threshold of combined CT/ultrasonography may provide an excellent current definition of clinically significant nodal metastasis, which could in turn form the basis of a rational and standard surgical plan for macroscopic nodal disease excision.

MATERIALS AND METHODS

Inclusion criteria

Patients with fine-needle aspiration (FNA)-positive newly diagnosed PTC (n = 95; group I), as well as patients previously treated with surgery +/− adjuvant radioiodine therapy for PTC with suspected or proven recurrence (n = 67; group II), underwent systematic preoperative lymph node assessment by the following modalities: (1) physical examination; (2) high-resolution cervical ultrasonography and (3) contrast-enhanced CT of the neck.

Ultrasound and CT studies were routinely performed on the same day in order of first availability and the studies were interpreted by an experienced head and neck radiologist. Ultrasound and CT scans were ordered specifically to assess for adenopathy in both the central and lateral neck in all cases with the requisition written: "Patient with PTC, please check for central and lateral lymph nodes.'' Established institutional criteria were used to designate lymph nodes as macroscopically positive or negative by imaging.

Ultrasound examinations were performed at 2 different sites with a linear high-resolution transducer (for example, a linear 12-5 MHz). Imaging was performed in a standardized manner, beginning with the thyroid gland itself and then progressing to evaluate the central neck for adenopathy (level 6 and as much of level 7 as could be seen angling the transducer inferiorly). Evaluation of the submental and lateral neck nodes was also performed to include levels 1 through 5. Images were reviewed in a prospective fashion by radiologists with subspecialty expertise in ultrasound and head and neck radiology.

CT scanning was performed on a Siemens Somatom Sensation 40-slice CT scanner. Unless the patient had a contraindication to contrast administration (allergy, renal insufficiency), 65 cc of omnipaque was given at a rate of 1.2 cc/second. Scanning began after a 60-second delay using a 1.2 mm collimator at a pitch of 0.75. Images were acquired at 120 kVp with mAs varying according to the thickness of the body part (utilizing the CARE Dose application). Imaging was performed from the skull base to the upper mediastinum. Raw data were presented with a slice thickness of 1.5 mm in the axial plane. These raw images were then reconstructed into 3.0 mm axial and 2.0 or 3.0 mm coronal images for review. All CT images were interpreted in a prospective fashion by subspecialty trained head and neck radiologists.

On ultrasound examinations, lymph nodes were considered suspicious for metastasis if they were enlarged, rounded, demonstrated a loss of the normal fatty hilum, demonstrated increased echogenicity, abnormal vascularity, or contained calcification or cystic change.[41,43–45] With the exception of size, any of these features alone was considered sufficient to deem the lymph node suspicious no matter where the node was located. Lymph node size is problematic as a sole criterion in young patients as they often have hyperplastic lymph nodes, particularly at level 2. Metastatic lymphadenopathy in patients with papillary cancer is more common in the lower rather than upper jugulodigastric chains.[45,46] Therefore, upper level 2 nodes, which were elongated and flat, but otherwise demonstrated normal architecture (fatty hilum), normal echotexture (hypoechoic), and normal vascular pattern (vessels limited to the hilum), were considered likely reactive in young patients. In addition, lymph nodes less than 5 to 8 mm might be considered equivocal if a normal fatty hilum could not be identified, recognizing that the evaluation was limited by the small size of the lymph node (Table 1). Therefore, size was incorporated as one of the important parameters in definition of nodal suspicion for malignancy but was not used independently of other nodal characteristics, including importantly the exact location in the neck.

TABLE 1. Imaging features suspicious for metastatic involvement of lymph nodes.

Contrast-enhanced CT	Ultrasound
Short axis greater than 1 cm in axial plane*	Short axis greater than 1 cm in transverse plane*
Enhancing	Increased vascularity
Cystic change	Cystic change
Calcification	Calcification
Rounded shape with loss of fatty hilum	Rounded shape with loss of fatty hilum
	Hyperechoic

* Size is not used as a sole criterion in upper jugulodigastric (level 2) lymph nodes.

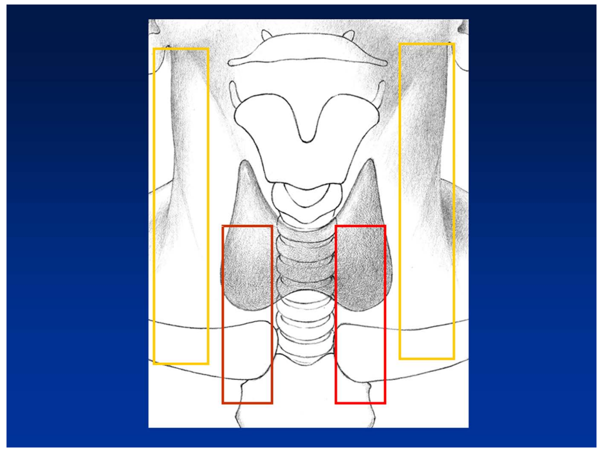

FIGURE 1. Outer boxes indicate the lateral neck nodal compartments, whereas the inner boxes indicate the central neck nodal compartments. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

On CT examinations, lymph nodes were evaluated for enlargement, asymmetry, calcification, increased enhancement, and cystic change. A lymph node was considered enlarged if it measured more than 8 to 10 mm in short transverse axis. However, as with the ultrasound evaluation, uppermost level 2 lymph nodes, which were mildly enlarged, might still be considered normal if they demonstrated normal fatty hilum, flattened morphology, and normal enhancement characteristics (Table 1).

