Review Article

Morbidity of central neck dissection for papillary thyroid cancer

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Abstract: Thyroid cancer has a very well-known propensity for nodal involvement, either in the central and lateral neck compartments. Neck dissection addressing the central compartment may be performed with an elective or therapeutic intent, the former concomitantly to a thyroidectomy whereas the latter may be accomplished also as a revision procedure for recurrent disease. In this paper complications of central compartment neck dissection will be described, analyzing separately primary and revision procedures.

Keywords: Central compartment; neck dissection; thyroid cancer

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Introduction

Papillary thyroid cancer (PTC) has the peculiar tendency to spread to central and lateral neck lymph nodes. PTC recurrences typically involve cervical lymph nodes in 60–75% of cases, with the central compartment being the most frequently involved site (1-3). While no controversy exists on the role of therapeutic central lymph node dissection (CND), concomitant with thyroidectomy or as a revision procedure, elective CND is still a debated issue. Indeed, the American Thyroid Association (ATA) guidelines (4) do not help in the controversy on elective treatment of level VI, due to an unclear prognostic role and a non-negligible rate of complications. The debate on morbidity of CND is prevalently focused on injury, transient or permanent, to the recurrent laryngeal nerve (RLN) and/or parathyroid glands. Chyle leakage is rare, and data in the literature are consequently scarce. No specific data have been reported on other complications such as hematoma, vascular or visceral injury, and wound infection.

There are important differences in the surgical technique and complication rate between CND associated with total thyroidectomy (TTCND) and revision CND (RCND); for this reason, we will provide a separate discussion for the two topics.

Surgical boundaries of the central neck compartment

The ATA consensus statement regarding the terminology and classification of the central neck (5,6) states that the CND contains the perithyroidal and paratracheal soft tissues as well as lymph nodes; it is limited superiorly by the hyoid bone, laterally by the common carotid arteries, anteriorly the by the superficial layer of the deep cervical fascia (and posterior aspect of the infrahyoid muscles), posteriorly by the deep layer of the cervical fascia (covering the prevertebral muscles and the oesophagus), and inferiorly by sternum and the innominate artery. The term CND, as defined by the ATA consensus, implies removal of prelaryngeal and pretracheal lymphatic tissue and at least one paratracheal lymph node. This is defined as unilateral CND, whereas in bilateral CND paratracheal nodes on both sides are removed (5,6).

Complications in CND associated with thyroidectomy

In recent years, the "pros" and "cons" of elective central compartment neck dissection were thoroughly analyzed but a significant disputation still remains: several authors, indeed, have suggested routine use of elective CND in differentiated thyroid carcinomas (7-10). On the other hand, despite the high prevalence of lymph node micro-metastases from PTC (ranging from 38% to 61%) (1,3,11), several investigators (11-15) have outlined the limits of such an approach, with a significant increase in the morbidity associated with standard total thyroidectomy and no differences in overall and disease specific survival.

One of the main reasons that led several authors to consider elective CND is the low accuracy of preoperative diagnostic tools in identifying nodal involvement at this level, especially when dealing with recurrent disease (16). Indeed, while neck ultrasonography (US) and cross-sectional imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), reliably evaluate lateral neck levels, they are less accurate in the assessment of the central compartment. Several studies have reported a low sensitivity of US and CT, with values ranging from 51% to 67%, and from 62% to 66%, respectively (17,18); this is due to the fact that lymph nodes are often small and located deeply in the neck, or just posterior to the sternum, thus hindering adequate visualization (13,19-21).

In 2006, the European Consensus Statement (22) emphasized that the benefits of elective CND in the absence of pre- or intraoperative evidence for nodal disease are controversial: in fact, there is no evidence that it decreases the rate of either recurrence or mortality; conversely, it may allow accurate staging of the disease that can modulate subsequent treatments and follow-up. Similarly, recommendations in the 2015 American Guidelines (4) are not clear-cut. Recommendation #36 suggests elective CND (ipsilateral or bilateral) in patients with PTC with clinically uninvolved central neck lymph nodes (cN0) and advanced primary tumors (T3 or T4) or clinically involved lateral neck nodes (cN1b), or if the information might be used to plan further steps in therapy (4).

Most authors agree with the observation that TTCND leads to a higher risk of complications when compared with total thyroidectomy alone, particularly with regards to hypoparathyroidism (HPT) rather than RLN injury (11,12,17,23-29). In fact, the RLN at the end of thyroidectomy is already exposed, visible, and only its most caudal part needs to be further dissected (17,25-27,29,30). For this reason, intraoperative nerve monitoring (IONM), despite its importance in the thyroidectomy phase, does not seem to play such an important role in RLN preservation during the CND phase (31). However, it is worth remembering that IONM may be helpful in identifying a loss of signal on the first side that could suggest to stage completion thyroidectomy, especially in case of non-aggressive thyroid cancer.

