Routine Central Neck Dissection in Differentiated Thyroid Carcinoma: A Systematic Review and Meta-Analysis

Cheng-Xiang Shan, MD; Wei Zhang, MD, PhD; Dao-Zhen Jiang, MD, PhD; Xiang-Min Zheng, MD, PhD; Sheng Liu, MD; Ming Qiu, MD, PhD

Objective/Hypothesis: The role of central neck dissection (CND) remains controversial in differentiated thyroid cancer (DTC).

Study Design: Systematic review and meta-analysis.

Methods: A systematic review and meta-analysis focusing on surgical morbidities and locoregional recurrence after total thyroidectomy (TT) with CND versus TT alone was performed.

Results: Sixteen trials were analyzed. There was no increased risk of recurrent laryngeal nerve (RLN) injury (temporary or permanent), permanent hypocalcemia, or locoregional recurrence when CND was performed in addition to TT. Postoperative temporary hypocalcemia was more common after TT with CND than after TT alone.

Conclusions: TT alone results in less surgical morbidity in the immediate postoperative period and an identical locoregional recurrence rate compared with TT plus CND.

Key Words: Differentiated thyroid carcinoma, central neck dissection, ipsilateral, bilateral, meta-analysis.

INTRODUCTION

Differentiated thyroid carcinoma (DTC) has become the fastest growing malignancy worldwide over the past 20 years. Although surgical resection is the gold standard for DTC, practical outworkings of this show great variation and constantly provoke fierce debate, such as extent of thyroidectomy, radioactive iodine (RAI) therapy, and the role and extent of central neck dissection (CND). The cervical central compartment (also known as level VI), is the primary zone of lymphatic involvement for most thyroid cancers. Even for clinically node-negative DTC, lymph node metastases (LNM) are found in 50% to 60% of the central lymph nodes (LNs) on pathology. Therefore, central cervical LNM in DTC troubles a sizeable portion of patients. However, the decision to perform CND remains an area of debate. Proponents claim that CND not only decreases regional recurrence and the surgical morbidity of reoperation, but also provides information on nodal metastasis, which can impact staging and radioactive iodine dosing. Conversely, those who challenge CND argue that total thyroidectomy (TT) alone offers an equal survival benefit to TT with CND. Furthermore, CND has associated risks, including increased rates of hypoparathyroidism and recurrent laryngeal nerve (RLN) injury when compared with TT alone.

The goal of surgical treatment for DTC is to eradicate the potential source of recurrence with minimal morbidity. We performed this systematic review and meta-analysis to determine whether TT with CND is superior to TT alone in decreasing regional recurrence without increasing surgical morbidity.

METHODS

Search Strategy

Electronic databases (Medline, ScienceDirect–Elsevier, Springerlink, and Embase) from January 1995 to April 2010 were searched by two individuals (C. X. Shan and W. Zhang) to identify all clinical trials comparing different extents of lymphadenectomy with TT for DTC. A search strategy comprising disease-specific search terms (e.g., differentiated thyroid carcinoma), management-specific terms (e.g., total thyroidectomy, lymph node dissection) and terms related to procedures of lymph node dissection (e.g., bilateral, ipsilateral) was used. All abstracts and citations were reviewed. The related-articles function was used to broaden the search, and references of the articles acquired were also searched.

Selection Criteria

Abstracts and full-text articles were initially screened, and then selected or rejected by the two reviewers (C. X. Shan and W. Zhang) on the basis of the following inclusion and exclusion criteria.

Inclusion Criteria

1. Comparative clinical trials involved in the efficacy and adverse results of different patterns of thyroidectomy and lymphadenectomy for differentiated thyroid cancer.
2. Initial and completion thyroidectomy with simultaneous lymph node dissection, therapeutic, and prophylactic lymph node dissection.
3. Trials involving both children and adults.
4. The exact data of dichotomous-type and continuous-type data, as well as standard deviation should be provided so as to integrate each single weight in each study.

