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Citation	Gland Surgery, 2013, v. 2 n. 4, p. 186-195
Issued Date	2013
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The pros and cons of routine central compartment neck dissection for clinically nodal negative (cN0) papillary thyroid cancer

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Abstract: Metastatic disease to regional lymph nodes (LNs) is common in papillary thyroid carcinoma (PTC). LN dissection is increasingly performed as part of the surgical management of PTC. The role of prophylactic central neck dissection (pCND) in PTC is unclear. There is limited evidence to support a routine pCND in clinical setting for nodal negative (cN0) PTC. The aim of this review was to examine the pros and cons of prophylactic neck dissection in cN0 PTC. In summary, the advantages of pCND are: removal of the central LNs that potentially harbor micro-metastases, more accurate staging of disease in order to plan more individualized management, reducing the need for re-operation to remove the metastatic LNs which have developed later and possible improvement in overall survival. The disadvantages are: an extensive surgery but lack of evidence of survival benefit, higher incidence of complications with little impact on local recurrence rate, possibility of over treating in cN0 patients and it does not sound like a cost effective approach in the management of small thyroid cancer. Considering low frequency of permanent morbidity, some authors believe that prophylactic neck dissection is safe in experienced hands even though its prognostic benefit has yet to be demonstrated.

Keywords: Central compartment neck dissection; nodal negative papillary thyroid cancer; prophylactic central neck dissection (pCND)



Submitted Aug 20, 2013. Accepted for publication Oct 31, 2013.

doi: 10.3978/j.issn.2227-684X.2013.10.10

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Introduction

Although thyroid cancers represent approximately 1% of all new cancer diagnoses in the United States each year, it is the most common endocrine related cancer (1). The American Cancer Society estimated that approximately 44,670 new cases of thyroid cancer would be diagnosed in 2010. The overall incidence has risen from 1.3/100,000 for women and 4.6/100,000 for men in the year 1935 to 16.3/100,000 for women and 5.6/100,000 for men in 2008 (2). The age & gender adjusted incidence has increased faster than that of any other malignancy in the recent years, with the majority of this increase belonging to small papillary thyroid carcinoma (PTC) (3).

Epidemiology

Thyroid cancers are divided into PTCs (80%), follicular

thyroid carcinomas (FTCs) (10%), medullary thyroid carcinomas (5-10%) and anaplastic thyroid carcinomas (1-2%). Primary lymphomas and sarcomas are rare (1). PTC and FTC make up the well-differentiated thyroid carcinomas. The prognosis of the differentiated thyroid carcinomas (DTC) is generally excellent. Ten-year relative survival rates in a large cohort of United States patients with papillary and follicular cancer were, respectively, 93% and 85% (4). In one cohort study, 40 years recurrence rates were about 35%, two thirds of which occurred within the first decade after initial therapy. Thirty years cancer mortality rates were about 12% with local recurrence and 43% with distant recurrence (5).

DTC

PTC is the most common type of differentiated thyroid

carcinoma. It is well known as a lymphotropic type of cancer and thus has high tendency to metastasize to regional lymph nodes (LNs) (6). Clinically evident nodal disease is present in approximately 5 to 10 percent of patients with PTC and a preoperative neck ultrasound can detect LN disease in up to 30 percent of patients (7-10). In contrast, less than five percent of patients with FTC develop nodal metastatic disease; the hematogenous rather than the lymphatic route is the primary pathway for metastasis (11). The prognosis of FTC is related to the age on presentation and the degree of capsular with or without vascular invasion. The diagnosis of FTC cannot always be made at the time of initial surgery. Prophylactic central neck dissection (pCND) during the first operation is of no value in FTC because the diagnosis of cancer is not established at that moment and also it tends not to spread via the lymphatic route.

Central neck dissection (CND) for PTC at the time of total thyroidectomy (TT)

The availability of non-invasive ultrasound and fine needle aspiration has led to detection of PTC in early stage. Higher incidence of small thyroid nodule with unknown cervical LNs status has posed a new management challenge to clinicians. Despite the excellent prognosis, many patients with PTC will develop nodal metastases in the central neck (level VI) or lateral neck (levels II, III, and IV) at the time of presentation or during the course of follow-up.