In the literature, the rate of transient RLN injury and HPT ranges from 0% to 7.3%, and from 8.7% to 86%, respectively (11,12,15,23,30,32). Furthermore, the reported rates of permanent unintentional RLN injury and permanent HPT ranges from 0% to 5.9%, and from 0% to 16.2%, respectively (*Table 1*). Different authors suggested that the rate of complications in patients treated with TTCND may be overestimated (15,32,47,48). In a pivotal paper by Giordano and colleagues (7), a comparative study on 1,087 patients affected by PTC with clinically negative lymph nodes was performed. Patients were divided in three homogeneous groups: patients treated with total thyroidectomy alone, unilateral TTCND, and bilateral TTCND. Overall, the results of the three groups were comparable to those reported in the literature: indeed, rates of transient RLN injury and HPT were 4.2% and 37.5%, respectively. Regarding permanent complications, the rates of RLN injury and HPT were 1.2% and 9.4%, respectively. The analysis comparing the three groups showed that neither unilateral nor bilateral TTCND were associated with a significantly increased rate of transient or permanent RLN injury. On the other hand, the rate of transient HPT was significantly higher in both unilateral and bilateral TTCND. Finally, the rate of permanent HPT was significantly increased in case of bilateral, but not unilateral, TTCND. These results were consistent with those reported in other studies (11,12,17,23-29). The increased rate of permanent HPT in bilateral TTCND may be due to the increased risk of traumatic and ischemic damage to parathyroid glands caused by surgical manipulation (7,30,49); therefore, it is strongly suggested to make every effort to preserve the vascular supply to the superior parathyroid gland. On the contrary, it may be more technically demanding to avoid ischemic injuries to the inferior parathyroid gland (1,7,11,25). It is worth mentioning that several authors demonstrated no significant effect on postoperative HPT in case of intraoperative ligation of the inferior thyroid artery (ITA) (50-53), although the preservation of the inferior thyroidal

Table 1 Review of the literature showing the rate of surgical complications after TTCND

Author	Year	N	Transient RLN palsy (%)	Permanent RLN palsy (%)	Transient HPT (%)	Permanent HPT (%)
Henry (12)	1998	50	4.0	0	14.0	4.0
Steinmuller (33)	1999	53	3.8	1.9	39.6	1.9
Pereira (14)	2005	43	0	7.0	60.0	4.6
Sywak (11)	2006	56	1.8	0	17.9	1.8
Lee (15)	2007	78	0 ipsilateral	0 ipsilateral	20.5 ipsilateral	0 ipsilateral
		25	0 bilateral	0 bilateral	48 bilateral	0 bilateral
Roh (25)	2007	82	7.3	3.6	30.5	4.9
Palestini (27)	2008	93	5.4 ipsilateral	0 ipsilateral	27.0 ipsilateral	0 ipsilateral
		64	7.8 bilateral	0 bilateral	31.0 bilateral	0 bilateral
Choi (34)	2008	48	2.1	0	16.7	0
Rosenbaum (29)	2009	22	–	0	86.0	5.0
Perrino (35)	2009	92	2.7	1.5	8.7	1.5
Hughes (36)	2010	78	–	0	26.9	0
Moo (37)	2010	45	8.9	0	31.1	2.6
Popadich (38)	2011	259	0.4	0.4	9.6	0.8
Giordano (7)	2012	385	3.9 ipsilateral	0.5 ipsilateral	36.1 ipsilateral	7.0 ipsilateral
		308	5.5 bilateral	2.3 bilateral	51.9 bilateral	16.2 bilateral
Lang (8)	2012	82	1.8	0.6	18.3	2.4
So (39)	2012	119	3.4	0.8	41.2	5.9
Raffaelli (40)	2012	62	1.6 ipsilateral	1.6 ipsilateral	25.8 ipsilateral	0 ipsilateral
		62	0 bilateral	0 bilateral	56.4 bilateral	1.6 bilateral
Wang (41)	2012	49	–	2.0	42.9	0
Barczynski (42)	2013	358	7.3	2.5	30.4	2.2
Calo (43)	2014	65	3.1	0	38.5	10.8
De Carvalho (44)	2015	102	11.8	5.9	46.1	11.8
Lee (45)	2015	153	3.3	1.3	36.6	3.3
Calo (46)	2017	30	3.3 ipsilateral	0 ipsilateral	23.3 ipsilateral	3.3 ipsilateral
		30	0 bilateral	0 bilateral	36.7 bilateral	3.3 bilateral

vein (ITV) seems to reduce postoperative hypocalcemia (54). In two papers, this finding was ascribed to a damage caused by insufficient blood discharge to whom a parathyroid is exposed if the ITV is sacrificed far from the thyroid parenchyma during CND (54,55).

Nevertheless, the inferior parathyroid gland can be removed and, after intraoperative histologic confirmation by frozen sections, re-implanted as an autograft in the sternal belly of the sternocleidomastoid muscle. Indeed, both Smith *et al.* (56) and Shaha *et al.* (57) showed conclusive data on the efficacy of parathyroid autotransplantation to reduce the risk of postoperative HPT when aggressive dissection, or vascular injury to the parathyroids, is performed.

