THERAPY OF ENDOCRINE DISEASE

Central neck dissection: a step forward in the treatment of papillary thyroid cancer

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Abstract

Since its introduction in the '70s and '80s, CND for papillary cancer is here to stay. Compartment VI should always be explored during surgery for papillary thyroid carcinoma (PTC) for obvious lymph node metastases. These can be easily spotted by an experienced surgeon or, eventually, by frozen section. No doubt, obvious nodal disease in the Delphian, paratracheal and subithmic areas should be dissected in a comprehensive manner (therapeutic central neck dissection), avoiding the selective removal of suspicious nodes. Available evidence for routine prophylactic CND is not completely satisfactory. Our group's opinion, however, is that it reduces or even eliminates the need for repeat surgery in the central neck, better defines the extent (and stage) of the disease and provides a further argument against routine radioiodine ablation. Thus, PTC is becoming more and more a surgical disease that can be cured by optimized surgery alone in the majority of cases. Prophylactic CND, however, involves a higher risk for the parathyroid function and should be skilfully performed, preferably only on the same side as the primary tumour and preserving the cervical portion of the thymus.

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Introduction

Surgery is the mainstay of treatment for papillary thyroid carcinoma (PTC). There has been a longstanding controversy, however, on the best type of operation for PTC in terms of reducing the mortality of the disease and its recurrences. There does not seem to be an ideal operation in terms of survival, because disease-specific mortality for PTC is <5% (1). In terms of recurrence, however, more extensive surgery has shown to be more efficient in reducing surgical bed and nodal recurrence and the need for reoperation (2). This makes sense for a malignant tumour of bizarre

biological behaviour that only rarely (<3%) metastasizes through the haematogenous route to the lungs or bones.

Total thyroidectomy gained popularity at the end of the last century as the best procedure to control the disease locally while at the same time making it possible to follow up on patients using thyroglobulin as a tumour marker (3). Thus, total or near-total thyroidectomy, TSH suppression and radioiodine ablation became the proposed standard treatments for PTCs > 1 cm in most specialised units about 20 years ago (4, 5).

Invited author's profile

Antonio Sitges-Serra was born in Barcelona in 1951 and currently heads the Endocrine Surgery Unit at the Hospital del Mar and he is Professor of Surgery at the Universitat Autònoma de Barcelona. He is Fellow *ad hominem* of the Royal College of Surgeons (Ed) and *Membre Associé Étranger de l'Académie Nationale de Chirurgie*. He has authored 200 indexed papers and 80 book chapters, mostly on nutrition, surgical infections and thyroid/parathyroid disease.

Even after the widespread implementation of this comprehensive management, however, recurrences persisted, with the central compartment being the preferential site for nodal recurrence followed by the ipsilateral II–IV lymph node compartments (6). This led to a revival of central node dissection (CND) at the turn of the century (7, 8, 9, 10) as an additional surgical manoeuvre aiming at diminishing the local recurrence rates. Currently available data indicate that extensive surgery including CND has reduced the recurrence rates in comparison to the early days of PTC treatment (11), but, on the other hand, some 3–10% of the patients with advanced (> 1 cm) PTC treated in this way will develop permanent hypoparathyroidism (9, 12, 13). Thus the challenge endocrine surgeons currently face is to improve the surgical technique to be able to perform thorough surgery while at the same time keeping the permanent hypoparathyroidism rate as low as possible.

In the present review we set to analyse the current role of CND in the surgical treatment of advanced (> 10 mm) PTC. Papillary microcarcinomas incidentally found in thyroidectomy specimens or in thyroid imaging for other reasons will not be considered here, as they can be cured with more conservative surgery and virtually no recurrences (14).

A bit of history

A step forward in the surgical management of PTC was taken by Hoie *et al.* (15) by implementing central neck dissection as part of the operation for both medullary and PTC. These authors reported a low 15% recurrence rate in 730 PTCs treated between 1956 and 1978 at a single Norwegian institution and followed for over 15 years without radioiodine ablation. In the neighbour country of Sweden, Tissell *et al.* (7) emphasized the need for meticulous lymph node dissection, including the central neck compartment, and were able to keep recurrences and mortality to a minimum with only 12 (6%) of their 195 patients being treated with radioiodine: four for distant metastases and eight for remnant ablation. They concluded that their surgical strategy improved clinical outcomes, and were among the first to suggest that radioiodine does not offer clinical benefit to properly operated PTC patients.

The proposal of adding a paratracheal lymph node dissection to total thyroidectomy for PTC gained support from endocrine oncologists and leading surgical units (16, 17, 18) on the basis of three main arguments: i) central lymph nodes (compartment VI) is very often involved in

PTC; ii) recurrence (or persistence) in the paratracheal basin is common and difficult to image; iii) reoperations in the central neck carry an additional risk of recurrent laryngeal nerve injury and hypoparathyroidism. Time has shown that these three main arguments are essentially valid.