**Exclusion Criteria**

1. Trials exploring the outcomes of lateral cervical node dissection or modified neck dissection instead of CND.
2. The contents of retrieved central LNs failing to comply with the standard regional classification of cervical LNs (Level VI LNs should be composed of prelyregeal, pretracheal, and paratracheal LNs at minimum).
3. Studies published repeatedly in different journals.

**Data Extraction**

The two reviewers independently extracted details from selected studies. The data comprised 1) basic information regarding the research: first author, year of publication; 2) quality of the research: comparative design, sample capacity, follow-up duration; 3) outcome analysis, including temporary or permanent hypocalcemia, temporary, or permanent RLN injury, and locoregional recurrence. Specific rules of data extraction were as follows. (a) Data on therapeutic CND, prophylactic CND, ipsilateral CND, and bilateral CND were pooled when comparing TT with CND versus TT alone. (b) If the extent of CND matched the inclusion criteria, all thyroidectomy types (lobectomy, subtotal thyroidectomy, total thyroidectomy) were arbitrarily considered TT. TT with lymph node “cherry-picking” was arbitrarily considered as TT alone. (c) Cases with cancer recurrence in the residual thyroid were excluded when analyzing cumulative recurrence rate.

**Statistical Analyses**

All individual outcomes were integrated with the meta-analysis software Review Manager Software 5.0 (Cochrane Collaborative, Oxford, England). Results were analyzed with the random effects method if significant heterogeneity ($P < .05$) was detected. Otherwise, a fixed-effect model was adopted. The risk difference (RD) was calculated for dichotomous data. In addition, subgroup analysis was performed to estimate if there was a difference in recurrence (nodal, purpose of lymph node dissection). Thus, four subgroups were established:

Subgroup 1: patients who underwent TT with CND or TT alone and developed central nodal recurrence;
Subgroup 2: patients who underwent TT with CND or TT alone and developed noncentral nodal recurrence;
Subgroup 3: patients who underwent therapeutic TT with CND versus those who underwent TT alone and developed nodal recurrence;
Subgroup 4: patients who underwent prophylactic TT with CND versus those who underwent TT alone and developed nodal recurrence.

**RESULTS**

**Identification of Studies and Patients**

We ultimately identified 16 trials1,8,14–27 comprised of 3,558 patients, published between January 1995 and April 2010, of whom 1,499 (42%) underwent TT with CND and 2,059 (58%) underwent TT alone. The heterogeneity of the studies and patients were identified by the reviewers. The majority of studies were retrospective trials or cohorts; only one randomized control trial (RCT) was retrieved. Patients in each group were well matched with regard to gender, age, comorbidities, and involvement of lateral lymph nodes. Furthermore, two authors reported significant differences in tumor size between groups21,24 (one author reported a larger tumor in the TT plus CND group, whereas the other reported the opposite). Five trials suggested that a significantly larger proportion of DTC patients had multifocal tumors in the TT plus CND versus the TT alone group.2,8,21,24–26 Only one author found a significant difference with respect to TNM stage.18 The remaining trials either addressed the equivalency of clinical pathological features between groups or neglected them. Study characteristics, patient demographics, and outcome analysis are listed in Table I.

**Surgical Morbidity**

A total of 11 studies assessed postoperative temporary hypocalcemia after TT with CND versus TT alone; 13 reported the prevalence of permanent hypocalcemia. The definition of temporary or permanent hypocalcemia ranged from subjective symptoms to objective laboratory examinations.25 The overall prevalence of temporary hypocalcemia after TT with CND was significantly higher than after TT alone (262/845, 31% vs. 293/1478, 16%; RD 0.15; 95% confidence interval [CI], 0.09–0.22; $P < .01$). With regard to permanent hypocalcemia, there was no difference between TT with CND and TT alone (17/1096, 1.6% vs. 22/1696, 1.3%; RD 0.15; 95% CI, −0.01–0.01; $P = .92$).