All imaging was completed within 6 months before the date of surgery. All patients needed to have at least 1 compartment dissected (ie, with a lymph node specimen sent for pathological examination) to be included in the study. Final pathological assessment of resected lymph nodes was used as the gold standard against which diagnostic accuracy of nodal detection by physical examination, ultrasonography, and CT was judged. This study has been reviewed and approved by the institutional review boards of both institutions (Massachusetts Eye and Ear Infirmary and the Massachusetts General Hospital). All patients included in this study were patients treated by the senior surgeon (G.W.R.) between 2003 and 2008 at the Massachusetts Eye and Ear Infirmary and the Massachusetts General Hospital, Boston, MA.

Study design

This study was designed to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of commonly used nodal detection techniques in the evaluation of patients with PTC: physical examination, ultrasonography, CT, and combined ultrasonography/CT. Each patient was considered to have 4 cervical compartments potentially harboring metastatic lymph nodes (right and left central compartments, and right and left lateral compartments; Figure 1). The findings for each nodal study (physical examination, ultrasonography, and CT) were reviewed for all patients (n = 162) in both the central and the lateral compartments. This group was then further subdivided into primary surgical patients with thyroid FNA cytology diagnostic for papillary cancer and no previous treatment (group I; n = 95) and patients with previously treated (surgery +/− RAI) PTC with suspicious or FNA-proven recurrent or persistent PTC presenting for revision surgery (group II; n = 67).

Surgical treatment was guided by results of nodal detection studies. Patients who were suspected to harbor metastatic nodal disease in any compartment by physical examination, ultrasonography, or CT underwent dissection in that compartment and the specimen was subject to pathologic examination through nodal bivalving of macroscopically enlarged nodes. All group I patients were treated by total thyroidectomy; central and/or lateral neck compartmental node dissection was performed only if at least 1 study was positive in the corresponding cervical compartment(s). All group II patients were treated by completion thyroidectomy as necessary and compartment-oriented neck dissection if any study was positive in that compartment. All 162 patients included in the study underwent neck dissection in at least 1 compartment (162 patients total; 648 potential compartments total considering that each patient has 2 central and 2 lateral cervical compartments, right and left; Figure 1).

Primary and revision patients were considered separately as distinct populations because of expected underlying disease prevalence differences. The sensitivity, specificity, PPV, and NPV for detecting pathologic lymph nodes were determined for physical examination, ultrasonography, CT, and combined ultrasonography/CT. This was performed for primary (group I) and revision (group II) patients in both central and lateral compartments. Findings from ultrasound and CT scans were evaluated independently. For the combined ultrasonography/CT examination, the study was considered positive if either ultrasonography or CT was positive in that compartment. In all cases, the final pathologic examination served as the gold standard for the presence or absence of metastatic nodal disease. If all studies were negative for a particular compartment, no dissection was performed and that compartment was assumed, for surgical purposes, to be free of clinical disease and was not included in the final analysis. In earlier studies, including work done at the Mayo Clinic and MD Anderson Cancer Center, if no lymph nodes were removed from a given compartment because of negative imaging (eg, ultrasonography), then the status of that compartment was considered N0 in the final statistical analysis.[29,47] In our final analysis, only

TABLE 2. Concordance between ultrasonography and CT stratified by patient type and location

	Agreements		Disagreements		
	US- and CT-	US+ and CT+	US+ and CT-	US- and CT+	Kappa*
Primary patients ($n = 95$)					
Lateral neck	145	23	0	12	0.61
Central neck	153	11	6	20	0.40
Revision patients ($n = 67$)					
Lateral neck	75	34	9	16	0.59
Central neck	74	38	12	10	0.65

* Kappa values represent moderate chance-corrected agreement (all $p < .001$). Lateral compartment in primary and revision patients include180 and 134 lymph nodes, respectively.

dissected compartments were included (ie, only compartments yielding a lymph node specimen for examination were included in the determination of diagnostic accuracy of nodal detection technique). This was done because we believed this method would provide a more accurate estimation of the false-negative rate and, therefore, study sensitivity and is similar to the work of others.[48,49] Pathologic assessment of all neck dissection compartments was performed in accordance with standard pathologic departmental protocol, with focus on pathologic assessment of grossly macroscopic nodal disease, specimens had no formal processing for the detection of microscopically positive nodes.

Definition of neck compartments

The central compartment is defined in the recent ATA consensus statement as node-bearing tissue lying between the common carotid arteries from the level of the hyoid bone superiorly to the level of the brachiocephalic vein/innominate artery and includes retro-carotid nodes, pretracheal, prelaryngeal, as well as paratracheal nodes (level VI).[50] Lateral neck nodes include all cervical nodes lateral to the internal jugular veins and includes the retrojugular nodes (levels II, III, IV, and medial portion of V). Each patient was considered to have 2 central compartments (based primarily on paratracheal nodes) and 2 lateral compartments (Figure 1).

Statistical analysis

Among the 95 primary patients and 67 revision patients, agreement between ultrasonography and CT was evaluated by the kappa coefficient for lateral and central neck compartments with strength of agreement determined by benchmarks of Landis and Koch.[51] For primary and revision patients, sensitivity and specificity were determined among lateral and central compartments for each study (physical examination, ultrasonography, CT, and ultrasonography/CT) to detect positive lymph nodes using pathology as the gold standard with 95% confidence intervals (CIs) determined using Wilson's method.[52] PPV and NPV were determined using the Bayes theorem using a prevalence of positive nodes of 95% for revision patients and 40% for primary patients; 95% CIs were calculated using the delta method.[53] Comparisons of sensitivity and specificity between methods were determined using the McNemar test for binary matched pairs and confirmed by generalized estimating equations to handle multiple compartments evaluated for the same patient.[54] Statistical analysis was performed using the SPSS software package (version 18.0, SPSS/IBM, Chicago, IL). Two-tailed values of $p < .05$ were considered statistically significant.