Surgical anatomy of compartment VI

In this review we adhere to the recent definition of compartment VI described in detail in the consensus statement by the European Society of Endocrine Surgeons (19). The surgical boundaries of the central node compartment of the neck (compartment VI) have been well described by Uchino *et al.* (20). The surgeon should clear the prelaryngeal Delphian node region plus the paratracheal basins between both carotid arteries and down to the upper part of the horn of the thymus. The pretracheal lymph nodes present below the thyroid isthmus should also be dissected. On the right, lymph nodes are distributed both anterior and posterior to the recurrent laryngeal nerve, whereas on the left, lymph nodes lie anteriorly. Thus, dissection of the right side of compartment VI is technically more demanding than dissection of the left side (Fig. 1). Surgical strategy may

Figure 1

Central neck dissection of the right paratracheal basin with node clearance anterior and posterior to the skeletonized inferior laryngeal nerve.

Figure 2

The complex surgical anatomy of the right central lymph node compartment, the parathyroid glands and the thymus in a therapeutic CND.

vary according to the experience of the surgeon but we advise two precautions: i) clearance of the paratracheal nodes is best performed by initially identifying the recurrent laryngeal nerve at the base of the neck and then proceed cranially; ii) the lower parathyroid glands should be identified and preserved before starting the lymph node dissection. This means that whenever possible the thymus horns should not be included in CND specimen since this is associated with a higher prevalence of hypocalcaemia (21) (Fig. 2). Thymus preservation should be the rule in prophylactic CND where the thyro-thymic ligament is not involved by metastatic nodes, the normal anatomy is well preserved and the lower parathyroid glands can be more easily identified and kept *in situ*. It is essential that the surgeon be acquainted with the variable anatomy of the inferior parathyroid glands and their vascular supply and the insertion of the thymic tongues.

Nodal yield after CND varies in relationship to its type (prophylactic vs therapeutic) and extension (uni- or bilateral). Average yield is six to nine lymph nodes, less for prophylactic CND (five to eight nodes) than for therapeutic CND (ten to 12 nodes) (10, 22, 23, 24). The most relevant surgical variable influencing the nodal yield is the length of the fresh specimen (25), indicating that the lymph nodes follow a cranio-caudal distribution in the paratracheal area along the tracheo-oesophageal groove (Fig. 3).

How often is the central neck compartment involved in non-microcarcinoma PTC?

Preoperative ultrasound investigation of compartment VI is technically difficult and often unreliable (26). This is why intraoperative assessment by an experienced surgeon is essential to spot macroscopic paratracheal lymph node metastasis, particularly those affecting the right retro-neural area. About two thirds of patients with advanced PTC will have lymph node metastasis in compartment VI, though only half of these will be obvious to the naked eye. The remaining half will be detected by the pathologist in the CND dissection specimen (8, 27, 28).

The clinical predictors of central neck involvement are the presence of a palpable Delphian node and/or metastasis to the lateral neck (N1b), age >45 years, male sex and increasing T (22). In some 5–10% of cases, N1b disease (lateral lymph node metastasis) may skip the central neck, usually in cases where the tumour is located in the upper poles of the thyroid (29). The most widely recognized pathological variable associated with central neck metastasis in advanced PTC is extrathyroidal invasion usually, but not always, associated with large tumours (28, 30, 31).

Therapeutic central neck dissection

There is consensus that lymph node metastases that are clinically detected, either pre- or intraoperatively, should be

Figure 3

The length of the fresh specimen of a CND influences its nodal yield.

surgically resected. No surgeon should leave behind gross nodal metastatic disease in the paratracheal area hoping that it will be eradicated by radioiodine ablation. There is also agreement that lymph node dissection, in any region of the neck, must follow an anatomical pattern and be compartment-oriented. There is no room for isolated node excision, the so-called ‘berry picking’ technique, because local recurrence is the rule (18, 32). Thus, surgeons operating on advanced PTC should be familiar with the anatomy of the central and lateral lymph node compartments as well as versed in the different modalities and potential complications of cervical lymph node dissection (33).

Therapeutic CND should be performed on both sides of the neck and may pose particular technical difficulty in cases of massive nodal involvement, extranodal tumour extension, calcified lymph nodes and recurrent laryngeal nerve entrapment. Accidental parathyroidectomy is a common (15–35%) event in this circumstance (10, 27, 34), since identification and appropriate *in situ* preservation of the parathyroid glands, particularly the inferior pair, may be impossible if large lymph nodes are found involving the thyrothymic ligament. This definitely contributes to postoperative hypocalcaemia and hypoparathyroidism (35). In addition, roughly 50% of patients requiring a therapeutic CND will also be submitted to a modified radical lateral neck dissection during the same surgical procedure and eventually will have a total thyroidectomy extended to surrounding structures (strap muscles, trachea, internal jugular vein) in order to obtain a complete resection, further increasing the chance of devascularisation of the whole parathyroid gland apparatus. Besides the number of parathyroid glands remaining *in situ* after total thyroidectomy, parathyroid ischaemia appears to be an important factor linking postoperative hypocalcaemia with the extension of the thyroid resection (36).

