**ORIGINAL ARTICLE – ENDOCRINE TUMORS** 

# Prophylactic Central Compartment Neck Dissection in Papillary Thyroid Cancer and Effect on Locoregional Recurrence

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## ABSTRACT

**Background.** Prophylactic central compartment neck dissection (pCCND) in addition to total thyroidectomy (TT) includes removal of central compartment lymph nodes in the absence of clinical involvement on preoperative and intraoperative evaluation. The data regarding the influence of pCCND on oncologic outcomes and surgical complication rates is mixed and, therefore, is the focus of this analysis.

**Methods.** A systematic review of the literature on total thyroidectomy with prophylactic central compartment neck dissection (TT + pCCND) from January 1990 to October 2017 identified 221 abstracts of which 17 met inclusion criteria and were reviewed (1 randomized-control trial, 13 retrospective cohort studies, and 3 meta-analyses).

**Results.** TT + pCCND was found to detect occult lymph node metastasis in approximately 50% of patients who had no clinical evidence of lymph node metastasis on preoperative imaging. Permanent hypoparathyroidism occurs more frequently following TT + pCCND (TT = 1.55% vs. TT + pCCND = 3.45%), but the rates of permanent recurrent laryngeal nerve dysfunction are similar (TT = 0.89% vs. TT + pCCND = 0.96%). The locoregional recurrence rates across all 14 studies included in this analysis was 6.75% for TT alone and 4.55% for TT + pCCND. The rate of locoregional recurrence was significantly lower in patients who underwent pCCND in a few

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D. T. Hughes, MD e-mail: davhughe@med.umich.edu; davhughe@umich.edu studies and one meta-analysis, but were not significantly different in the majority of studies.

**Conclusions.** TT + pCCND in clinically node-negative papillary thyroid cancer will detect occult lymph node metastasis in approximately half of patients. This may change their postoperative management with regard to adjuvant radioiodine therapy. There is a higher risk of hypoparathyroidism with pCCND, and the effect on rates of locoregional recurrence remains uncertain.

The annual incidence rate of papillary thyroid cancer (PTC) in the United States is approximately 60,000 cases per year and is on the rise.<sup>1</sup> Most patients with PTC will undergo surgical treatment consisting of thyroidectomy with or without lymph node dissection as dictated by the extent of disease noted on preoperative evaluation and intraoperative inspection.<sup>2</sup> The typical preoperative workup for patients should include cervical ultrasound and/ or cross-sectional imaging to evaluate for cervical lymph node metastasis in the central and lateral neck compartments.<sup>2</sup> For patients with a suspicion of cervical lymph node metastases, a therapeutic compartment-orientated neck dissection of the involved lymph node basins should be included at the time of total thyroidectomy (TT).<sup>2</sup> However, for patients without evidence of lymph node metastases on preoperative evaluation, the additive value of a prophylactic central compartment neck dissection (pCCND) at the time of thyroidectomy has been debated in the literature. Multiple studies comparing TT alone to TT with pCCND, which reported complications, recurrence rates, and patient outcomes, have had varying conclusions.



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The definition of a bilateral central compartment neck dissection (CCND) is the removal of the lymph nodes in level 6 lymph node basin from the hyoid bone cranially to the innominate artery on the right and the associated level on the left caudally, laterally to the medial border of the common carotid artery, and from the strap muscles anteriorly to the prevertebral fascia posteriorly to also include the lymph nodes posterior to the recurrent larvngeal nerves.<sup>3,4</sup> An ipsilateral CCND includes the lymph nodes in level 6 on the side of the primary tumor and extends to the midline pretracheal and prelaryngeal lymph nodes. The complications associated with CCND are similar to and may be additive to thyroidectomy and include recurrent laryngeal nerve injury with resulting voice dysfunction and parathyroid devascularization or removal with resultant temporary or permanent hypoparathyroidism. Several studies have demonstrated that in experienced centers, central compartment neck dissection is performed safely with low rates of complications.<sup>5,6</sup>

The most common location for lymph node metastases in patients with PTC is the central compartment (level 6). Studies have reported rates of clinically evident nodal metastases of 20-31% based on preoperative ultrasound, which would then necessitate compartment-orientated therapeutic neck dissection.<sup>7-11</sup> In patients without evidence of cervical lymph node metastasis on preoperative evaluation, the rates of occult central neck lymph node metastases detected by pCCND have ranged from 24 to 82%.<sup>5,12,13</sup> The risk factors for lymph node metastasis include patient age, larger size of the primary tumor, multifocality, and extrathyroidal extension.<sup>5,14–16</sup> The number of central neck lymph nodes that need to be excised during pCCND to achieve an accurate assessment of lymph node status seems to be dependent on the associated risk of the primary tumor and range from three excised level 6 lymph nodes in patients with T1b tumors up to eight excised nodes in patients with T3 tumors to achieve a < 10% false-negative rate.<sup>17</sup>