The guideline from the National Comprehensive Cancer Network recommends CND only in the presence of clinically nodal disease. Similarly, the current standard of care for thyroid cancer based on the consensus guideline from American Thyroid Association (ATA), includes TT and a “therapeutic” LN dissection for patients with clinical evidence of nodal disease or a “prophylactic” CND in patients with a tumor more than 4 cm (T3 or T4 tumor) even in the absence of clinical evidence of nodal involvement (3). Most endocrine surgeons agree that compartment-based nodal dissection is appropriate for enlarged LNs that are identified on preoperative or during intraoperative inspection and palpation. However, substantial controversy still exists regarding the role of “prophylactic” neck dissection for patients with PTC.

The neck dissection is defined by ATA as compartment oriented removal of all the lymphatic tissue with the fibroadipose tissue en bloc within the neck while preserving critical structures. A pCND is defined as resection of level VI LNs that appear normal in preoperative imaging and

intra-operative assessment. Anatomical neck level VI or central compartment of the neck refers to the LNs that located between the carotid arteries from the innominate artery to the hyoid bone, includes the pretracheal, prelaryngeal and paratracheal LNs (3).

In general, cervical nodal metastasis tends to spread in a stepwise fashion from the thyroid to the ipsi-lateral central (level VI), then to the lateral compartment (level II to V) and/or contra-lateral central compartment. Therefore, the central compartment is considered to be the first echelon of nodal metastasis in thyroid cancer. Theoretically, removal of central LNs may alter the prognosis of thyroid cancer especially in PTC. Many endocrine surgeons have advocated pCND in their patient without clinical or radiographic evidence of LN involvement at the time of TT (12). The actual role of pCND in thyroid cancer remains a major topic of debate. This article aimed to review the arguments for and against pCND in PTC.

Arguments for pCND in clinically nodal negative (cN0) PTC

(I) Metastatic disease to central compartment LNs is frequently identified in patients with PTC. Nodal disease is an important issue in managing patients with thyroid cancer. According to ATA, LN metastasis is present in up to 20-50% of the patients undergoing an elective node dissection for PTC and up to 90 percent of patients will have microscopic metastatic disease (13,14). Sergio Zuniga *et al.* demonstrated that in 136 patients who underwent pCND, 82.3% (112 patients) had metastatic LNs (15). Similar conclusion was drawn by Roh *et al.* in which 51 (62.2%) out of 82 patients with neck dissection had LN metastases in the central neck compartment (16). Therefore, there were significant numbers of patients undergoing TT for cN0 PTC without pCND are likely to have occult nodal disease left behind in the neck.

(II) Some studies have raised the possibility that failure to remove tumour bearing cervical LN could be detrimental in patient with PTC. Cervical LN metastasis is associated with higher risk of disease recurrence and cancer mortality. This is supported by the following studies:

- (i) In a retrospective review by Wada *et al.*, among 134 patients with papillary thyroid cancer undergoing TT with neck dissection, 17 patients (12.7%) developed local recurrence in cervical LNs. Recurrence rate was significantly higher for patients undergoing a therapeutic neck dissection

Table 1 A comparison of local regional recurrence rates between those underwent total thyroidectomy with prophylactic neck dissection (TT + CND) and those underwent total thyroidectomy (TT) alone

Author	Follow up period	No of patients		Local regional recurrence rate (%)		P-value
		TT + CND	TT	TT + CND	TT	
So <i>et al.</i> 2012 (20)	44.7 months (CND); 45.4 months (TT)	119	113	1.7	3.5	Not significant
Lang <i>et al.</i> 2011 (21)	Median: 26 months	82	103	3.7	2.9	1.0
Moo <i>et al.</i> 2012 (22)	3.1 years	45	36	4.4	16.7	0.13
Costa <i>et al.</i> 2009 (23)	Mean: 47 months (CND); 64 months (TT)	126	118	6.3	7.7	0.83
Gemsenjager <i>et al.</i> 2003 (24)	Median: 6.5 years	29	88	3	2	Not reported
Wada <i>et al.</i> 2003 (25)	Mean: 52 months	235	155	0.43	0.65	Not significant
Syawak <i>et al.</i> 2006 (26)	Median: 24.5 months (CND); 70 months (TT)	56	391	3.6	5.6	Not reported
Roh <i>et al.</i> 2007 (16)	Mean: 52 months	82 (PCND: 40)	73	0	2.6	0.37
Bardet <i>et al.</i> 2008 (27)	15 months	181 (with lateral neck dissection)	161	2.8	3.7	Not reported