A total of 10 trials investigated the incidence of temporary RLN injury after TT with CND or TT alone and 11 researchers outlined the incidence of permanent RLN injury. Unlike varying definitions of hypocalcemia, the diagnosis of RLN injury was made consistently, with unilateral or bilateral vocal cord dysfunction under direct or indirect laryngoscopy. The cumulative prevalence of temporary RLN injury after TT with CND trended slightly higher than after TT alone (44/847, 5.2% vs. 38/1331, 2.9%; RD 0.01; 95% CI, 0.00–0.03), but this difference was not found to be statistically significant. The prevalence of permanent RLN injury after TT with CND appeared similar to that of permanent RLN injury after TT alone (15/918, 1.6% vs. 19/1423, 1.34%), but this also was not significant (RD 0.00; 95% CI, −0.01–0.01; $P = .88$).

**Locoregional Recurrence**

Postoperative regional or local recurrence in DTC was evaluated in 12 studies. However, the definition of locoregional recurrence was inconsistent in the surgical literature. Most surgeons agreed that an increasing thyroglobulin or antithyroglobulin antibody level, or positive imaging (by ultrasound, computerized axial tomography, or radiiodine whole-body scan) indicated...
### TABLE I.
Summarize the Details of Selected Trials Comparing Different Surgical Patterns for Patients with DTC.