The impact of pCCND on the outcomes of patients with PTC should include an analysis of the complication rates associated with this more extensive surgery, a determination of the effect that the nodal status and stage migration may have on the subsequent treatment or follow-up of patients, and the effect that pCCND has on the rates of locoregional recurrence, disease-free survival, and overall survival. Studies that have compared the surgical complication rates of pCCND to TT alone generally come to the conclusion that the rates of recurrent laryngeal nerve injury are similar, but that the rates of temporary and possibly permanent hypoparathyroidism are higher with pCCND.<sup>6,13,15,18–22</sup> Several studies have demonstrated that the impact of microscopic lymph node metastasis on the overall survival of patients with PTC is at most, minimal.<sup>23–25</sup> However, some studies have shown that pCCND may improve the accuracy of cancer nodal staging, reduce the burden of disease through excision of lymph node metastasis, and subsequently decrease the risk of loco-regional recurrence.<sup>2,26</sup> More specifically, some reports suggest that pCCND allows for a more tailored use of radioiodine therapy due to improved lymph node staging, will lead to lower postoperative thyroglobulin levels and lower radioiodine uptake on follow-up scans, and will decrease locoregional recurrence and improve disease-free survival.<sup>5,18,24,26-32</sup> With this apparent variance in the published literature on the outcomes of TT versus TT + pCCND in the treatment of clinically node-negative patients, this comprehensive and expert review of the literature attempts to evaluate critically the key research present recommendations for patient studies and management.

#### METHODS

A PUBMED database search of English language literature from January 1990 to October 2017 was performed for the search terms "prophylactic," "routine," "elective," "central neck," "lymph node," "dissection," "lymphadenectomy," "PTC," "local recurrence," "locoregional recurrence," "regional recurrence," "hypoparathyroidism," "recurrent laryngeal nerve," and "survival." A consort diagram of the literature search results is presented in Table 1. Guidelines and consensus statements from the American Thyroid Association, the National Cancer Center Network, and the European Society of Endocrine Surgeons also were reviewed.<sup>3,33,34</sup> Randomized, controlled studies were preferred when available; however, when not available, retrospective institutional studies and cohort studies

TABLE 1 Consort diagram as of November 7th, 2017

Central neck dissection-1307
English—1150
Humans—948
Central neck dissection, papillary thyroid cancer-482
Central neck dissection, level 6-94
Central neck dissection prophylactic-221
Central neck dissection routine-112
Central neck dissection recurrence—320
Central neck dissection local recurrence-222
Central neck dissection, loco-regional recurrence-10
Total number of papers manually reviewed—34
Studies included—17

with a minimum of 100 patients were used. Published meta-analyses on the subject also were reviewed to include a search of references from these studies.

Articles that included patients having undergone a therapeutic central or lateral neck dissection in the setting of clinically involved lymph nodes were excluded. Studies were also excluded if there were less than 100 patients, they did not have preoperative imaging to assess the central and lateral neck compartments for lymph node metastasis, or if follow-up for locoregional recurrence did not include cervical ultrasound, thyroglobulin levels, and radioiodine scanning. Recurrence was defined clinically as detectable tumor in the thyroidectomy bed, metastatic cervical lymph nodes, or distant metastasis after completion of primary treatment (surgery with or without radioiodine therapy). Studies that included patients with benign thyroid disease were excluded. A flow diagram of the literature search results and selection process is presented in Fig. 1. The authors then met to critically review the selected studies to ensure that these met inclusion and exclusion criteria, evaluate the results and the strength of evidence, and develop clinical practice recommendations.

# RESULTS

After the literature search was performed and exclusion criteria applied, 17 manuscripts were reviewed in detail. Of the 17 articles reviewed, there was one randomized, control trial, 13 nonrandomized, retrospective cohort studies (Table 2), and 3 meta-analyses (Table 3).<sup>5,6,14,15,18,21,25,28,32,35–42</sup> A critical review of the 17 highest quality studies provides the best available

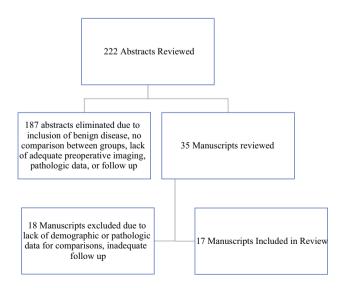


FIG. 1 Flow diagram of publications selected for review

information for analysis of the impact of pCCND on the initial treatment of patients with clinically node-negative PTC.