Abbreviations: TT, total thyroidectomy; CND, central neck dissection.

for suspicious lymphadenopathy (n=42) when compared to patients undergoing an elective neck dissection (END) with no lymphadenopathy [23.8% (10 patients) versus 7.6% (7 patients)]. Microscopic disease was identified in 62 of 92 patients (67.4%) undergoing an END. Of the 62 patients with microscopic nodal disease, the local recurrence rate was 11.3%. Of the 30 patients with histologically negative nodes, there were no local recurrences. Of the 104 patients with histologically positive nodes, the local recurrence rate was 16.3%. Thus, he concluded that lymphadenopathy and microscopic nodal status were significantly associated with recurrences and disease free survival rates (17).

- (ii) In a Cox regression model, studied of 1,355 patients with 30 years of follow-up, the likelihood of cancer death was increased by regional lymph-node metastases in patients without distant metastases (18).
- (iii) Additional data from Surveillance Epidemiology and End Results database comprising 19,918 patients showed that for those with LN metastasis, the 14-year survival rate was 79% and was 82% in non-metastatic patients (P<0.05) (19).

Based on the above findings, there are potential benefits of lower recurrence in those who underwent pCND. *Table 1*

summarizes the local regional recurrence rates between those underwent TT with prophylactic neck dissection and those who underwent TT alone.

In contrast, a recent meta-analysis by Zetoune *et al.*, comprising five retrospective comparative studies (n=1,264), found that there was an “insignificant” trend toward lower overall recurrence rate in the group who underwent either unilateral or bilateral pCND when compared to those who had TT only (2.02% versus 3.92%, odds ratio =1.05, 95% CI, 0.48-2.31) (28). Furthermore, people may argue that the subclinical LN metastasis could be ablated by radioactive iodine post operation. But, it is worth noting that not all tumours will respond to RAI ablation.

(III) Ultrasound neck and aspiration cytology are currently the preferred investigation tools for evaluation of the thyroid and cervical LN. However, detection of central compartment LN metastasis using ultrasound remains difficult even in expert hand because the abnormal central LNs are often small in size and frequently located deep inside the neck or just posterior to the sternum (29-31), where the overlying thyroid gland often hinders adequate visualization (32).

Kim *et al.* found that preoperative ultrasound has an accuracy of 77% only in detection of LN metastasis. Despite the fact that ultrasound has high specificity of

92% and positive predictive value of 81%, the sensitivity is only 51% and the negative predictive value is 76% (33,34). Other sophisticated imaging modalities such as computer tomography and magnetic resonance imaging have not shown any additional advantage, they are more beneficial in patients with extensive nodal involvement. Because of the lymphadenopathy cannot be reliably assessed by imaging studies, pCND has been advocated. Prophylactic CND allows histology examination of LNs and more accurate pathological staging.

Wang *et al.* reviewed 49 patients (48%) who were cN0 PTC and found that pCND resulted in detection of unsuspected metastasis lymphadenopathy in 20 (41%) of patients and changed RAI recommendation in 14 (33%) of patients (35). Similarly, in a study performed in our hospital, of 82 patients underwent pCND, 17.1% were upstaged from stage I/II to stage III due to detection of nodal metastasis after surgery (21).