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Design</th>
<th>Sample Capacity of Each Group</th>
<th>Additional Dissection for Lateral Disease</th>
<th>Postoperative/ Radioiodine Therapy</th>
<th>Mean Follow-up (Month)</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davidson et al., 2008¹</td>
<td>RT</td>
<td>Group1: TT + TCND 19</td>
<td>73 LNDs in total</td>
<td>Routine performed</td>
<td>78</td>
<td>3b, Level B</td>
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<td></td>
<td></td>
<td>Group2: TT + TLND 73</td>
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<td></td>
<td></td>
<td>Group3: TT + TCND + TLND 14</td>
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<td>Group4: TT + Nodes plucking 77</td>
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<tr>
<td>Wada et al., 2003²</td>
<td>RT</td>
<td>Group1: TT + TCND + TLND 24</td>
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<td>&gt;53</td>
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<td></td>
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<td>Group2A: TT + PCND + PLND185</td>
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<td></td>
<td>Group2B: TT + PCND 50</td>
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<td></td>
<td>Group3: TT Alone 155</td>
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<tr>
<td>Sadowski et al., 2009¹⁴</td>
<td>RT</td>
<td>Group1: TT + BCND 168</td>
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<td>38.8</td>
<td>3b, Level B</td>
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<td>Group2: TT + ICND 11</td>
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<td>Group3: TT Alone 130</td>
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<td>Gemsenjager et al., 2003¹⁵</td>
<td>ICS</td>
<td>Group1: TT + TCND 42</td>
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<td>97.2</td>
<td>2b, Level B</td>
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<td></td>
<td></td>
<td>Group2: TT + PCND 29</td>
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<td>Group3: TT Alone 88</td>
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<tr>
<td>Henry et al., 1998¹⁶</td>
<td>RT</td>
<td>Group1: TT Alone 50</td>
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<td>12</td>
<td>3b, Level B</td>
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<td></td>
<td>Group2: TT + PCND 50</td>
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<tr>
<td>Roh et al., 2007¹⁷</td>
<td>ICS</td>
<td>Group1: TT + BCND 82 (TT + TCND 42; TT + PCND 40)</td>
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<td>Group3: TT Alone 155</td>
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<td>Roh et al., 2009¹⁸</td>
<td>RCT</td>
<td>Group1: TT + CND 148</td>
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<td>36</td>
<td>1b, Level A</td>
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<td></td>
<td>Group2: TT Alone 49</td>
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<tr>
<td>Rosenbaum et al., 2009¹⁹</td>
<td>RT</td>
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<td></td>
<td>&gt;33.6</td>
<td>3b, Level B</td>
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<td></td>
<td>Group2: TT + PCND 88</td>
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<tr>
<td>Sywak et al., 2006²⁰</td>
<td>ICS</td>
<td>Group1: TT + ICND 55</td>
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<td>&gt;24.5</td>
<td>2b, Level B</td>
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<td></td>
<td>Group2: TT Alone 391</td>
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<tr>
<td>Palestini et al., 2008²¹</td>
<td>RT</td>
<td>Group1: TT + BCND 64</td>
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<td>No detail</td>
<td>3b, Level B</td>
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<td></td>
<td>Group2: TT + ICND 93</td>
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<td>No detail</td>
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<td></td>
<td></td>
<td>Group3: TT Alone 148</td>
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<tr>
<td>Besic et al., 2009²²</td>
<td>ICS</td>
<td>Group1: TT + TCND or PCND 30</td>
<td>55 LNDs in total</td>
<td>124¹³¹ ablations in total</td>
<td>56</td>
<td>2b, Level B</td>
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<td></td>
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<td>Group2: TT Alone 224</td>
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<tr>
<td>Steinmüller et al., 1999²³</td>
<td>RT</td>
<td>Group1: TT + CND 53</td>
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<td></td>
<td>72</td>
<td>4, Level C</td>
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<td></td>
<td></td>
<td>Group2: TT + LND 15</td>
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<td></td>
<td>Group3: TT Alone 70</td>
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<tr>
<td>Moo et al., 2010²⁴</td>
<td>RT</td>
<td>Group1: TT + PCND 45</td>
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<td>37.2</td>
<td>3b, Level B</td>
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<td>Group2: TT Alone 36</td>
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<tr>
<td>Zuniga et al., 2009²⁵</td>
<td>ICS</td>
<td>Group1: TT + PCND 136</td>
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<td>82.8</td>
<td>2b, Level B</td>
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<td></td>
<td></td>
<td>Group2: TT Alone 130</td>
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<tr>
<td>Shen et al., 2010²⁶</td>
<td>RT</td>
<td>Group1A: TT + TCND + TLND 81</td>
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<td></td>
<td>&gt;24</td>
<td>3b, Level B</td>
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<td></td>
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<td>Group1B: TT + TCND 110</td>
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<td></td>
<td></td>
<td>Group2: TT Alone 191</td>
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<tr>
<td>Perrino et al., 2009²⁷</td>
<td>ICS</td>
<td>Group1: TT + TCND 92</td>
<td></td>
<td>140¹³¹ ablations in total</td>
<td>69.2</td>
<td>2b, Level B</td>
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<tr>
<td></td>
<td></td>
<td>Group2: TT Alone 159</td>
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</table>

RT = retrospective trial; ICS = individual cohort study; RCT = randomized controlled trial; TT = total thyroidectomy; CND = central neck dissection; LND = lateral neck dissection; TCND = therapeutic CND; PCND = prophylactic CND; BCND = bilateral CND; ICND = ipsilateral CND; TLND = therapeutic LND; MRND = modified radical neck dissection.
recurrence, and would be confirmed by pathology during reoperation.

As previously described, we first pooled every recurrence after therapeutic CND, prophylactic CND, ipsilateral CND, and bilateral CND, and compared them with the results of TT alone. We found that the cumulative prevalence of locoregional recurrence was slightly higher after TT than after TT with CND (119/1520, 7.8%) vs. 71/1050, 6.8%), but this difference was not statistically significant (RD 0.00; 95% CI, 0.03–0.03; P = .92, Fig. 3A).