In the one randomized, controlled trial by Viola et al., the authors randomized 98 patients to either TT alone or TT + pCCND.<sup>15</sup> At the time of surgery, five patients in the TT arm were found to have evidence of lymph node metastasis and underwent therapeutic CND and were therefore excluded. Patients were followed for 5 years; the primary endpoints were successful ablation (defined by stimulated thyroglobulin levels < 1 ng/mL and no uptake on posttherapeutic radioiodine scanning) and the development of persistent/recurrent disease. The secondary endpoints were rates of surgical complications and the effect of pCCND on the stage of disease. When the demographic and pathologic characteristics of the two groups were compared, there were no significant differences in age, sex, the size of the primary tumor, or rates of multifocality, extrathyroidal extension, aggressive pathologic variants, or BRAF positivity. The rates of lymph node positivity were, as expected, higher in the TT + pCCNDgroup at 46%, and the TT alone group had a 6.8% rate of lymph node metastasis in the incidentally removed lymph nodes in the perithyroidal tissue. The majority of patients in both groups received radioiodine ablation (98.7%); however, more patients in the TT along group required more than one dose of radioiodine to achieve successful TT + pCCND = 3.4%;ablation (TT = 17.4%)vs. p = 0.002). The rates of permanent hypoparathyroidism were significantly higher in the TT + pCCND group (19.4%) compared with the TT alone group (8%; p = 0.02). During the 60-month follow-up period, the rates of persistent disease defined by either detectable thyroglobulin level or radiographically evident disease was similar between the TT alone group (8%) and the TT + pCCND group (7.5%; p = 0.9). Overall, the authors concluded that there was no significant benefit of pCCND for patients with clinically node-negative PTC.

In-depth analysis of the remaining 13 nonrandomized, retrospective cohort studies comparing TT alone to TT + pCCND revealed several themes regarding these surgical treatment strategies (Table 2). The mean characteristics and outcomes of both groups across all 13 studies are shown in Table 4 along with notations about the statistical significance for each variable. These studies were primarily single institution studies and the use of TT or TT + pCCND was based on physician preference which created significant selection bias. Additionally, the TT alone cohorts often included patients who did not have a preoperative diagnosis of PTC (due to indeterminate preoperative fine-needle aspiration cytology or because there was another benign indication for thyroidectomy) and were later found to have PTC on surgical pathology, which

Author and time	Dates of study	Procedure		Mean tumor size (cm)	Lymph node positivity rate (%)	Mean follow up months	Recurre	Recurrence rate
		TT	TT + pCCND	TT TT + pCCND		TT TT + pCCND	TT	TT + pCCND
Sywak <sup>28</sup>	1995-2005	391	56	2.3 2	38	70 24.5	5%	3.6%
			TT + iCND = 56			24.5		
Costa <sup>35</sup>	1994–2001	118	126	1.5 1.7	47	64 47	7.7%	6.3%
Zuniga <sup>36</sup>	1983–1999	130	136	NR NR	82	Overall 82.8	19%	14%
							DFS 5 versu	DFS 5 years 85.6 versus 88% NS
Moo <sup>37</sup>	1999-2009	36	45	2.4 1.4	33	Overall 37.2	16.7%	4.4%
				(p = 0.02)				
Hughes <sup>18</sup>	2002-2009	65	78	2 1.9	62	$27.5  19.1 \ (p = 0.05)$	4.6%	5.1%
Popadich <sup>32</sup>	1995-2009	347	259	2.2 2.3	49	50 32 ( $p < 0.001$ )	8.4%	5%
			TT + iCCND = 202					
Lang <sup>14</sup>	2004-2010	103	82	1 1.5	54.9	27 25	2.9%	3.7%
			TT + iCCND = 82					
Barczynski <sup>25</sup>	1993–2002	282	358	NR NR	30.2	129 126	13.1%	4.2%
							p = 0.001	001
							<b>DFS 10</b>	DFS 10 years 92.5
							versu	versus 98%
							(p = 0.03)	)3)
Conzo <sup>21</sup>	1998-2005	390	362	1.7 1.9	41	Overall 114	3.8%	3.3%
Calo <sup>38</sup>	2002-2010	220	65	1.6 1.7	26.2	Overall 100	2.1%	3.1%
Ywata de	1996-2007	478	102	1 1.5	67.2	67.4 80.2	1.5%	3.9%
Carvalho						(p < 0.001)		
Raffaelli <sup>40</sup>	2008-2010	62	124	1.2 1.3	42	25.5 16.8	0%0	0.5%
			TT + iCCND = 62					
			TT + bCCND = 62					
Viola <sup>15</sup>	2009-2015	88	93	1.6 1.6	46.2	Overall 60	8.0%	7.5%
Kim <sup>41</sup>	1997-2015	2834	8735	0.8 0.9	41.7	Overall 62.6	2.9%	2.1%
		Lobectomy = 1259	LT + iCCND = 2107					
		Total = 1575	TT + iCCND = 3377					
			TT + bCCND - 3251					