RESULTS

The primary purpose of this study was to determine the relative additional value of CT over physical examination and ultrasonography in detecting nodal disease. Table 2 demonstrates the concordance between ultrasonography and CT by procedure and location. In summary, the studies may be said to have moderate overall agreement in their identification of metastatic lymph node involvement (Kappa agreement: 0.40–0.65).

Table 3 demonstrates the diagnostic accuracy of lymph node detection tests in group I patients by cervical compartment. Physical examination has low sensitivity for lymph node detection in primary patients in both the central and the lateral neck (10% and 38%, respectively). The sensitivity of ultrasonography is equivalent to that of a CT scan in the lateral neck for group I patients (79%). However, the sensitivity of a CT scan is far superior to ultrasonography in the central neck of primary patients (50% vs 26%). In both the central and lateral neck, the

TABLE 3. Group I (primary patients): diagnostic accuracy characteristics of nodal detection tests.

	Evaluation of lateral neck				Evaluation of central neck			
	PE	US	CT	US/CT	PE	US	CT	US/CT
Sensitivity	38%	79%	79%	97%*	10%	26%	50%	54%*
95% CI	24–55	63–90	63–90	85–99	4–21	16–40	37–63	40–67
Specificity	93%	87%	83%	77%	100%	95%	94%	89%
95% CI	79–98	70–95	66–93	60–88	95–100	88–98	87–97	80–94
PPV	79%	80%	76%	74%	100%	78%	85%	77%
95% CI	69–89	70–90	67–85	64–84	97–100	71–85	80–90	70–84
NPV	69%	86%	86%	98%	63%	66%	74%	75%
95% CI	60–78	78–94	78–94	95–100	55–71	58–74	67–81	68–82

Abbreviations: PE, physical examination; US, ultrasound; US/CT, combination of both US and CT; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.
Pathology is based on 196 compartments (64 lateral necks, 132 central necks).
* Sensitivity of US/CT is significantly higher than ultrasound alone for lateral necks ($p = .013$) and central necks ($p < .001$). Confidence intervals were determined for sensitivity and specificity using Wilson's method.[1] PPV and NPV were determined using Bayes' theorem using a prevalence of 0.40 and 95% CIs calculated using the delta method.

TABLE 4. Group II (revision patients): diagnostic accuracy characteristics of nodal detection tests.

	Evaluation of lateral neck				Evaluation of central neck			
	PE	US	CT	US/CT	PE	US	CT	US/CT
Sensitivity	24%	72%	76%	88%*	9%	77%	76%	93%*
95% CI	14–37	58–83	63–86	76–95	4–20	65–87	62–85	82–97
Specificity	84%	84%	76%	64%	100%	68%	74%	63%
95% CI	65–94	65–94	57–89	45–80	83–100	46–85	51–88	41–81
PPV	97%	99%	98%	98%	100%	98%	98%	98%
95% CI	93–100	97–100	95–100	95–100	98–100	95–100	95–100	95–100
NPV	5%	14%	14%	22%	5%	13%	14%	31%
95% CI	0–10	6–22	6–22	15–30	0–10	5–22	6–22	21–41

Abbreviations: PE, physical examination; US, ultrasound; US/CT, combination of both US and CT; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.
Pathology is based on 147 compartments (75 lateral necks, 72 central necks).
* Sensitivity of US/CT is significantly higher than ultrasound alone for lateral necks ($p < .001$) and central necks ($p < .001$). Confidence intervals were determined for sensitivity and specificity using Wilson's method.[1] PPV and NPV were determined using Bayes' theorem using a prevalence of 0.95 and 95% CIs were calculated using the delta method.

greatest sensitivity is delivered by the combination of ultrasonography/CT (54% for central and 97% for lateral, respectively). It should be noted that the difference in sensitivity of ultrasonography/CT versus ultrasonography alone is statistically significant in both cervical compartments in group I ($p = .013$ for lateral neck and $p < .0001$ for central neck).

The benefit of increased sensitivity is accompanied by a slightly decreased specificity in all detection studies. Physical examination has the highest specificity in group I patients in both the central and lateral neck (100% and 93%, respectively). The specificity of ultrasonography and CT is comparable in both the central (95% and 94%, respectively) as well as the lateral (87% and 83%, respectively) cervical compartments. Combined ultrasonography/CT has the lowest specificity in group I patients; 89% in the central neck and 77% in the lateral neck.

Table 4 demonstrates the diagnostic accuracy of nodal detection tests in group II patients by cervical compartment. Once again, physical examination has the lowest sensitivity in both the lateral and the central neck (24% and 9%, respectively). In revision patients, the sensitivity of ultrasonography and CT are comparable in both the lateral (72% and 76%, respectively) as well as the central (77% and 76%, respectively) cervical compartments. However, once again, combined ultrasonography/CT has significantly higher sensitivity in revision patients in both the lateral (88%) as well as the central (93%) cervical compartments. It should be noted that the increased sensitivity of ultrasonography/CT versus ultrasonography alone is statistically significant in both cervical compartments in group II patients. The increased sensitivity is once again accompanied by lower specificity values.