We performed subgroup analyses because the recurrence locations varied in each trial (lateral, central, and multifocal recurrence). After preliminary selection, 10 trials were found that investigated the incidence of central neck recurrence after TT with CND and TT alone; and subgroup analysis was performed. The prevalence of central neck recurrence was similar between groups (CND after TT, 14/805, 1.7%; vs. 30/1288, 2.3%, RD −0.01; 95% CI, −0.03–0.01; P = .29, Fig. 3B).

The efficacy of prophylactic versus therapeutic CND, versus TT alone, in reducing postoperative nodal recurrence, was also investigated. Seven studies outlined the incidence of recurrence after TT with prophylactic CND versus TT alone, and seven others described the prevalence of TT with therapeutic CND or TT alone. We found that TT alone did not result in a higher risk of postoperative recurrence than TT with therapeutic or prophylactic CND; in either subgroup 3 (9.3%, 39/419 vs. 5.2%, 43/812; RD 0.05; 95% CI, 0.04–0.14; P = .25) or subgroup 4 (5.0%, 30/599 vs. 7.7%, 80/1041; RD 0.04; 95% CI, −0.09–0.02; P = .20; Fig. 3C).

**DISCUSSION**

The role of CND in thyroidectomy for DTC is controversial. Survival is a reasonable and accurate index for evaluating the benefits of different CND procedures for DTC with central LNM; and it has been argued that treating metastatic LNs in DTC would benefit patients by increasing survival. However, due to the indolent nature of DTC, it is difficult to obtain accurate long-term survival data after a fairly long duration of follow-up. Death from other causes occurs frequently during the observation period. Furthermore, the crucial role of CND on improving the survival of DTC had not yet been elucidated. Thus, surgeons were required to shift the main endpoint from long-term survival or mortality to surgical morbidity and disease-free status in comparing the effectiveness and applicability of each procedure.
Surgical Morbidity

The current meta-analysis revealed a significantly higher rate of temporary hypocalcemia in patients undergoing TT with CND than TT alone. This risk is expected, as more extensive dissection of the central compartment can interfere with the blood supply to the parathyroids, particularly the ipsilateral inferior gland. Moreover, TT with incidental parathyroidectomy, or without simultaneous parathyroid gland transplantation, would also cause postoperative temporary hypocalcemia. The slightly higher rate of temporary vocal cord palsy after TT plus CND could be due to mild injury of the RLN due to surgical manipulation, local edema, or small-scale regional hematoma. TT alone still leads to 1% to 2% permanent hypocalcemia or permanent nerve injury (recurrent laryngeal, external branch of the superior laryngeal) even when performed by experienced surgeons. The results of our analysis were consistent with this observation, as 1.30% and 1.34% of PTC patients after TT alone developed permanent hypocalcemia and permanent RLN injury, respectively. Interestingly, permanent surgical morbidity did not rise if CND was performed alongside TT. Therefore, additional CND did not increase the risk of permanent surgical morbidity.

Recurrence

Although larger tumors, older patients, male gender, invasiveness (vascular invasion and extracapsular extension), and proven lateral LNM are all negative prognostic indicators, the correlation between positive central LNM and poor prognosis was a matter of fierce debate. In other words, these risk factors might be predictive of positive central LNM, affecting postoperative mortality. Because mortality in DTC is a difficult endpoint to use, surgeons focused on locoregional recurrence, a more meaningful assessment of intervention in the eyes of patients. Although it has been traditionally accepted that cervical LNM is associated with locoregional recurrence, no significant difference was detected in recurrence between patients undergoing TT alone versus TT with CND (7.83% vs. 6.76%). As the location of recurrence varied among trials, we performed subgroup analyses to evaluate the incidence of central nodal recurrence after each procedure, and found no statistical difference between subgroups. As the significance of prophylactic and therapeutic CND was thought to be quite different, another subgroup analyses to evaluate the efficacy of both techniques in reducing postoperative nodal recurrence was carried out. However, even though the disease staging of tumor in the TT with therapeutic CND...
group was more advanced than that in the TT-alone group, the difference did not reach the statistical significance between subgroups. Therefore, adding CND may not affect recurrence and may not reduce the possibility of nodal recurrence. TT alone could offer equivalent efficacy of disease control compared with TT with TCND or PCND. Similarly, Cranshaw39 claims that locoregional recurrence in patients with PTC and lymph node micrometastases is equivalent to that of patients with PTC with no metastases. Thus, the benefit of performing CND to decrease locoregional recurrence might be overestimated. A major reason for routine CND was that recurrence in the central compartment was technically difficult to resect, and risked recurrent nerve injury and permanent hyperparathyroidism.32 However, increasing evidence has shown that performing secondary CND does not result in additional morbidity even when performed as a second stage procedure.40,41 Ferlito42 argued that even patients with proven paratracheal recurrence might be observed without treatment to assess tumor biology, if