TABLE 2 continued								
Author and time	Dates of study Permanent hypoparath	Perman hypopar	Permanent hypoparathyroidism	Permanent recurre nerve dysfunction	Permanent recurrent laryngeal nerve dysfunction	Radioic	Radioiodine use	Comments
		TT	TT + pCCND	TT	TT + pCCND	TT	TT + pCCND	
Sywak <sup>28</sup>	1995–2005	0.5%	1.8%	1%	9%0	NR		
						NR		
Costa <sup>35</sup>	1994–2001	NR	NR	53%	69%			
Zuniga <sup>36</sup>	1983–1999	NR	NR	42%	58%			
Moo <sup>37</sup>	1999–2009	5%	0%	0%	0%0	72%	68%	
Hughes <sup>18</sup>	2002-2009	0%0	2.6%	3.1%	0%0	86%	92%	
Popadich <sup>32</sup>	1995-2009	0.45%	0.8%	1.8%	0.4%	Overall 98%	98%	Upstage 5%
								RFS lower for TT
Lang <sup>14</sup>	2004-2010	1%	2.4%	05%	0.6%	68%	$76\% \ (p = 0.023)$	Upstage 12.5%
Barczynski <sup>25</sup>	1993–2002	0.7%	2.2%	1.1%	1.3%	28%	$65\% \ (p < 0.001)$	Local control rate 87.6 versus 94.5% $p = 0.003$ better for TT + bCCND
Conzo <sup>21</sup>	1998-2005	1%	$3.6\% \ (p = 0.018)$	0.8%	1.7%	Overall 86%	86%	
Calo <sup>38</sup>	2002-2010	4.5%	10.7%	0%	0%0	88%	100%	
Ywata de Carvalho <sup>39</sup>	1996–2007	2.3%	$11.8\% \ (p < 0.01)$	1.5%	5.9% ( $p = 0.02$ )	44%	56%	
Raffaelli <sup>40</sup>	2008-2010	0%0	0.5%	0%	0.5%	NR		
Viola <sup>15</sup>	2009-2015	8.0%	19.4%	8.0%	4.3%	Overall	Overall 96.7%	RCT
			(p = 0.02)					Lower Tg levels in pCCND group after RAI
Kim <sup>41</sup>	1997–2015	1.6%	$3.6\% \ (p = 0.004)$	0%0	0.2%	40.4%	$40.4\%  60.8\% \ (p < 0.01)$	
<i>cm</i> centimeters, <i>pCC</i> compartment neck dis	ND prophylactic section, NR not re	central c	compartment neck dis PFS disease-free surviv	ssection, <i>T1</i> al, <i>RFS</i> recu	r total thyroidectomy, <i>i</i> urrence-free survival, <i>RC</i>	<i>CCND</i> ips T randomi	silateral central con zed control trial, $T_g$	cm centimeters, <i>pCCND</i> prophylactic central compartment neck dissection, <i>TT</i> total thyroidectomy, <i>iCCND</i> ipsilateral central compartment neck dissection, <i>bCCND</i> bilateral central compartment neck dissection, <i>NR</i> not reported, <i>DFS</i> disease-free survival, <i>RFS</i> recurrence-free survival, <i>RCT</i> randomized control trial, <i>Tg</i> thyroglobulin, <i>RAI</i> radioiodine, <i>LT</i> thyroid lobectomy

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<b>TABLE 3</b> Meta-analyses oftotal thyroidectomy (TT) versustotal thyroidectomy with	Meta-analysis author, year	TT (n)	$\begin{array}{c} TT + pCCND \\ (n) \end{array}$	LRR TT	LRR TT + pCCND	LRR rate significantly different?
prophylactic central compartment neck dissection	Zetoune <sup>6</sup>	713	161	5.5%	5.6%	No
(TT + pCCND) and	Wang <sup>42</sup>	995	745	7.9%	4.7%	No
locoregional recurrence rate	Lang <sup>5</sup>	1739	1592	8.6%	4.7%	Yes
(LRR)	Total patients	3447	2498	Mean	Mean	

**TABLE 4** Mean rates of pathology, follow-up, recurrence, and complications between total thyroidectomy and total thyroidectomy with prophylactic central compartment neck dissection in patients

with clinically node negative papillary thyroid cancer from studies outlined in Table  ${\bf 2}$ 

	Total thyroid $N = 4197$	Total thyroid with pCCND $N = 10,528$	p value
Tumor size (cm)	1.60 cm	1.65 cm	NS
Lymph node positivity (%)	N/A	50.4	N/A
Radioiodine therapy (%)	66.8	77.1	NS in all but three studies (Lang, Barczynski, Kim)
Follow-up time (months)	65.9	59.6	NS in all but three studies (Hughes, Popadich, Ywata de Carvalho)
Recurrence (%)	6.75	4.55	NS in all but one study (Barczynski)
Permanent hypoparathyroidism (%)	1.55	3.45	NS in all but four studies (Conzo, Ywata de Carvalho, Viola, Kim)
Permanent RLN dysfunction (%)	0.89	0.96	NS in all but one study (Ywata de Carvallo)

