Cervical Lymphadenectomy in Papillary Thyroid Cancer

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8.1 Introduction

Thyroid cancer is the commonest endocrine malignancy and is increasing in incidence mainly due to the increasing diagnosis of the most common histological subtype, papillary thyroid cancer (PTC). Papillary carcinoma represents up to 90% of all thyroid cancer diagnoses [1]. Its increasing incidence is largely due to the incidental ultrasonographic detection of microcarcinomas but also to a lesser extent to the diagnosis of larger locally advanced and metastatic thyroid cancers. However, the age-adjusted mortality from thyroid cancer remains the same or at most is marginally rising [2].

Lymph node metastases are common in PTC, in particular in the central neck compartment where 21–35% of patients may have a preoperative suggestion of nodal disease [3, 4]. This increases to as high as 85% when occult micrometastases found on histology are included in the calculation of node positivity [3–5]. There is a consensus view reflected in international guidelines (American Thyroid Association and National Comprehensive Cancer Network) that compartmental clearance of macroscopically involved central lymph nodes (cN1) reduces the risk of local disease recurrence and may, more controversially, impact on disease-free survival [6–8]. However, the clearance of nodal compartments, whether therapeutic or prophylactic, is associated with a higher risk of complications; with hypoparathyroidism and recurrent laryngeal nerve (RLN) injury being the principal hazards in central nodal clearance.

The prognosis for most PTC remains excellent, with overall 5-year survival of over 90% [3] but locoregional recurrence (LRR) can occur in up to 30% of patients [4]. The overall excellent prognosis and slow disease progression of PTC underlines the need for a careful assessment of the benefit of reduced LRR against the risk of

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M. Testini, A. Gurrado (eds.), *Thyroid Surgery*, Updates in Surgery,
https://doi.org/10.1007/978-3-031-31146-8_8

troublesome morbidity associated with a nodal dissection. This chapter will contextualize this debate by describing the indications for, and ongoing controversies regarding, cervical lymphadenectomy in PTC.

8.2 Definitions

There is varied anatomical and procedural terminology used in describing lymphadenectomy in PTC, particularly in relation to the central compartment. There are several iterations of thyroid cancer staging and the perceived clinical relevance of nodal metastases in PTC has evolved over the last few decades. This has been followed by changes in clinical management, which has created difficulties when comparing patient populations over time.

8.2.1 Anatomical Terminology

Robbins et al. first attempted to standardize the terminology used in the dissection of cervical lymph nodes in 1991 [9]. This classification was then adapted by the American Academy of Otolaryngology – Head and Neck Surgery. The purpose of the anatomical definitions was to standardize the description in the treatment of squamous cell carcinomas of the head and neck rather than thyroid cancer, which is associated with a different pattern of spread. There are at least four systems used for staging cervical nodal basins internationally [9–12].

The American Academy of Otolaryngology system divides the neck into six nodal compartments [9]. The central compartment is divided into levels Ia, Ib and VI, and the lateral into IIa, IIb, III, IV, Va, and Vb. The upper mediastinum is often referred to as level VII. This is relevant to thyroid cancer since level VI and VII are common sites for initial nodal spread in PTC. The margins of level VI are the hyoid bone cranially and the sternal notch caudally; the common carotid artery is the lateral limit and the trachea represents the midline. The prevertebral fascia marks the posterior limit of the central compartment. The prelaryngeal, pretracheal and paratracheal lymph nodes lie within the central compartment. The Delphian or precricoid node is contained within the prelaryngeal group. In thyroid cancer the described anatomical boundaries are not respected by PTC spread and are arguably mainly used for ease of communication and the identification of structures at risk during surgery [13].

The Japanese Society of Thyroid Surgery Classification [10] is similar to the American system in that the upper mediastinum is excluded. However, the central compartment is comprised of nodal groups I–IV (prelaryngeal, pretracheal, paratracheal and paraglandular groups, respectively) and lateral groups V–VII. The International Union Against Cancer (UICC) describes eight regions, with the central comprising groups 1, 2 and 8 and the lateral 3–7 [11]. Dralle et al. described the

Compartment Classification system for use in medullary thyroid cancer [12] but which can be adapted to PTC. They described four lymph node regions, and theirs is the only classification that includes the superior mediastinal compartment as part of its descriptive system (1a right central, 1b left central, 2 right lateral, 3 left lateral, 4a right upper mediastinum and 4b left upper mediastinum).

Each of these classification systems has its respective advantages and limitations and sadly they are largely reciprocally incompatible. Whilst not necessarily the best classification system specific for thyroid cancer, the American Academy of Otolaryngology system is the most prevalent in the English-speaking world and Europe. It is used in the American Thyroid Association (ATA), European Thyroid societies and the British Association of Endocrine and Thyroid Surgeons. It is also the system used in the authors' institution and will be referenced to in the rest of this chapter. In this classification system particular note should be made of levels VI and VII, which are the areas first involved by metastatic lymph nodes in PTC.