When there is massive nodal involvement requiring a bilateral therapeutic CND, thymectomy and parathyroidectomy may be unavoidable. The surgeon may decide to implant the devascularized parathyroid gland(s) (if he or she succeeds in finding it) after chopping it in 1-mm³ pieces, into the ipsilateral sternocleidomastoid muscle. There is growing evidence, however, that autotransplantation of normal parathyroid tissue increases the rate of postoperative hypocalcaemia and does not prevent permanent hypoparathyroidism (35).

Prophylactic central neck dissection

There is ongoing controversy about the need to perform a CND in patients with no evidence of clinical lymph node

involvement. The fact is that some 30–60% of clinically negative central necks will harbour metastatic lymph nodes (10, 27, 30). Some authors do not consider subclinical lymph node involvement as a risk factor for recurrence, because usually metastatic nodes are few in number and will be sterilized by routine radioiodine ablation (37). On the other hand, a more prevalent opinion holds that central neck micrometastasis (Fig. 4) may be the cause of persistent elevation of thyroglobulin levels and of local recurrence (38). It also must be stressed that intentional, routine, prophylactic CND will discover obvious metastatic disease that otherwise would be overlooked, thus converting prophylactic surgery into a therapeutic intervention (Fig. 5). The pros and cons of prophylactic CND have been extensively discussed in a recent consensus document of the European Society of Endocrine Surgeons (19) (Table 1).

The main reason for the current controversy around prophylactic CND lies in its potential complications rather than in its oncologic rationale. Postoperative hypocalcaemia, and eventually permanent hypoparathyroidism, occur more often if central lymphadenectomy is performed, due to accidental parathyroidectomy, parathyroid autotransplantation and/or devascularisation of the parathyroid glands. To reduce to a minimum the parathyroid risk, prophylactic CND is usually performed only in the ipsilateral and pretracheal regions, sparing the contralateral central neck. This approach seems reasonable from the oncologic point of view, since contralateral occult metastasis in a clinically negative ipsilateral central neck

Figure 4

Lymph node micrometastasis of PTC (thyroglobulin-positive cells) in a prophylactic CND specimen.

Figure 5
A distal PTC metastatic node in a total thyroidectomy and a left CND specimen initially thought to be prophylactic.

are relatively uncommon in low-risk PTC (39, 40, 41). Furthermore, surgical expertise undoubtedly plays a role in the complication rate of CND. In our team experience, the complications of CND in an unselected population of advanced PTCs cluster in patients submitted to therapeutic rather than prophylactic CND (Table 2).

Interestingly, most clinical and oncologic variables are not different between patients with or without metastatic lymph nodes detected by the pathologist in prophylactic CND specimens. In a study on 119 prophylactic CNDs (27), N0 and N1a patients were similar in age, gender, tumour size and MACIS score.

The controversy on prophylactic CND in recent meta-analysis

Concerns about systematic implementation of prophylactic CND revolve around whether its potential permanent complications can be outweighed by a significant reduction of local nodal recurrence.

Five meta-analyses are available on prophylactic CND (19, 42, 43, 44, 45, 46) (Table 3). None of these meta-analyses identified significant differences in the rates of temporary or permanent nerve injury in patients undergoing prophylactic CND compared to patients undergoing total thyroidectomy alone. Almost every single comparative study reported a higher incidence of postoperative hypocalcaemia after prophylactic CND. Consequently, four of the five meta-analyses highlight this higher postoperative hypocalcaemia rate, albeit with different definitions and varied levels of significance. The risk for postoperative hypocalcaemia is between 2.0 and 2.7 times higher when CND is performed.

The prevalence of permanent hypoparathyroidism varies widely among retrospective series. The increased risk detected by some studies did not translate into a significantly higher relative risk in any of the meta-analyses. It must be noted that the rate of permanent hypoparathyroidism would be significantly higher in non-specialized units, and in some population-based multicenter studies the proportion of permanent hypoparathyroidism doubles when prophylactic CND is added to total thyroidectomy.

The effect of prophylactic CND on the nodal loco-regional recurrence is addressed by comparative studies and four meta-analyses, but few separate the worrisome recurrences in the central neck area from lateral neck node recurrences. A clear interpretation of this critical outcome is blurred further by the varied prevalence of radioiodine administration in different studies pooled together in the meta-analyses. The latest and more detailed meta-analysis

Table 1 Pros and cons for prophylactic central neck dissection (modified from (19)).