introduces another significant selection bias. Studies included both ipsilateral and bilateral pCCND as defined by the relationship to the location of the primary tumor with some studies only performing ipsilateral pCCND. The size of the primary tumor averaged 1.6 cm across these studies and included patients with papillary microcarcinoma in some studies, particularly in the largest study by Kim et al., which had a mean tumor size of only 0.8 and 0.9 cm for the TT and TT + pCCND groups respectively.<sup>41</sup> Additionally, in the report by Kim et al., the pCCND group was significantly older, had higher T stage, higher BRAF positivity rates, more multifocality, more extrathyroidal extension, and higher rates of TT (as opposed to thyroid lobectomy). This study design may introduce potential confounding factors that could influence the ability to compare complication rates and recurrence rates between treatment groups. Across all studies, the lymph node positivity rate with pCCND ranged from 26.2 to 82% (mean 50.4%) and was likely influenced by the extent of neck dissection, the number of lymph nodes examined, and the varying pathologic identification of micrometastatic nodal disease, introducing yet another potential set of confounding factors. The rates of permanent recurrent laryngeal nerve injury were all less than 1% and were not significantly different between the groups in all but one study (Ywata de Carvalho et al.)<sup>39</sup>. The rates of temporary hypoparathyroidism were significantly higher with pCCND in several studies, and this translated to a significantly higher rate of permanent hypoparathyroidism in some studies.<sup>15,21,39,41</sup> With a mean follow-up of 5.2 years across these studies, the overall locoregional recurrence rates ranged from 0 to 19% and were not significantly different between groups in all but the report by Barczynski et al.<sup>25</sup>. Zuniga et al. reported no significant difference in the rates of disease-free survival between the two groups at 5 years (TT = 85.6% vs. TT + pCCND = 88%; p = not significant).<sup>36</sup> In contrast, Barczynski et al. reported an improved disease-free survival at 10 years (TT = 92.5% vs. TT + pCCND = 98%; p = 0.03) and better locoregional control with pCCND (TT = 87.6% vs. TT + pCCND = 94.5%; p = 0.003).<sup>25</sup>

There were three meta-analyses that compared TT to TT + pCCND and reported locoregional recurrence rates. When combined, these studies totaled 3447 patients treated with TT and 2498 treated with TT + pCCND (Table 4). While two of the studies (Zetone et al. and Wang et al.) showed no statistically significant differences in recurrence rates between the groups, the study by Lang et al. showed lower locoregional recurrence rates with pCCND (TT = 8.6% vs. TT + pCCND = 4.7%; incidence rate ratio =

0.65; confidence interval 0.18–0.86).<sup>5,6,27</sup> However, the study by Lang et al. also noted that patients treated with pCCND had higher rates of radioiodine ablation. Therefore, it is unclear how much of the difference in recurrence was due to this confounding factor. Additionally, the lack of randomization of patients to TT or TT + pCCND introduced a significant selection bias to nearly every study included in the meta-analyses.

## DISCUSSION

The available literature which has compared TT alone to TT + pCCND in the treatment of patients with clinically node-negative PTC is comprised of weak levels of evidence due to comparative, retrospective, and often single-institution reports. To answer this question effectively, a large, multi-institutional, randomized, controlled trial with an appropriate number of patients and length of follow-up to provide adequate power would be required.<sup>43</sup> From the data available for this review, some generalized conclusions and some soft recommendations can be made regarding the utility of pCCND in patients with PTC.

In the current literature, the surgical complication rates associated with TT alone and TT + pCCND seem similar with regard to recurrent laryngeal nerve injury, but there is a trend towards higher rates of hypoparathyroidism when pCCND is performed. It should be noted that the majority of the studies reporting complication rates associated with TT + pCCND for PTC are from centers and surgeons who care for a higher volume of such patients. Complications during thyroidectomy have been directly correlated with surgeon volume and, therefore, rates of recurrent laryngeal nerve injury and hypoparathyroidism may be higher when pCCND is performed by less experienced surgeons or surgeons who do not routinely perform neck dissection for thyroid cancer.<sup>44</sup> The higher rates of hypoparathyroidism with pCCND are likely secondary to the close association of the inferior parathyroid glands to the level 6 lymph nodes, and therefore, these parathyroid glands often are removed or devascularized during either a prophylactic or therapeutic procedure. The utilization of parathyroid autotransplantation should be considered whenever a devascularized parathyroid is noted or can be retrieved from a surgical specimen. Achieving a balance between the increased risk of temporary, and in some cases permanent, hypoparathyroidism and the potential benefits of pCCND with regard to nodal staging and patient outcomes requires careful consideration on a case-by-case basis.

After pCCND, approximately 50% of patients will be found to have radiographically/clinically occult metastatic level 6 lymph nodes. However, the impact of micrometastatic lymph node involvement on overall recurrence and survival seems minimal compared with macroscopic lymph node involvement, which has been associated with increased recurrence rates and decreased survival in some studies.<sup>3,23,45–49</sup> Why there is a difference in patient outcome based on the extent of lymph node involvement is not clear. In contrast to other solid tumors, patients with PTC live many years/decades after initial treatment-durations that are long enough to allow microscopic disease to become macroscopic even in the absence of differences in tumor biology, the extent of nodal involvement, or sensitivity to radioiodine. Given that most studies have limitations of often modest follow-up duration and the inconsistent/nonstandard use of adjuvant radioiodine, the currently available literature does not suggest that removal of clinically undetectable central neck nodal disease with pCCND will reduce the rates of persistent and recurrent PTC. This is in contrast to patients with macroscopic lymph node metastases who should be treated with compartment-oriented lymph node dissection of the involved nodal basins to prevent persistent disease.<sup>3,45–49</sup>