8.2.2 Operative Terminology

Cervical lymphadenectomy is the process of removal of the lymph nodes within a designated nodal compartment of the neck. In PTC, level I is almost never involved, so the neck dissection when indicated includes the central (level VI & VII) and lateral (levels II–V) compartments. Selective neck dissection – where lymph node compartments are removed and the key structures preserved if not involved – is the most common oncological strategy. This differs from head and neck malignancy where level I is included in the dissection. Radical neck dissection with additional sacrifice of the sternocleidomastoid and the accessory nerve are infrequently required in PTC but the sacrifice of the internal jugular vein and vagus nerve may occur especially when high volume level IV disease with extracapsular spread encases the carotid sheath [14].

If the patient is fit for surgery and lymph node metastases are detected either pre- or intraoperatively, a therapeutic lymphadenectomy is the uncontroversial recommendation. The surgical removal of macroscopic lymph node metastases is fundamental for PTC disease control and reduces local recurrence [15]. Equally uncontroversial is the abandonment of "berry picking", where individual suspicious lymph nodes only are removed rather than a formal compartmental dissection. The berry picking approach is associated with a high local recurrence [14, 16] and the need for intervention in a re-operative field with higher associated operative risk [14].

A prophylactic (or "elective") nodal dissection implies routine clearance of nodal tissue in a patient who has no clinical or radiological evidence of nodal involvement (cN0) [13]. This has been an area of controversy for several decades and the debate remains in part unresolved, although guidelines in the US and Europe have moved away from this except possibly in high-risk disease where it can be considered (Table 8.1) [6, 7, 17–19]. The technical principles of lymphadenectomy are beyond the scope of this chapter and are found in surgical technique textbooks.

Table 8.1 International guidelines in regard to pCND

Guideline	Recommendation
American Thyroid Association 2015 [6]	Considered in cN0 PTC patients with T3/4 tumors, cN1b disease, or if the information will be used to plan further therapy
National Comprehensive Cancer Network 2022 [7]	Not recommended in cN0 patients with PTC
British Thyroid Association 2014 [17]	Not recommended in the absence of high-risk features. Bilateral pCND is recommended if high-risk features are present – Personalized decision-making recommended
European Thyroid Association 2019 [18]	For T3/4 tumors, pCND may improve regional control
Japanese Association of Endocrine Surgeons 2020 [19]	Routinely recommended in PTC

pCND prophylactic central node dissection, *PTC* papillary thyroid cancer

8.3 Controversies in the Management of Nodal Disease in Papillary Thyroid Cancer

8.3.1 Difficulties in Preoperative Diagnosis of Nodal Metastases in the Central Neck

Nodal clearance in PTC is performed with the aim of reducing LRR and disease-specific mortality. Staging of the lateral neck with high resolution ultrasound (US) or computed tomography (CT) is very effective at identifying nodal pathology and this can be biopsied for confirmation [15, 20]. There is no indication for prophylactic lateral nodal dissection; however, it may still be adopted in some countries [19] based on the unproven rationale that the non-use of radioiodine (RAI) mandates more aggressive surgery.

The preoperative staging of the central neck for nodal metastases is hindered by the presence of the thyroid and trachea that may obscure the view of level VI and the sternum and clavicles that obscure level VII. The sensitivity of US in identifying pathological lymph nodes in the central neck ranges from 23–55%, whereas the detection rate of US in the lateral neck is 94% [20, 21]. The sensitivity of CT in the central neck is 41–62% [20–22], but it has limited value in detecting small lymph node metastases and the use of iodine contrast may delay the use of RAI postoperatively. Normally the decision on therapeutic nodal clearance of the central compartment is made either if there is nodal disease on staging or intraoperatively, based on the presence of nodal pathology. Clinical features of metastatic lymph nodes include size >1 cm, dark discoloration and firmness on palpation. Intraoperative clinical judgement can be challenging and there is a notoriously low sensitivity and specificity (35.7% and 72.5%, respectively) and high rates of false positives and false negatives in the intraoperative diagnosis of central lymph node metastases [22].

The arrival of data suggesting that prophylactic central node dissection (pCND) can reduce the level of postoperative thyroglobulin [23–25] (a surrogate marker of disease burden), the need for RAI or the total RAI dosage as well as reducing the

rate of LRR started a move towards prophylactic level VI surgery at the beginning of the new millennium. Advocates of pCND promoted the view that prophylactic dissection should be performed on all PTC patients due to the high rates of occult lymph node metastases and their presumed consequence, namely the need for re-operation in the central neck.