(IV) A detectable post-operation Thyroglobulin (Tg) level is a surrogate marker of persistent or recurrent thyroid cancer after TT and RAI ablation. Prophylactic CND results in a higher rate of stimulated athyroglobulinemia after surgery. Hence, it could facilitate follow up and cancer surveillance of the neck. The relation between pCND and Tg was illustrated by the following studies:

- (i) Sywak *et al.* examined 447 patients with clinically node-negative PTC. 56 patients underwent TT plus pCND. There was a significantly lower level of stimulated Tg at six months after RAI ablation (mean: 0.4 versus 9.3 mg/L, $P < 0.02$) and higher proportion of athyroglobulinemia (72% versus 43%; $P < 0.001$) (26).
- (ii) In a study compared serum Tg level in 113 patients underwent TT alone with 119 patients underwent TT in conjunction with pCND bilaterally: the post-operative Tg was significantly less in pCND group (1.07 vs. 2.24 ng/mL respectively; $P = 0.022$). However, the two groups became similar after low dose radioactive iodine treatment (0.44 vs. 0.69 ng/mL respectively; $P = 0.341$). There was also no significant difference in three years local-regional control rate in both the studied groups (98.35% vs. 96.5%; $P = 0.368$). Thus, he concluded that pCND lower the serum Tg level but is not helpful in decreasing short term recurrence in patient with cN0 PTC (20).
- (iii) Lang *et al.* analysed 185 patients with PTC retrospectively. In this study, 82 (44.3%) patients underwent unilateral TT with pCND and found that this group of patient has lower median pre-

ablative-stimulated Tg level (< 0.5 versus 6.7 $\mu\text{g/L}$, $P < 0.001$) and achieved a higher rate of pre-ablative athyroglobulinemia (51.2% versus 22.3%, $P = 0.024$) than those who underwent a TT only. However, these differences were not observed six months after ablation (31). The most likely explanation for this difference was that the residual microscopic disease was ablated by RAI ablation subsequently. Thus, the group without pCND achieved similar stimulated Tg levels and similar rate of athyroglobulinemia six months after ablation (36).

Unlike the above studies, no difference was found by Raffaelli M *et al.* concerning mean post-operative basal and stimulated Tg after a prospective evaluation of total 186 patients with cN0 underwent TT with or without; ipsi- or bilateral CND (37). Similarly, Hughes *et al.* also found that there was no difference in post-ablation median-stimulated Tg level or rate of athyroglobulinemia between patients underwent TT with or without bilateral pCND (38).

(V) Thyroid cancer patients without pCND are at higher risk of neck recurrence which may require second operation. Re-operation is associated with a higher morbidity than pCND when done at the time of initial TT. Complications such as iatrogenic injuries of the nerve and parathyroid gland would be higher in re-operative central lymph node dissection (CLND) because of the scarring in the operative field and distorted anatomy in the central neck after TT. For example, Segal *et al.* who had reviewed 503 patients retrospectively found that reoperation had a significantly higher complication rate of permanent recurrent nerve injury (25% versus 5.8%) and hypoparathyroidism (8.3% versus 5.0%) compared with primary operation (39). Other studies also revealed similar outcomes (40-43). It is reasonable to dissect LNs in the central compartment routinely, because subsequent surgery for node metastases in this area poses more difficulties. On the other hand, Shen *et al.* argued that neck reoperation could also be performed as safely as first operation by an "experienced" surgeon. In his study, the initial and re-operative CLND had similar complication and recurrence rates (44).

Arguments against pCND in cN0 PTC

(I) The most frequently quoted data arguing against the need for routine pCND is increased risk of transient hypoparathyroidism. Risk of transient hypocalcemia has been consistently shown in many studies (Table 2).

Table 2 A comparison of the rate of hypoparathyroidism (hypocalcemia) between total thyroidectomy (TT) alone and total thyroidectomy with central neck dissection (TT + CND)