If the intent of pCCND is not to remove micrometastatic lymph nodes to prevent progression to macroscopic disease, is there a benefit to improving the accuracy of staging (Nx vs. N0 vs. N1a) in an effort to refine the indications for adjuvant radioiodine therapy and facilitate postoperative surveillance and follow-up? In the studies reviewed, several demonstrated higher rates of radioiodine administration or the dose of radioiodine in patients with central lymph node metastases.<sup>5,14,18,25,41</sup> In otherwords, pCCND appeared to increase the intensity and frequency of administration of radioiodine therapy (and potentially, the subsequent risk of treatment-associated sialadenitis). One would assume that the more frequent use of radioiodine therapy in patients who are found to be node positive after pCCND (compared with those treated with TT alone) is in the context of the common practice of not using radioiodine when the status of local-regional lymph nodes is unknown (Nx) or negative (N0). In many centers, this may not be the case; for example, patients with Nx disease may routinely receive radioiodine rather than not receiving adjuvant therapy. In such a senerio, those patients proven to be N0 after pCCND would actually be spared the administration of radioiodine. The recent ATA guidelines have recommended a more selective use of radioiodine according to disease biology, and therefore, the confirmation of N0 disease with pCCND may allow for avoidance of adjuvant radioiodine in patients who had TT alone and would have been staged Nx and therefore would have received radioiodine.<sup>2</sup> Thus, a soft recommendation can be made for pCCND if the additional information on nodal status will influence the use of adjuvant radioiodine. Nodal status may be of limited value in otherwise very low-risk patients (young age, small tumor, lack of gross

extrathyroidal extension) in whom the absence of nodal information would not influence the use of radioiodine. If a more selective approach to the use of RAI is combined with TT alone, central compartment recurrence may potentially increase if radiodiodine is effective for the treatmentment of micrometastatic lymph node metastases. However, the low frequency of the detection of central compartment recurrence combined with the long duration of follow-up needed for accurate assessment of recurrent disease makes this question impossible to answer.

With regard to the value of nodal staging in influencing postoperative surveillance and follow-up, it is probably true that recurrence rates in the central and lateral neck compartments are a function of how hard one looks for them. If pCCND influences rates of recurrence, it will likely be in the population of patients who are aggressively monitored with postoperative cervical ultrasound and stimulated serum thyroglobulin levels and in whom recurrence presents in the form of small volume nodal metastasis. While the current treatment guidelines allow for flexibility in the rigor of postoperative monitoring, especially in low-risk patients, the reality of medical practice may result in a mismatch of TT alone with a very aggressive postoperative surveillence. We have all seen the low-risk patient returned to the surgeon after a TT (and no pCCND) with a mild elevation in stimulated thyroglobulin and a 4-mm abnormality on cervical ultrasound that has questionable long-term clinical significance-hence, the controversy over the optimal extent of operation for clinically node-negative patients with PTC continues.

## CONCLUSIONS

Approximately 50% of patients with PTC treated with TT + pCCND will have lymph node metastasis found on final pathologic evaluation of the surgical specimen. The finding of occult central neck lymph node metastasis may change postoperative management with regard to the use of adjuvant radioiodine therapy and the intensity of surveillance, but this should be considered in the context of a higher risk of hypoparathyroidism compared with TT alone. In the currently available literature, the addition of pCCND to TT does not seem to improve rates of locoregional recurrence compared with TT alone.

### REFERENCES

- National Cancer Institute Surveillance, Epidemiology, and end results program. (https://seer.cancer.gov/statfacts/html/thyro.htm l). Accessed 19 Nov 2017.
- Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association

Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;26(1):1–133.