8.3.2 Effect of pCND on Recurrence

Macrometastatic nodal disease in the central neck has been shown to represent an independent risk factor for recurrence [5, 26, 27] and reduced long-term survival [28–30]. Occult lymph node metastases are identified in up to 85% of patients after pCND [3]. The adoption of pCND in all PTC patients would theoretically ensure removal of all subclinical lymph node metastases in the central neck and offer better disease control. Barczyński et al. demonstrated a significant reduction in both LRR and disease specific survival after bilateral pCND in their study [8]. The 10-year LRR rate was 12.4% after total thyroidectomy alone and 5.5% after total thyroidectomy with pCND ($p = 0.003$). The 10-year disease-specific survival rate was 98% after pCND, 5.5% higher than total thyroidectomy alone ($p = 0.03$). Popadich et al. also found a reduction in central compartment recurrence after total thyroidectomy with pCND (4.6% less than total thyroidectomy alone, $p = 0.004$) [25]. However, both of these were retrospective cohort studies with high rates of adjuvant RAI so the effect of pCND on outcome is difficult to measure with confidence. Two subsequent, large systematic reviews and meta-analyses also concluded that rates of central compartment recurrences were lower after pCND, but the reductions were of modest magnitude (1.76–2.3%) [31, 32].

The natural evolution of micrometastases is still not well understood and the data surrounding genuine clinical benefit is controversial [4, 15]. It is possible that the benefit of pCND will never be established because prospective studies are invariably underpowered. The ATA feasibility calculation for a randomized control trial of pCND in cN0 PTC estimated that 5840 patients would be needed for sufficient statistical power to detect differences in outcomes [33]. Despite this, five prospective randomized control trials have been identified [34–38] and none demonstrated a difference in recurrence with or without pCND after an average follow-up of 5 years. A systematic review and meta-analysis of these five studies yielded 763 patients [39] and no difference was found in structural or biochemical recurrence. The estimated number needed to treat per recurrence was 500. Nixon et al. performed a large retrospective analysis of 1798 cN0 patients who had total thyroidectomy without CND [40]. One-third ($n = 539$, 30%) had T3 or T4 tumors and 13.5% ($n = 240$) had pN1a disease despite no formal level VI dissection being performed. Almost half (41.3%) of patients received RAI. The 5-year recurrence-free survival was 96.6%, and disease-specific mortality was 0. Only 12 patients had central neck recurrence (<1%) and all of these were salvaged successfully with re-operative surgery. This study had a relatively short median follow-up of 46 months but nevertheless suggests that prophylactic dissection offers limited benefit.

8.3.3 Effect of pCND on Staging and Radioiodine Use

Routine central nodal dissection on all PTC patients adds staging information over thyroidectomy alone. Patients who have intermediate risk tumors may have tailored RAI administration or more accurate dose calculations based on their nodal status after pCND [4]. However, upstaged patients, due to the presence of occult lymph nodes, may receive arguably unnecessary RAI as a result of this. This effect was demonstrated by both Bonnet et al. and Hughes et al., who found that performing pCND resulted in RAI being administered in 58% and 29% of patients, respectively, who otherwise would not have been given treatment [41, 42]. The argument that pCND in intermediate risk PTC patients allows the identification of pN0 patients – who can safely avoid RAI and possibly decrease the duration and intensity of surveillance [43] – is probably unjustified with current sensitive thyroglobulin assays.

The overtreatment with RAI due to the frequency of micrometastases in cN0 patients and the uncertain relationship between micrometastases and recurrence [15] is increasingly important as the value of RAI in lower risk disease appears to be highly questionable. The Hi-Lo trial was a randomized non-inferiority trial comparing low (1.1 GBq) vs high dose (3.5 GBq) as the initial dose of RAI in PTC [44]. They found that recurrence was not higher after low-dose RAI after a mean follow-up of 6.5 years; however, the study was not powered to assess long-term recurrence and there was a need for repeat RAI treatments in 10% of the low-dose group. Another randomized trial, the Iodine or Not (IoN) trial, aims to determine whether or not RAI is necessary for low-risk patients with differentiated thyroid cancer, but the results are not expected until 2031. It must also be noted that the importance of nodal disease in staging has been revisited and positive nodal status no longer upstages thyroid cancer in patients older than 55 years (AJCC Staging, 8th ed.) [45].

If CND was without morbidity, it could be advocated even in the presence of a small benefit. However, any benefit of pCND has to be counterbalanced against the well-established morbidity of the procedure, in particular the hypoparathyroidism, which is much more common in patients that have a nodal dissection added to a total thyroidectomy.

8.3.4 Increased Rates of Operative Complications

Central node clearance requires more extensive dissection than thyroidectomy alone, particularly around the RLN and parathyroid glands. The higher rates of RLN palsy and postoperative hypoparathyroidism are thought to be due to more extensive manipulation and devascularization of these structures [4]. Considering that the benefit provided by performing pCND is contentious, it is vital to know whether performing pCND confers additional morbidity.