Author	No of patients		Transient hypocalcaemia/ hypoparathyroidism (%)		P-value	Permanent hypocalcaemia/ hypoparathyroidism (%)		P-value
	TT + CND	TT alone	TT + CND	TT alone		TT + CND	TT alone	
Moo <i>et al.</i> 2010 (22)	45	35	31	5	0.001	0.0	5.0	0.41
So <i>et al.</i> 2012 (20)	119	113	41.2	33.6	0.235	5.9	1.8	0.105
Lang <i>et al.</i> 2011 (21)	82	103	18.3	8.7	0.017	2.4	1.0	1.000
Shindo <i>et al.</i> 2010 (45)	122	134	13.1	25.4	0.02	0.8	0.7	0.99
Palestini <i>et al.</i> 2008 (46)	93	148	26.9	12.8	0.003	0.0	2.7	0.2
Roh <i>et al.</i> 2007 (16)	82	73	30.5	9.6	0.001	4.9	0.0	0.056
Sywak <i>et al.</i> 2006 (26)	56	391	18	8	0.02	1.8	0.5	0.27
Giordano <i>et al.</i> 2012 (47)	385 (unilateral), 308 (bilateral)	394	36.1 (unilateral), 51.9 (bilateral)	27.7	0.014 (unilateral), 0.001 (bilateral)	7.0 (unilateral), 16.2 (bilateral)	6.3	0.818 (unilateral), <0.001 (bilateral)

Abbreviations: TT, total thyroidectomy; CND, central neck dissection.

- (i) Moo *et al.* found that the rates of temporary hypocalcemia were higher in CND group compared to no neck dissection group (31% versus 5%; $P=0.01$). Interestingly, the rate of permanent hypocalcemia were the same (5% versus 0%; $P=0.41$) (22).
- (ii) A meta-analysis found that patients with pCND were almost 2.5 times more likely to have temporary hypocalcemia than those who underwent TT alone (26.0% vs. 10.8%; $OR=2.56$; 95% CI: 1.75-2.57) (48).
- (iii) So *et al.* reviewed 232 patients who underwent surgery for clinically node negative papillary thyroid micro-carcinoma from 1999 to 2006, reported that the frequency of permanent hypocalcemia was approximately 3 times greater in TT with pCND (5.9%) than TT only (1.8%) although this finding did not reach statistical significance (20).
- (iv) A recent systematic review of five retrospective studies, evaluated the morbidity of pCND and found that there was one extra case of transient hypocalcaemia for every eight pCNDs performed (49). However, there was no increased risk of permanent hypocalcaemia and recurrent laryngeal nerve injury. The higher rate of temporary hypoparathyroidism could be explained by the higher chance of

unintentional removal or devascularisation of parathyroid glands during dissection.

Prophylactic CND also contributes to the higher rate of temporary recurrent laryngeal nerve injury in a study by Shindo *et al.* (45) (Table 3). Palestini *et al.* reported four times higher rate of transient recurrent laryngeal nerve injury in patients underwent TT plus bilateral neck dissection (1.4% versus 5.4%, $P=0.059$), although it was not statistically significant (46). To date, no studies have shown an increase risk of “permanent” recurrent laryngeal nerve injury in patient underwent pCND. A good example was a study by Giordano *et al.* as shown in Table 3 (47).

In general, surgical morbidity correlates with the extent of surgical dissection and the operation skill of surgeons. Since the risks of transient complications are high, especially when performed by low volume surgeons (fewer than 50 cases/year), a selective approach should be considered by determine which patients are likely required pCND pre-operatively and the experience of the surgeon (51).

Several studies described the risk factors that associated with LN metastasis in PTC but the results were inconsistent (46,52,53). In a study by So *et al.*, the male gender, tumour multi-focality and extra-thyroidal extension were independently predictive of subclinical central LN

Table 3 Recurrent laryngeal nerve or vocal cord injuries in the total thyroidectomy with and without central neck dissection