Fig. 3. (A) Pooled analyses, using the Mantel-Haenszel method and a random-effects model, of locoregional nodal recurrence after TT plus CND versus TT alone. (B) Pooled analyses, using the Mantel-Haenszel method and a random-effects model, of central and noncentral nodal recurrence after TT plus CND versus TT alone. (C) Pooled analyses, using the Mantel-Haenszel method and a random-effects model, of locoregional nodal recurrence after TT plus TCND or PCND versus TT alone.
the mass was not clearly enlarging. Thus, the role of CND might be reconsidered.43

The American Thyroid Association (ATA) had provided a revised version of their guidelines on DTC in the November 2009 issue of *Thyroid*.44 The recommendations (27a–c and 28) were correlated to the surgical strategy for loco-regional lymph node involvement. The committees were more cautious on the subject of CND, and they recommended prophylactic CND for high-risk patients with T3 and T4 diseases. Even so, the level of evidence only reached rank C, which meant these recommendations were based on expert opinions. Still, the committee acknowledged that prophylactic dissection is an ongoing controversial issue. Thus, these recommendations (27b–c) were interpreted in light of available surgical expertise. One valid strategy suggested was to perform thyroidectomy alone, with reoperation for recurrences in the small minority who eventually developed detectable lymph node metastases, thus avoiding unnecessary morbidity in the majority of patients.45

**Limitations**

A total of 11 studies in our analysis reported postoperative administration of radioiodine therapy after thyroidectomy. This would be a reason of the apparent discordance between the relatively high rates of occult nodal metastasis detected by prophylactic CND, and the relatively low rates of recurrence after thyroidectomy without CND. However, detailed information on the proportion of patients in different groups who received RAI therapy, and whether patients with lymph nodal recurrence received RAI were impossible to obtain, preventing us from performing further analysis.

The other limitation of this analysis was that the majority of reports were retrospective cohorts. Patients with DTC were divided into TT plus CND or TT-alone groups based upon surgeon preference or expertise rather than randomization, which would increase heterogeneity between groups. The difference between multifocality, tumor size, and TNM stage are representations of this heterogeneity and reflects the fact that baseline characteristics might not be well matched. Therefore, selection bias was unavoidable (though impossible to completely eliminate in meta-analysis) and affects the validity of our analysis. However, we attempted to retrieve the most valuable comparative trials, selecting and integrating them to evaluate the benefits and adverse outcomes of various surgical approaches in CND for DTC. Our work should provide future directions for continued study on this controversial area. In addition, multicenter randomized controlled trials to estimate morbidity and disease-free survival between different surgical approaches are warranted. As RCTs minimize selection bias, the results of such trials would provide the most appropriate guidance to the role of prophylactic CND.

**CONCLUSION**

With regard to surgical morbidity and locoregional recurrence, we found no benefit in performing TT with CND versus TT alone in DTC. Instead, we demonstrated a higher risk of temporary hypocalcemia from subsequent CND with additional dissection in the central cervical compartment.
BIBLIOGRAPHY