Volume-outcome is a robust tenant of endocrine surgery, with clear correlation between high surgeon volume and decreased morbidity [2]. A recent randomized control trial by Sippel et al. evaluated the complications after total thyroidectomy

alone and with pCND as the primary outcome [35]. They demonstrated that, in experienced hands, there was no difference between groups in regard to temporary or permanent hypoparathyroidism or vocal cord palsy. However, their rates of hypoparathyroidism and RLN injury were somewhat higher than those generally published by expert endocrine surgeons. This may be a result of a strict follow-up regimen and under-reporting in other series.

There is, nevertheless, a vast body of evidence suggesting an increased morbidity associated with total thyroidectomy and pCND (Table 8.2). This difference reaches statistical significance most commonly in transient hypoparathyroidism [8, 24, 32, 35, 46, 47], though many studies demonstrate that this difference persists in the long-term also [26, 32, 34, 46]. However, the data is again heterogenous as many studies did not differentiate between unilateral and bilateral pCND, and the practice of parathyroid reimplantation varies. Higher rates of hypoparathyroidism are seen more commonly after bilateral level VI dissection than in unilateral [48]. Some studies demonstrated significantly higher rates of temporary RLN palsy after pCND [25, 46, 47], but this is less common, particularly in high volume centers.

Table 8.2 Complications after thyroidectomy with and without pCND

Complication		Thyroidectomy alone (%)	Thyroidectomy + pCND (%)	P-value	Study	Design	Laterality of pCND
Hypoparathyroidism	Temporary	16.3	32.2	<0.001	Kim [46]	RCS	NS
		17.5	28.7	<0.001	Zhao [32]	MA	Mixed
		4.1	9.7	0.026	Popadich [25]	RCS	Mixed
		8.7	18.3	0.017	Lang [24]	RCS	Unilateral
		14.8	25.8	<0.001	Chen [47]	MA	Mixed
		13.1	30.4	<0.001	Barczyński [8]	RCS	Bilateral
	Permanent	8.0	19.4	0.02	Viola [34]	RCT	Bilateral
		1.6	3.6	0.004	Kim	RCS	NS
		2.3	4.1	0.03	Zhao	MA	Mixed
		0.45	0.8	0.99	Popadich	RCS	Mixed
		1.0	2.4	1.0	Lang	RCS	Unilateral
		1.95	4.1	<0.001	Chen	MA	Mixed
		0.7	2.2	0.12	Barczyński	RCS	Bilateral
Recurrent laryngeal nerve injury	Temporary	2.6	5.9	0.04	Kim	RCS	NS
		2.3	0.4	0.05	Popadich	RCS	Mixed
		0	1.8	0.32	Lang	RCS	Unilateral
		1.99	3.5	0.006	Chen	MA	Mixed
		3.2	3.6	0.67	Barczyński	RCS	Bilateral
	Permanent	4.3	8.0	0.3	Viola	RCT	Bilateral
		0	0.2	1.0	Kim	RCS	NS
		1.8	0.4	0.12	Popadich	RCS	Mixed
		0.5	0.6	0.44	Lang	RCS	Unilateral
		0.75	0.9	0.34	Chen	MA	Mixed
		1.1	1.3	0.75	Barczyński	RCS	Bilateral

pCND prophylactic central node dissection, *MA* meta-analysis, *NS* not stated, *RCS* retrospective cohort study, *RCT* randomized control trial

8.4 Salvage Treatment for Central Node Recurrence

A key indication for pCND is the avoidance of reoperation in the central compartment, which is associated with greater morbidity than primary surgery [23]. However, there is increasing data to show that reoperation in the central neck is both effective and has comparable morbidity in expert hands [49, 50]. Ethanol and radiofrequency ablation of local recurrence are also emerging as non-operative treatments for nodal recurrence. While surgery remains the first-line treatment for recurrent PTC, these procedures can be performed under local anesthetic with minimal morbidity, particularly in patients with single detected lymph node metastases or who are not candidates for reoperation [51].

8.5 Conclusion

Nodal dissection of the lateral and central compartments in the presence of radiological or clinical metastases is universally accepted. The routine pCND in PTC remains controversial due to a debatable risk-benefit ratio. The largely favorable outcomes of most PTC render an adequately powered randomized controlled trial prohibitive in terms of resources and cost. The available evidence trends toward lower LRR in patients who have had total thyroidectomy in combination with pCND, although the risk of morbidity (particularly hypoparathyroidism) is significantly higher. Whether or not to perform CND rests on an individual patient risk-benefit assessment; however, based on the current literature, pCND in all patients cannot be recommended.

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