Author	No of patients		Transient vocal cord palsy (%)		P-value	Permanent vocal cord palsy (%)		P-value
	TT + CND	TT alone	TT + CND	TT alone		TT + CND	TT alone	
So <i>et al.</i> 2012 (20)	119	113	3.4	3.5	0.941	0.8	1.8	0.531
Giordano <i>et al.</i> 2012 (47)	385 (unilateral), 308 (bilateral)	394	3.9 (unilateral), 5.5 (bilateral)	3.6	0.404	0.5 (unilateral), 2.3 (bilateral)	1.0	0.099
Lang <i>et al.</i> 2011 (21)	82	103	1.8	0.0	0.324	0.6	0.5	0.443
Shindo <i>et al.</i> 2010 (45)	122	134	0.0	4.5	0.03	0.0	0.0	–
Sadowski <i>et al.</i> 2009 (50)	169	130	8.9	4.6	0.18	2.4	3.1	1.0
Palestini <i>et al.</i> 2008 (46)	93	148	5.4	1.4	0.059	0.0	1.4	0.344
Roh <i>et al.</i> 2007 (16)	82	73	7.3	4.1	0.394	3.6	2.7	0.747
Sywak <i>et al.</i> 2006 (26)	56	391	1.8	1.0	0.62	0.0	1.0	0.45

Abbreviations: TT, total thyroidectomy; CND, central neck dissection.

metastasis. It was recommended that patient with these features should be considered for pCND (52). However, realistically only male sex is known preoperatively. Some researchers also believed that large tumour size, patients who have decreased capacity for RAI and those with *BRAF* mutation should be undergoing pCND at the time of TT (36). Alternatively, suspected LN that found intra-operatively may be confirmed by frozen section examination before proceeding to neck dissection.

(II) LN involvement in papillary thyroid cancer can be macroscopic (identified on preoperative imaging or intraoperative inspection) or microscopic (identified on pathologic review only). Macroscopic LN involvement is associated with a significant higher rate of local recurrence (10-42%) (54,55). It is unknown what the natural history is, in PTC with only microscopic LN involvement/subclinical nodal metastasis.

Studies have shown that only subclinical metastatic LNs would be identified at the time of pCND for small PTC (56). Wada *et al.* studied microscopic regional LN status in 92 patients with PTC underwent pCND and found that only few nodes (mean 2.7 nodes/17.8%) were involved pathologically when there was no lymphadenopathy clinically (31). Besides, Vergez *et al.* also found in their study that most of these pathologically involved LN were subclinical and less than 5 mm in size (66%) (57).

With the advances of radio-active iodine ablation, these micrometastasis wouldn't ultimately result in poorer prognosis. Additionally, it is doubtful that this subclinical occult LN metastasis would eventually develop into clinically significant recurrences in the future.

- (i) In another data presented by Wada *et al.* on 259 patients with papillary microcarcinoma of thyroid, of mean 53 months follow up, LN metastasis was frequent in the pCND group (60.9%) for central compartment and 39.5% for ipsilateral lateral compartment. While, only 0.43% patient underwent prophylactic neck dissection developed recurrence despite high microscopic LN involvement (25). The nodal recurrence did not differ between the pCND group and the no-dissection group (0.43% *vs.* 0.65%).
- (ii) Gemsenjäger *et al.* reported a similar finding in their study of 159 patients with PTC and concluded that the rate of occult nodal disease was relatively low and it did not frequently progress to clinical recurrent disease (24).

In summary, for patients harbouring central neck compartment "micrometastasis", pCND dissection may only provide a limited benefit in terms of reducing recurrence. Routine CND targeted at subclinical LN metastasis has little prognostic benefit. Unnecessary CND will prolong

Table 4 Mean doses of radioactive iodine ablative therapy

Author	No of patients		Mean dose of I-131 per treatment		P-value
	TT + CND	TT alone	TT + CND	TT alone	
Moo <i>et al.</i> 2010 (22)	45	36	102.7 mCi	66.3 mCi	0.002
Hughes <i>et al.</i> 2010 (38)	78	65	150.0 mCi	30.0 mCi	0.01
Sywak <i>et al.</i> 2006 (26)	56	391	5.2 GBq	4.8 GBq	0.2

Abbreviations: TT, total thyroidectomy; CND, central neck dissection.

operation time and increase surgical complications.

(III) There is also little evidence to show that pCND improves cancer-specific survivals in “cN0 PTC”.