Pros	Cons
Subclinical lymph node metastasis are common	Only a small proportion of these will develop clinically significant recurrence
Reduces recurrences and prolongs survival	No level-I evidence for increased survival
Lymph node metastasis cannot be detected preoperatively	Yes, they can
Intraoperative assessment unreliable	Reliable for metastatic nodes
Does not increase the complication rate	It definitely increases the risk of postoperative hypocalcaemia
Improves tumour staging	Upstaging is a rare event and may lead to overtreatment
Reoperation for recurrence associated with greater morbidity	Reoperation can be safely performed by experienced surgeons
Lowers postoperative thyroglobulin values	The effect vanishes 6 months after ¹³¹ I ablation

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Table 2 Oncologic variables and complication rates of prophylactic vs therapeutic central neck dissection for non-microcarcinoma PTC at the Hospital del Mar (1999–2012).

	Therapeutic CND (n=81)	Prophylactic CND (n=79)
Tumour size (mm)	27 ± 15	26 ± 20
Extrathyroidal invasion (%)	40	30
Nodal yield	12 ± 8	5.6 ± 1*
Number of N+	5 ± 4	0.7 ± 1*
Added lateral neck dissection (%)	53	9*
RLN oncological resection (%)	9	2.7
Iatrogenic RLN injury	1/81	0/79
s-Ca <8 mg/dl at 24 h postop (%)	62	42**
Permanent hypoparathyroidism (%)	7.5	2.5
Lateral recurrences (%)	13	4
Central neck recurrences (%)	0	0

* $P < 0.001$; ** $P = 0.01$. RLN, recurrent laryngeal nerve.

(46) suggests that loco-regional recurrence rate may be reduced by half in patients who have undergone prophylactic CND compared to those with total thyroidectomy alone. This finding suggests that if carefully performed, prophylactic CND may be associated with a lower risk of recurrent PTC, a finding not previously highlighted in other systematic reviews and meta-analyses. It must be noted, however, that the two most recent meta-analyses (43, 46) are heavily influenced by a single comparative

study with more than 600 patients, favoring prophylactic CND (47).

Finally, the only clinical trial performed is a non pre-registered, single-institution, prospective randomized trial recently published (48), including 181 patients randomly assigned to total thyroidectomy alone or to total thyroidectomy plus CND. After 5 years of follow-up, no difference was observed in the recurrence rate. A higher percentage of patients with total thyroidectomy alone were treated with more ^{131}I courses, whereas a very high, previously unnoticed, prevalence of permanent hypoparathyroidism was observed both after total thyroidectomy plus prophylactic CND (19%) and after total thyroidectomy alone (8%).

Conclusion

Therapeutic and prophylactic modalities of CND are an important adjunct to total thyroidectomy for the treatment of PTC. CND helps in reducing local recurrences and probably the need for radioiodine ablation. Optimized surgery (49, 50) is becoming the mainstay of treatment of PTC but should be performed by trained surgeons, in order to diminish its long-term adverse effects, mostly permanent hypoparathyroidism.

Table 3 Summary of the meta-analyses on prophylactic central neck dissection vs total thyroidectomy alone for papillary thyroid cancer.

	First author				
	E J Chisholm	T Zetoune	C-X Shan	B H H Lang	T S Wang
Year	2009	2010	2012	2013	2013
No. of included studies	5	5	16	14	6
Patients	1132	1264	3558	3331	1342
Focus	CPL	LRR	LLR/CPL	LRR/CPL	LRR/CPL
Strong	First in class	First in class	Biggest	Data gathering	Recent
Weakness	No LRR Some w/benign	CPL not assessed Variable F-Up	Subgroups analysis Some therapeutic studies (separate) No time assessed	Variability tests Fixed effect model	Cleanest
Methodology details	Basic	Basic	Risk difference Mixed Effect model	Incidence rate ratio OR	Risk difference Random effect model
Transient hypocalcaemia (odds ratio)	pCND worst ($\times 2.7$)	–	pCND worst ($\times 2.0$)	pCND worst ($\times 2.6$)	pCND worst ($\times 2.5$)
Permanent hypoparathyroidism	No differences	–	No differences	No differences	No differences
Permanent RLN injury	No differences	–	No differences	No differences	No differences
Temporary RLN injury	No differences	–	No differences	No differences	No differences
Lymph node regional recurrence	–	No differences	No differences		40% reduction
Type of analysis of LLR	–	Three subgroups	Pooled ^a	Pooled ^a	Pooled ^a

CPL, complications; LLR, lymph node regional recurrence.

^aPooled recurrences in the central neck and lateral neck compartments.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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