Impact of CT

In addition to the above analysis, we wanted to know to what degree a CT scan impacted the surgical plan and increased positive lymph node yield on final pathology. To do this, we examined all patients in which ultrasonography was a false negative but CT scan was true positive. Overall, CT scans correctly changed the surgical plan in 26% of patients (ie, identified a compartment as positive, which yielded positive macroscopic lymph nodes by pathology with ultrasonography being negative in that compartment). These patients benefited from more extensive surgery based on additional information gathered from the CT scan that was not available by ultrasonography alone. If the ultrasonography information alone was used for surgical planning, these involved lymph nodes would not have been removed. For group I (primary) patients, CT scan results correctly changed the surgical plan for the better in 25% overall (12% in the lateral compartment and 21% in the central compartment). Examining group II (revision) patients, CT scan results correctly changed the surgical plan for the better in 27% overall (23% in the lateral compartments and 14% of the central compartments; Figure 2).

DISCUSSION

Rates of macroscopic versus microscopic node positivity

Numerous studies on PTC document clinically apparent macroscopic cervical nodal metastasis as determined by preoperative physical examination, ultrasonography, and intraoperative detection in 21% to 35% of patients at presentation.[5,12–14,55] Thus, nodal surgery is required in just over one third of patients presenting with PTC. However, small volume microscopically positive nodes are far more prevalent, occurring in 23% to 81% of patients with clinically negative preoperative nodal assessments who are operated on prophylactically.[2–6,11,19,21,23,56–61]

Nodes and prognosis

Traditionally, PTC nodal metastasis are thought to increase locoregional recurrence risk[25,62,63] but are believed to have a weak relationship to overall survival.[64,65] In fact, lymph node status has been omitted from prognostic schemes which include age, distant metastases, extent of disease, and size (AMES), patient age, tumor grade, tumor extent, and tumor size (AGES), and metastases, patient age, completeness of resection, local invasion, and tumor size (MACIS).[66–73] Although, 2 recent Surveillance, Epidemiology, and End Results database reports suggest that nodal disease is in fact a determinant of tumor-related survival in patients over 45 years

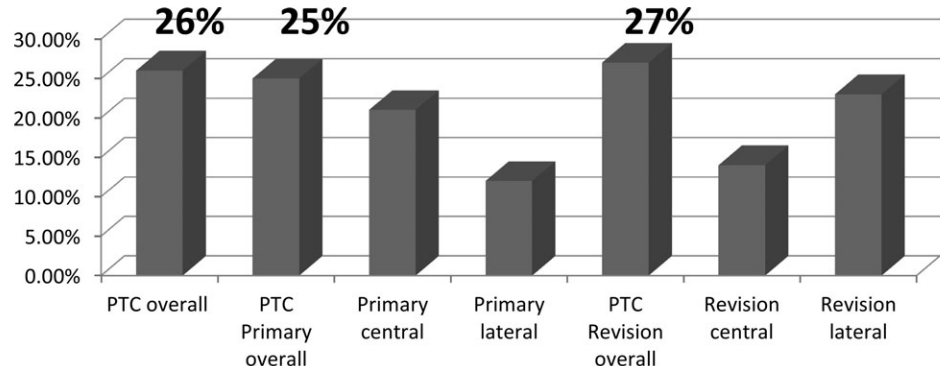

FIGURE 2. CT correctly identified macroscopic nodal disease missed by ultrasonography allowing for correct expansion of surgery in 26% overall, 25% for primary patients, and 27% for revision patients.

of age,[55,74] clearly the bulk of prognostic importance for PTC nodes centers on recurrence.

Prognostic difference between microscopic versus macroscopic metastasis: the rationale for preoperative radiographic mapping

Recent work has shown that patients with PTC (primary tumor >1 cm) have rates of microscopic nodal disease in up to 62% of central neck compartments judged preoperatively to be N0 but have recurrence rates of only 1% to 6% if undissected. It seems that both papillary microcarcinoma and macroscopic PTC are often associated with subclinical microscopic lymph node metastases that usually do not progress and seldom become clinically relevant even if untreated.[75–80]

Gemsenjäger et al,[12] in a study of 159 patients with PTC followed for up to 27 years, found that the prognostic significance of nodal positivity resided primarily in clinically macroscopic nodes rather than microscopically positive nodes and felt this validated clinical use of nodal staging. Further, they found significantly higher recurrence in patients with clinically positive nodes compared to those who were clinically negative. It was also shown that using preoperative physical examination, preoperative ultrasonography, and intraoperative inspection accurately targeted clinically relevant nodes yielding positive histology with a positive predictive value of 100%. Bardet et al,[14] in a study of 545 patients with PTC, also found a significant relationship between macroscopic nodal positivity and recurrence risk that was not present for microscopically positive nodes. Cranshaw and Carnaille[13] found that recurrence rates were equal for patients with pathologically negative nodes and for those with microscopically positive nodes (6% and 5%, respectively), and were significantly higher in patients with macroscopic nodal metastases (32%). Ito's work study supports the prognostic significance of radiographically identified nodes. Regardless of tumor size, radiographically (ultrasonography) identified macroscopic nodes in the lateral neck were associated with significantly worse recurrence-free survival rates as compared to pathologically positive, ultrasonography negative nodes (ie, micrometastases).[35]

A number of studies in patients initially judged clinically N0 reveal an average rate of recurrence of 4%.[13,14,25,81] This is more or less indistinguishable from patients with clinically N0 necks who have microscopic cervical lymph node metastases identified by prophylactic neck dissection (microscopic pN1) with an average of 6%.[13,14,25,35] These 2 groups substantially diverge from the group of patients with PTC who present with clinically apparent N1 disease with an average nodal recurrence rate of over 20%.[13,14,25,35,40,73,81]

This body of work strongly suggests that nodal prognostic significance resides in macroscopically abnormal nodes, which can be preoperatively identified radiographically and that no such prognostic significance is present in radiographically negative nodes. Therefore, the term "clinically apparent nodal disease'' describes a prognostically important group of patients with nodal disease.