- 3. American Thyroid Association Surgery Working Group, American Association of Endocrine Surgeons, American Academy of Otolaryngology-Head and Neck Surgery, American Head and Neck Society, Carty SE, Cooper DS, et al. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. *Thyroid.* 2009;19(11):1153–8.
- Sancho JJ, Lennard TW, Paunovic I, Triponez F, Sitges-Serra A. Prophylactic central neck dissection in papillary thyroid cancer: a consensus report of the European Society of Endocrine Surgeons (ESES). Langenbeck's Arch. Surg./Deutsche Gesellschaft fur Chirurgie. 2014;399(2):155–63.
- Lang BH, Ng SH, Lau LL, Cowling BJ, Wong KP, Wan KY. A systematic review and meta-analysis of prophylactic central neck dissection on short-term locoregional recurrence in papillary thyroid carcinoma after total thyroidectomy. *Thyroid*. 2013;23(9):1087–98.
- Zetoune T, Keutgen X, Buitrago D, Aldailami H, Shao H, Mazumdar M, et al. Prophylactic central neck dissection and local recurrence in papillary thyroid cancer: a meta-analysis. *Ann Surg Oncol.* 2010;17(12):3287–93.
- Solorzano CC, Carneiro DM, Ramirez M, Lee TM, Irvin GL, 3rd. Surgeon-performed ultrasound in the management of thyroid malignancy. *Am Surg.* 2004;70(7):576–80 (discussion 580–2).
- 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(1):4–10.
- Stulak JM, Grant CS, Farley DR, Van Heerden JA, Hay ID, Reading CC, et al. Value of preoperative ultrasonography in the surgical management of initial and reoperative papillary thyroid cancer. *Arch Surg.* 2006;141(5):489–94 (discussion 494–6).
- Kouvaraki MA, Shapiro SE, Fornage BD, Edeiken-Monro BS, Sherman SI, Vassilopoulou-Sellin R, et al. Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. *Surgery*. 2003;134(6):946–54 (discussion 954–5).
- 11. O'Connell K, Yen TW, Quiroz F, Evans DB, Wang TS. The utility of routine preoperative cervical ultrasonography in patients undergoing thyroidectomy for differentiated thyroid cancer. *Surgery*. 2013;154(4):697–701 (discussion 701-3).
- Wada N, Duh QY, Sugino K, Iwasaki H, Kameyama K, Mimura T, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. *Ann Surg.* 2003;237(3):399–407.
- Som PM, Curtin HD, Mancuso AA. Imaging-based nodal classification for evaluation of neck metastatic adenopathy. *AJR Am J Roentgenol.* 2000;174(3):837–44.
- 14. Lang BH, Wong KP, Wan KY, Lo CY. Impact of routine unilateral central neck dissection on preablative and postablative stimulated thyroglobulin levels after total thyroidectomy in papillary thyroid carcinoma. *Ann Surg Oncol.* 2012;19(1):60–7.
- 15. Viola D, Materazzi G, Valerio L, Molinaro E, Agate L, Faviana P, et al. Prophylactic central compartment lymph node dissection in papillary thyroid carcinoma: clinical implications derived from the first prospective randomized controlled single institution study. *J Clin Endocrinol Metab.* 2015;100(4):1316–24.
- Roh JL, Kim JM, Park CI. Central lymph node metastasis of unilateral papillary thyroid carcinoma: patterns and factors predictive of nodal metastasis, morbidity, and recurrence. *Ann Surg Oncol.* 2011;18(8):2245–50.
- Robinson TJ, Thomas S, Dinan MA, Roman S, Sosa JA, Hyslop T. How many lymph nodes are enough? Assessing the adequacy of lymph node yield for papillary thyroid cancer. *J Clin Oncol.* 2016;34(28):3434–9.

- Hughes DT, White ML, Miller BS, Gauger PG, Burney RE, Doherty GM. Influence of prophylactic central lymph node dissection on postoperative thyroglobulin levels and radioiodine treatment in papillary thyroid cancer. *Surgery*. 2010;148(6):1100–6 (discussion 1106–7).
- Roh JL, Park JY, Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. *Ann Surg.* 2007;245(4):604–10.
- Lang BH, Chan DT, Wong KP, Wong KK, Wan KY. Predictive factors and pattern of locoregional recurrence after prophylactic central neck dissection in papillary thyroid carcinoma. *Ann Surg Oncol.* 2014;21(13):4181–7.
- Conzo G, Calo PG, Sinisi AA,De Bellis A, Pasquali D, Iorio S, et al. Impact of prophylactic central compartment neck dissection on locoregional recurrence of differentiated thyroid cancer in clinically node-negative patients: a retrospective study of a large clinical series. *Surgery*. 2014;155(6):998–1005.
- Shan CX, Zhang W, Jiang DZ, Zheng XM, Liu S, Qiu M. Routine central neck dissection in differentiated thyroid carcinoma: a systematic review and meta-analysis. *Laryngoscope*. 2012;122(4):797–804.
- 23. Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid*. 2012;22(11):1144–52.
- Ji YB, Yoo HS, Song CM, Park CW, Lee CB, Tae K. Predictive factors and pattern of central lymph node metastasis in unilateral papillary thyroid carcinoma. *Auris, Nasus, Larynx.* 2016;43(1):79–83.
- Barczynski M, Konturek A, Stopa M, Nowak W. Prophylactic central neck dissection for papillary thyroid cancer. *Br J Surg.* 2013;100(3):410–8.
- Hartl DM, Leboulleux S, Al Ghuzlan A, Baudin E, Chami L, Schlumberger M, et al. Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma. *Ann Surg.* 2012;255(4):777–83.
- Wang TS, Evans DB, Fareau GG, Carroll T, Yen TW. Effect of prophylactic central compartment neck dissection on serum thyroglobulin and recommendations for adjuvant radioactive iodine in patients with differentiated thyroid cancer. *Ann Surg Oncol.* 2012;19(13):4217–22.
- Sywak M, Cornford L, Roach P, Stalberg P, Sidhu S, Delbridge L. Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer. *Surgery*. 2006;140(6):1000–5 (discussion 1005–7).
- 29. Bonnet S, Hartl D, Leboulleux S, Baudin E, Lumbroso JD, Al Ghuzlan A, et al. Prophylactic lymph node dissection for papillary thyroid cancer less than 2 cm: implications for radioiodine treatment. *J Clin Endocrinol Metab.* 2009;94(4):1162–7.
- Evans DB. Papillary carcinoma of the thyroid: balancing principles of oncology with emerging technology. Surgery. 2011;150(6):1015–22.
- Laird AM, Gauger PG, Miller BS, Doherty GM. Evaluation of postoperative radioactive iodine scans in patients who underwent prophylactic central lymph node dissection. *World J Surg.* 2012;36(6):1268–73.
- 32. Popadich A, Levin O, Lee JC, Smooke-Praw S, Ro K, Fazel M, et al. A multicenter cohort study of total thyroidectomy and routine central lymph node dissection for cN0 papillary thyroid cancer. *Surgery*. 2011;150(6):1048–57.
- Tuttle RM, Ball DW, Byrd D, et al. NCCN clinical practice guidelines in oncology (NCCN guidelines): thyroid carcinoma. J Natl Compre Cancer Netw. 2010;8:1228–74.
- Sancho JJ, Lennard TW, Paunovic I, Triponez F, Sitges-Serra A. Prophylactic central neck dissection in papillary thyroid cancer: a