- (i) A survival benefit for pCND in DTC was suggested in a study carried out by Tisell *et al.* (58). They evaluated 175 patients who underwent TT with CND and compared with contemporaneous controls from two other studies conducted on patients in Norway and Finland (59,60). They showed that patients who underwent TT with pCND had a higher survival rate (1.6% versus 8.4-11.1%). However, this study was limited by lack of statistical comparison between the studies.
- (ii) In the retrospective review of 244 patients by Costa *et al.*, found that central neck metastasis was predictive of disease recurrent but not influencing the prognosis. The overall recurrence rate in his paper was 6.35 % (8/126; mean follow-up of 47 months) in TT plus pCND group and 7.7% (9/118; mean follow-up of 64 months) in TT alone group (P=0.83). Of those underwent pCND, 47% were diagnosed pN1a but there was no difference in survival rate statistically (23).
- (iii) Additional finding came from a cohort analysis of 266 patients with 6.3 years mean follow up and the study reported that the 5-year disease-free survival was comparable; 88.2% in the CND group versus 85.6% in the group that did not undergo CND (P=0.72) (15). Absence of survival benefit with more extensive surgery and longer operation time have limited the routine application of pCND (24).

(IV) The number of positive cervical LNs could affect the disease stage. Prophylactic CND provides more accurate pathological staging and hence, greater incidence of N1a is found. In a study conducted by our hospital demonstrated that 17.1% of 82 patients were upstage from stage I/II to III after pCND (21). Basically, the pathological staging of the tumour for patients aged more than 45 years old are changed to higher stage III (AJCC/UICC TNM

staging system) even without any extra-thyroidal extension or other poor prognostic factors (61,62). The outcome of stage migration will be reflected in the overall cancer-specific survival rate. Confusion may occur as they would be classified as stage III with lower 10-year survival (85-90%) while those patients younger than 45 would still remain as stage I with 10-year survival rates of more than 95% (31,61-64).

(V) Because of upstaging, more patients would receive RAI ablation and higher doses of RAI, which might not be necessary in certain patients. In a retrospective study, Hughes *et al.* had observed that patients in the TT plus pCND group received significantly higher dose of RAI than those in the TT group (150 *vs.* 30 mCi, P=0.01). Despite a higher dose of RAI, there was no difference in central neck recurrence between TT plus pCND and TT alone group. The author concluded that pCND allows stratification of patient to receive higher doses of RAI but not affected the local recurrence rate (38). *Table 4* revealed the published series of doses of I-131 used during RAI ablation. pCND increased LN positivity and has encouraged higher usage of RAI. This is foreseeable that increase of health care costs will be one of the major concerns in the future.

Although the treatments with 131-I are generally safe and well-tolerated, patients would still be subjected to potential short- and long-term side-effect of RAI. RAI is contraindicated in patients who are pregnant or breastfeeding. Men who receive RAI treatment for thyroid cancer may have decreased sperm counts and temporary infertility for a period of roughly two years (65,66). Furthermore, Lee *et al.* found that nausea, vomiting, ageusia (loss of taste), salivary gland swelling, sialoadenitis associated xerostomia, dental caries, pulmonary fibrosis, naso-lacrimal outflow obstruction, and, more importantly, increased risk of second primary malignancies are associated with radioiodine therapy (67,68). I-131 is preferentially taken up by normal and malignant thyroid follicular cells, but it is also accumulated in the stomach, salivary glands, colon, and bladder; salivary glands and breast tissue contain sodium iodide transporters. The risk of salivary gland,

breast, bladder and gastrointestinal cancers can theoretically increase in thyroid cancer patients treated with radioiodine. The risk is typically more prominent between two and ten years after therapy with a prevalence of about 0.5% (65,66).

Conclusions

The extent of dissection in the neck is a balance between the greater morbidity of a more extensive neck dissection and the possibility of leaving residual untreated metastatic LN. There is little good evidence (level II or better) to justify pCND in all cN0 PTC. Our review has summarized the conflicting recommendations in which the applicability to clinical practice remains questionable. Further studies in this controversial subject are much needed.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Chan AC, Lang BH, Wong KP. The pros and cons of routine central compartment neck dissection for clinically nodal negative (cN0) papillary thyroid cancer. *Gland Surg* 2013;2(4):186-195. doi: 10.3978/j.issn.2227-684X.2013.10.10