These studies provide strong support for the use of preoperative radiographic imaging to define clinically relevant nodal metastases in patients with PTC in order to plan an optimal, individualized operation appropriate for that patient's extent of disease at presentation.[35,40,62]

Physical examination

Physical examination contains little information to determine extent of nodal surgery, with a sensitivity of 9% to 10% in the central neck and 24% to 38% in the lateral neck in our series. Given this, it is not surprising that data for intraoperative palpation in detection of nodal disease has also been shown to have low sensitivity and reliability. Moley and DeBenedetti[82] showed intraoperative palpation was associated with sensitivity of 64% and specificity of 71% in the detection of nodal disease in patients with medullary thyroid carcinoma. Other authors have shown experienced surgeons are able to identify less than 50% of grossly positive nodes through intraoperative palpation.[4,42] Our data and the referenced literature clearly show that palpation, whether preoperative or intraoperative, is clearly insufficient for detection of macrometastasis.

Ultrasound

High-resolution ultrasonography has an established role in the assessment of thyroid nodules and in lymph node evaluation in patients with suspected or known metastatic thyroid cancer.[31] It is low cost, involves no radiation, and provides accurate evaluation of discrete nodal lesions via assessment of size, borders, shape, hilum, microcalcifications, cystic change, and vascular flow.[83,84] In previous studies, the benefit of ultrasonography over physical examination has been well demonstrated. When compared with physical examination alone, ultrasonography information changed the planned surgical procedure in 32.9% to 39% in patients undergoing surgical treatment for primary or recurrent PTC.[29,47] For the detection of papillary carcinoma nodal disease, sensitivities in the literature range from 50% to 84% with specificities ranging from 95% to 97%, but data regarding the sensitivities of ultrasonography in central and lateral neck locations have been lacking.[29,36,47,85]

Unfortunately, ultrasound before thyroidectomy misses 50% to 90% of level VI lymph node metastases.[73,86] In our series, ultrasonography demonstrated a sensitivity of only 26% in the central neck of primary surgical patients, whereas the sensitivity of CT scanning in the central neck of primary patients was twice that despite equivalent specificities. In recent work looking at ultrasonography sensitivity in both central and lateral neck in primary patients, Ito et al[8,40] found a sensitivity of only 10.5% in the central neck and a sensitivity of only 27% in the lateral neck. Recently, the work of Hwang and Orloff[41] in 99 patients with PTC showed an ultrasonography sensitivity lymph node detection of 27% in the central neck with a 73% false-negative rate. The lack of ultrasonography sensitivity, especially in the central neck, has been studied and noted by multiple authors.[79,80] Its accuracy can be compromised by difficulty of distinguishing metastatic nodes immediately adjacent to the thyroid from the gland itself. In addition, a number of normal anatomic structures cause significant acoustic shadowing, effectively obscuring the regions posterior to them, including air filled structures such as the larynx and trachea, and areas deep to the clavicles, jaw, and sternum. This significantly limits ultrasound evaluation of mediastinal and retropharyngeal regions, regardless of the interest and expertise of the operator. All these areas are routinely visualized on CT. Ultrasonography also fails to deliver comparably detailed anatomic information relating nodal location in relation to important adjacent cervical viscera including larynx, trachea, esophagus, and the great vessels of the mediastinum, which is essential to the surgeon. This significantly restricts its utility as a single modality for complete macroscopic lymph node mapping in patients with PTC undergoing preoperative surgical evaluation.

CT scanning

The emerging data available in the literature regarding CT in PTC nodal assessment is supportive of our data and encouraging regarding the utility of CT.[49,87] Yoon et al[49] compared sensitivity, specificity, and diagnostic accuracy of ultrasonography and CT in 37 primary patients presenting with PTC. Overall sensitivity of CT scan (77%) was significantly higher than for ultrasonography (62%) and exceeded ultrasound sensitivity in both the central and lateral neck. In agreement with our work, they found ultrasonography sensitivity was lowest in the central neck. Kim et al[87] also have recently published evidence supporting the superiority of CT in nodal detection in the central neck of primary PTC and the superior sensitivity of combined ultrasonography/CT in detecting metastatic lymph nodes in both the lateral and central neck in patients with PTC. Because CTs performed as part of combined PET/CT examinations are often noncontrast scans, often with large fields of view, we have found PET/CT is a lower resolution study than a dedicated fine-cut neck CT with contrast. CT imaging of the cervical soft tissues is performed in a standardized repeatable fashion and is not operator dependent, providing detailed information systematically from base of skull to mediastinum. CT with contrast has proven its utility in nodal assessment for squamous cell carcinoma[88,89] as well as through 4D CT in accurately imaging parathyroid adenoma, a pursuit not dissimilar to the search for metastatic nodes in patients with PTC.[90] CT can assess lateral lymph nodes as well as central lymph nodes in the perithyroidal, paralaryngeal, paratracheal, retropharyngeal, retrosternal, and mediastinal locations with superior sensitivity, as demonstrated by our data. It also provides detailed axial anatomic information that is familiar to most thyroid surgeons. This precise anatomic nodal location information relative to adjacent cervical viscera is, of course, the most essential feature of a preoperative radiographic map and, in our hands, correlates well with safe and successful nodal surgery.