consensus report of the European Society of Endocrine Surgeons (ESES). *Langenbeck's Arch Surg.* 2014;399(2):155–63.

- Costa S, Giugliano G, Santoro L, De Carvalho AY, Massaro MA, Gibelli B, et al. Role of prophylactic central neck dissection in cN0 papillary thyroid cancer. *Acta Otorhinolaryngol Italica*. 2009;29(2):61–9.
- Zuniga S, Sanabria A. Prophylactic central neck dissection in stage N0 papillary thyroid carcinoma. Arch Otolaryngol Head Neck Surg. 2009;135(11):1087–91.
- Moo TA, Umunna B, Kato M, Butriago D, Kundel A, Lee JA, et al. Ipsilateral versus bilateral central neck lymph node dissection in papillary thyroid carcinoma. *Ann Surg.* 2009;250(3): 403–8.
- 38. Calo PG, Pisano G, Medas F, Marcialis J, Gordini L, Erdas E, et al. Total thyroidectomy without prophylactic central neck dissection in clinically node-negative papillary thyroid cancer: is it an adequate treatment? *World J Surg Oncol.* 2014;12:152.
- 39. Ywata de Carvalho A, Chulam TC, Kowalski LP. Long-term results of observation vs. prophylactic selective level VI neck dissection for papillary thyroid carcinoma at a cancer center. *JAMA Otolaryngol Head Neck Surg.* 2015;141(7):599–606.
- Raffaelli M, De Crea C, Sessa L, Giustacchini P, Revelli L, Bellantone C, et al. Prospective evaluation of total thyroidectomy versus ipsilateral versus bilateral central neck dissection in patients with clinically node-negative papillary thyroid carcinoma. *Surgery*. 2012;152(6):957–64.
- 41. Kim SK, Woo JW, Lee JH, Park I, Choe JH, Kim JH, et al. Prophylactic central neck dissection might not be necessary in papillary thyroid carcinoma: analysis of 11,569 cases from a single institution. JACS. 2016; 222(5):853–64.
- 42. Wang TS, Cheung K, Farrokhyar F, Roman SA, Sosa JA. A metaanalysis of the effect of prophylactic central compartment neck dissection on locoregional recurrence rates in patients with papillary thyroid cancer. *Ann Surg Oncol.* 2013;20(11):3477–83.
- 43. Carling T, Carty SE, Ciarleglio MM, Cooper DS, Doherty GM, Kim LT, et al. American Thyroid Association design and feasibility of a prospective randomized controlled trial of prophylactic central lymph node dissection for papillary thyroid carcinoma. *Thyroid.* 2012;22(3):237–44.
- 44. Adam MA, Thomas S, Youngwirth L, Hyslop T, Reed SD, Scheri RP, Roman SA, Sosa JA. Is there a minimum number of thyroidectomies a surgeon should perform to optimize patient outcomes? *Ann Surg.* 2017;265(2):402–7.
- 45. Podnos YD, Smith D, Wagman LD, Ellenhorn JD. The implication of lymph node metastasis on survival in patients with welldifferentiated thyroid cancer. *Am Surg.* 2005;71(9):731–4.
- 46. Adam MA, Pura J, Goffredo P, Dinan MA, Reed SD, Scheri RP, et al. Presence and number of lymph node metastases are associated with compromised survival for patients younger than age 45 years with papillary thyroid cancer. *J Clin Oncol.* 2015; 33(21):2370–5.
- Zaydfudim V, Feurer ID, Griffin MR, Phay JE. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. *Surgery*. 2008;144(6):1070–7 (discussion 1077–8).
- 48. Leboulleux S, Rubino C, Baudin E, Caillou B, Hartl DM, Bidart JM, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. J Clin Endocrinol Metab. 2005;90(10):5723–9.
- 49. 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(2): 139–48.