Iodinated CT contrast

A central argument against the use of contrast-enhanced CT scan in patients with PTC is based on the use of iodine-based contrast media. Certainly, the iodine load associated with CT imaging requires consideration in postoperative I^{131} radioisotope scanning, ablation, and treatment (RAI). It has been proposed that radioiodine treatment may be delayed for up to 12 weeks after administration of iodinated contrast medium without loss of ablation efficacy.[91,92] However, to put this debate in proper context, one should consider several issues. First, the current timeframe of postoperative RAI administration has been followed by convention rather than by evidence-based analysis. Often in our practice, RAI is given 1 or 2 months after surgery. With previous administration of contrast with preoperative CT, it is given 3 months after surgery; a delay of 4 weeks beyond the normal timeframe. There is no evidence suggesting that a several week delay in ablation is at all meaningful prognostically to the patient, although it does represent a change from the typical postoperative endocrine routine. Ito et al's[76] observations suggest even more significant delays in treatment for low-risk patients is of no consequence. Second, according to the most recent ATA guidelines, RAI is beneficial to only a limited subset of patients with advanced PTC. For the vast majority of patients (with stage I and stage II disease), the beneficial effects of adjuvant radioiodine ablation in preventing recurrence or improving survival are questionable.[31,93–96] Third, it is currently standard practice to obtain CT with contrast in patients whose preoperative examination suggests advanced or invasive disease, such as those with recurrent laryngeal nerve paralysis on preoperative laryngeal examination in order to accurately assess laryngeal or tracheal invasion. Thus, those patients who would be expected to benefit most

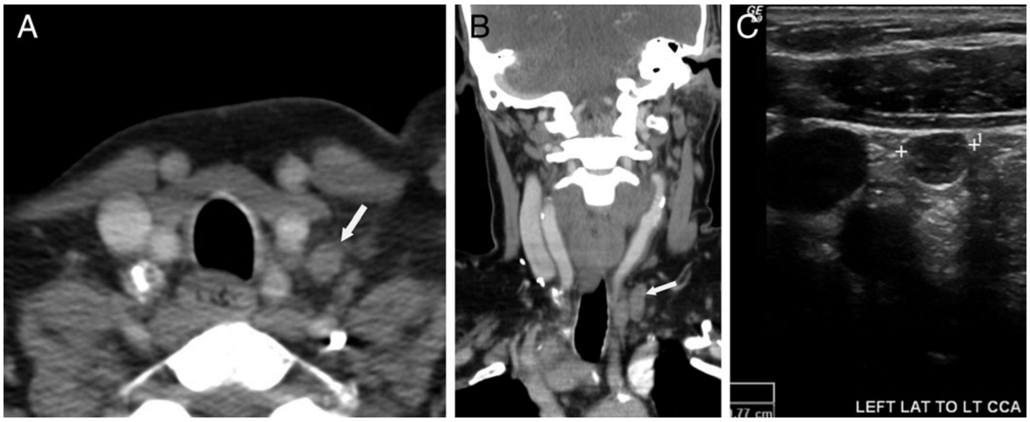

FIGURE 3. Left lateral neck lymph node seen on both CT scan (axial A and coronal B) and ultrasonography (C).

from postoperative radioactive iodine ablation are those who have routinely received iodinated contrast as part of their preoperative evaluation as current standard procedure. Fourth, recent work by Tala Jury et al[95] has suggested that the total body iodine content may not be important in determining the efficacy of ablative radioisotope and that there is lack of association between urinary iodine excretion and successful thyroid ablation in patients with thyroid cancer. These data certainly call into question previously held assumptions regarding the perhaps incompletely understood physiology of iodinated contrast medium and its effect on therapeutic radioiodine ablation of thyroid tissue.

Radiation risk from neck CT

Addition of contrast-enhanced CT to the evaluation of a patient with thyroid cancer will result in increased exposure to ionizing radiation. Recent work has suggested that low-dose radiation of the type experienced during CT scanning has the potential to increase cancer risk.[97] Risks are highest in children but are also higher in young women, a group well represented within the cohort of patients with papillary thyroid cancer. A useful way to think of CT effective dose is to compare it to the effective dose of a chest radiographic series (PA and lateral) or a mammographic series. Neck CT doses are roughly equivalent to 55 chest radiograph series or 9 mammography series.[97] In the case of mammography, the dose delivered in 9 years of screening mammography is considered appropriate despite the fact that it is a screening test performed in a patient without cancer. In a patient who already carries a diagnosis of cancer, a similar dose is appropriate if it results in more accurately targeted, effective cancer treatment. Based on the results of this study, we believe benefits conferred to patients who have proven malignancy justify the risk of CT, especially if it can help to avoid revision s–urgery.

Combined CT/ultrasonography — complimentary studies

Our data show sensitivity of combined ultrasonography/CT radiographic mapping is significantly superior to ultrasonography alone in primary patients both in the central and lateral neck ($p < .05$). Furthermore, combined ultrasonography/CT mapping is significantly more sensitive than ultrasonography alone in revision patients in both the central and lateral neck ($p < .05$). In comparison with ultrasonography alone, CT sensitivity is higher for lymph node detection in both primary and revision patients and in all compartments. This advantage is most profound in the central compartment of patients undergoing primary surgical therapy. This improved sensitivity allows for better surgical planning and the best possible chance of removing all clinically significant nodal metastasis at operation, whether primary or revision. Macroscopic disease that had been missed by ultrasound was radiographically detected by CT scan in 26% for patients with PTC overall. For primary patients, 25% had disease identified by CT scan that was missed by ultrasound; 21% in the central neck and 12% in the lateral neck. For revision patients, 27% had nodal disease successfully identified by CT scan that had been missed on ultrasound; 14% in the central neck and 23% in the lateral neck.

CT and ultrasonography complement each other well in the assessment of papillary cancer. Ultrasonography provides sensitive focal lesional information including calcifications, cystic change, and hilum anatomy. A CT scan provides high resolution localization of the individual lesion relative to the surrounding cervical viscera in a

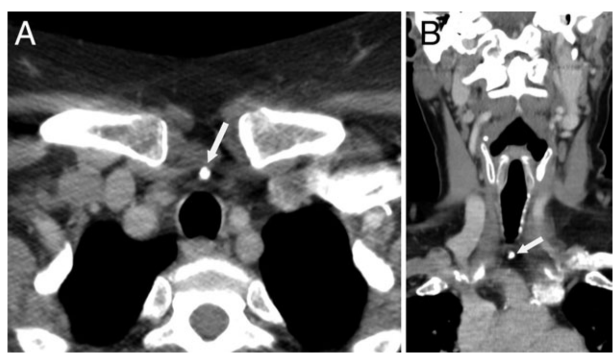

FIGURE 4. Central neck lymph node (arrows) seen only on CT, not seen on ultrasonography (axial A and coronal B). Node was surgically excised.

FIGURE 5. Central neck lymph node (arrows) seen only on CT, missed on ultrasonography (axial A and coronal B). Node was surgically excised.

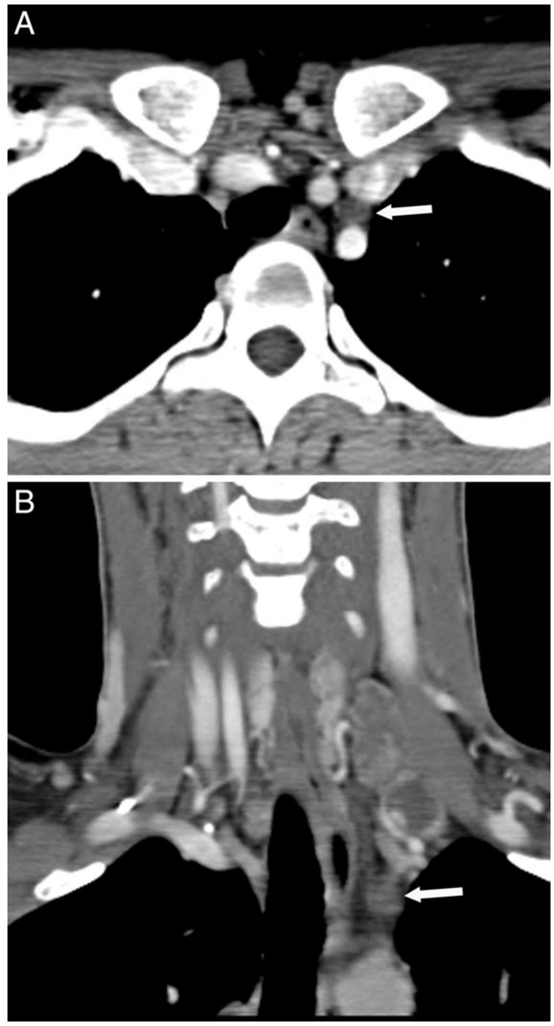

FIGURE 6. Cystic mediastinal node seen only on CT, not seen on ultrasonography (axial A and coronal B). Node was surgically excised.

way that can be easily interpreted and used by the surgeon. Through combined CT and ultrasonography cervical mapping, an objective framework is constructed upon which to base the extent of nodal surgery for papillary carcinoma of the thyroid.

A commonly invoked argument against routine use of combined ultrasonography/CT scanning preoperatively for all patients with primary or persistent/recurrent PTC is one of cost versus benefit. We feel that the relatively nominal additional cost of the CT is an investment that will pay for itself considering the protracted natural history of this disease process in the majority of cases and the high reported rates of persistent and recurrent disease. Comprehensive surgical treatment and higher positive macroscopic nodal yield may reasonably be expected to lead to lower post-treatment thyroglobulin levels; fewer investigative tests searching for recurrence, fewer biopsies for suspicious lymph nodes discovered by surveillance ultrasonography, and hopefully fewer reoperations and other secondary treatments for persistent/recurrent disease.

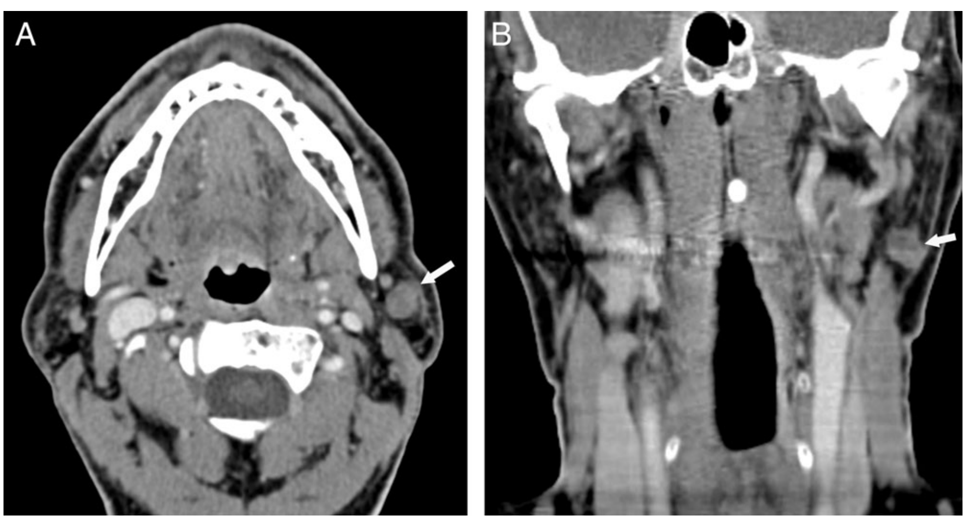

FIGURE 7. Intraparotid node positive for papillary thyroid carcinoma (PTC) seen on CT not seen on ultrasonography (axial A and coronal B). Node was surgically excised.

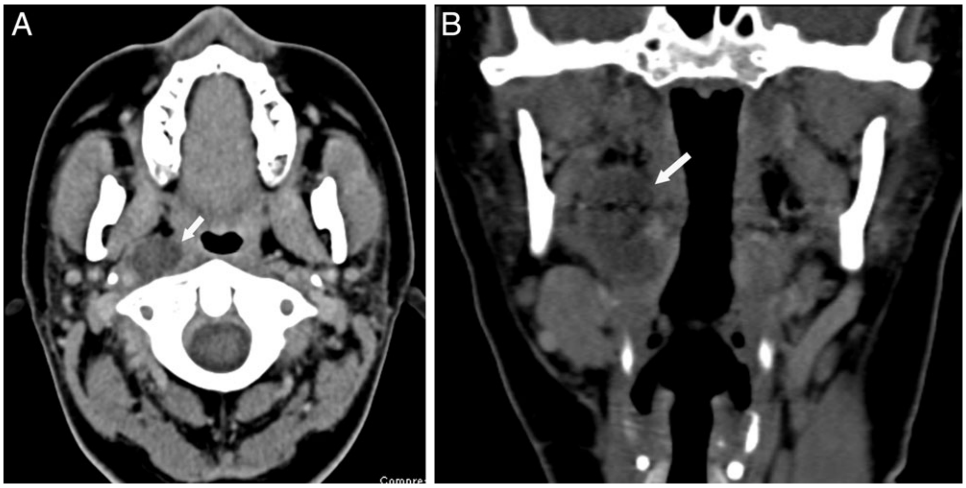

FIGURE 8. CT scan showing Node of Rouvier (right retropharyngeal node) not seen on ultrasonography (axial A and coronal B).

We believe this initial investment will actually lead to a cost savings over the long term; not to mention the intangible psychological benefit to patients who might endure less intense post-treatment oncologic scrutiny by virtue of having been treated optimally from the outset. In summary, we have found ultrasonography and CT to be highly complementary studies; ultrasonography for high resolution lesional information and CT for 3D localization relative to adjacent cervical viscera and for detection of disease in ultrasound blind spots (Figures 3–8).

CONCLUSIONS

Approximately one third of patients presenting with PTC harbor clinical nodal disease in either the central or lateral neck, requiring surgery. If this is not detected preoperatively, it will be detected by current postoperative endocrine algorithms using serial high-resolution ultrasonography and stimulated thyroglobulin measures. The thyroid cancer surgeon needs to offer a comparably sensitive preoperative analysis or the operative suite will be revisited far too frequently. The real hotbed of nodal disease in PTC (the central neck) is seen poorly by ultrasonography with sensitivity of only 26% in the present study. Combined ultrasonography/CT significantly and appropriately expanded the scope of surgery in 26% of patients with PTC overall; in 25% of primary patients and in 27% of revision patients.

We feel that a sensitive ultrasonography/CT nodal map provides an objective baseline that can be revisited later and an accurate framework upon which to base the extent of nodal surgery. This nodal surgery is not offered because the patient is at risk for nodal disease by virtue of, for example, extrathyroidal disease or BRAF positivity, or because of the surgeon's or endocrinologist's personal philosophy favors prophylactic central neck dissection, but because the patient has clinical nodal disease that is radiographically demonstrable and anatomically localized on preoperative analysis. We recommend ultrasonography and CT with contrast in every patient with PTC preoperatively whether primary or revision.

Study limitations

This study had limitations. First, as with any study involving less than complete bilateral level I through VI lymph node dissection, for all patients, the false-negative rate of a given nodal detection test will be necessarily underestimated. This fact could potentially affect sensitivity and NPVs. Alternatively, the relatively high prevalence of clinically insignificant microscopic lymph node involvement in papillary thyroid carcinoma might be expected to increase the false-negative rate and decrease the overall false-positive rate theoretically increasing both specificity and PPV. However, we feel that positive pathology reports in our study likely tract with the macroscopic disease evident preoperatively in these dissected compartments rather than radiographically negative microscopically positive nodal disease. This hurdle in estimating diagnostic accuracy will not be easily overcome. CT scanning or any preoperative radiographic modality may potentially be associated with some false-positive findings leading to unnecessary surgery in the identified compartment. One must balance this risk with current algorithms in play including routine prophylactic central neck dissection associated with pathology reports that are negative for even microscopic disease in up to 60% of patients.

Also, in our study, sensitivities of both ultrasound and CT scan were poor in the central neck. We cannot exclude, given the formatting of the data, that small nodes were identified on the surface of the thyroid gland and were assessed pathologically because of their close association with the thyroid gland leading to some false-negative radiographic findings and lower sensitivities in the central neck. Also, our study involves CT scan reading by dedicated head and neck radiologists with great expertise and this may not be routinely available in all centers. Last, the clinical benefit of our approach might be supported by incorporating outcome data including, in the short term, posttreatment stimulated thyroglobulin measurements and initial posttreatment ultrasound results and, in the longer term, recurrence and mortality rates.

These future investigations represent a logical and exciting extension of the present study.

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