Since the risk of central compartment involvement is mainly on the same side of the tumor (58) and contralateral metastases, conversely, are rare without ipsilateral positive

nodes, several authors have recommended to perform TTCND ipsilateral to the tumor in case of differentiated thyroid carcinomas, thus finding a reasonable balance between morbidity and oncologic outcome (7-10).

The results presented by Giordano and colleagues (7), were also confirmed in a recent meta-analysis published by Zhao *et al.* (59). Patients who underwent TTCND with elective intent had a significantly increased risk of postoperative hypocalcemia than patients who underwent total thyroidectomy alone, including temporary hypocalcemia (28.7% *vs.* 17.5%, OR =2.37), and permanent hypocalcemia (4.1% *vs.* 2.3%, OR =1.93). On the other hand, the risk of temporary and permanent RLN injury was confirmed to be similar in the two groups (OR =1.22 and 1.17 respectively) (59). However, regarding overall complications, the meta-analysis indicated that the TTCND group has a significantly increased overall morbidity (OR =2.56), although it was similar after excluding temporary hypocalcemia (OR =1.14).

Chyle leakage is a rare complication of thyroid surgery, with or without CND, with an estimated prevalence of less than 1% (60-63). Lee *et al.* (61) retrospectively analyzed 2,314 patients who underwent TTCND (unilateral or bilateral) for thyroid carcinoma: 14 (0.6%) patients were reported to have postoperative chyle leak, with a mean duration of the leakage of 4.3 days and a mean chyle volume of 53.2 mL/day. Before this paper, to the best of our knowledge, only a single case had been reported in the literature (60). All patients were treated conservatively by pressure dressings, a fat-free diet, and repeated percutaneous drainage. The authors ascribed the chyle leakage in patients who did not undergo lateral neck dissection to the presence of minor lymphatic ducts in the central compartment. These small ducts, when injured during dissection, may immediately collapse, and thus chyle leakage may be not intraoperatively detected. Due to its limited entity, chyle leak is commonly managed with conservative maneuvers and revision surgery is generally not required.

Complications in revision CND

Recurrent disease in the neck central compartment should be suspected in presence of lesions greater than 8 mm at US; these lesions should be considered for cytologic evaluation, Thyroglobulin aspirate rinsing analysis, and eventually, revision surgery (16). Surgery for recurrent disease in the central neck compartment is a complex procedure, and specific data regarding surgical morbidity are scarce, mainly as a result of the limited number of patients requiring RCND (64,65).

Indications for revision surgery in central neck compartment include recurrent metastatic thyroid carcinoma to central compartment lymph nodes and inadequate initial surgery (5,66). RCND is technically demanding because of the abundant scar tissue and distorted anatomy, which may lead to a higher risk of injury to the RLN and parathyroid glands. RLN may be, indeed, in a less predictable location after thyroidectomy; in addition, the parathyroid glands and RLN may be encased within fibrotic tissue, making them indistinguishable from the tumor (16).

Central neck lymph node metastases are usually detected during follow-up by means of increased serum Thyroglobulin levels and by radiological examinations (US, radioactive iodine scan, or PET-CT), and subsequently confirmed with fine-needle aspiration cytology (FNAC) and contrast enhanced MRI or CT (18,21,67).

Several series have reported a higher incidence of permanent RLN palsy in RCND compared to primary setting procedures, with rates ranging from 1% to 12% (64,65,68-70). Regarding HPT, in RCND the parathyroid glands are at increased risk for devascularization or inadvertent removal. Several series (1,68,71-73) have reported an incidence of temporary and permanent HPT after revision surgery, ranging from 0.3% to 15%, and from 0% to 4.9%, respectively. Kim *et al.* (64) reported their experience of RCND on 20 patients. All patients had a normally preoperatively and postoperatively functioning larynx. Furthermore, 4 (20%) patients experienced transient postoperative HPT, with no evidence of permanent HPT. The authors emphasised the importance of a meticulous surgical dissection with identification of RLN in the lower part of tracheoesophageal groove, and the use of IONM. More recently, Cayonu *et al.* (65) retrospectively revised a single center series of 61 patients treated for central compartment lymph node recurrence from thyroid cancer. The authors suggested a step-by-step technique for identification and preservation of RLN and parathyroid glands. Interestingly, they did not routinely use IONM. They reported an acceptable rate of complications: temporary RLN palsy in 4 patients (6.6%), temporary HPT in 8 (13.1%), and permanent HPT in 3 (4.9%). No permanent RLN palsy, wound infection, or hematoma were reported.

Onkendi *et al.* (74) reported their experience in 410 patients operated for recurrent PTC. One-hundred-twelve patients underwent unilateral and 107 bilateral CND (58%

of the series) with 80% of positive lymph nodes at definitive histologic examination. Unfortunately, an important limitation of the study is that the rate of complications is calculated on the whole series, including revision surgery on thyroid gland and lateral neck dissection: the overall complications rate was 6%, with 3% permanent HPT, and 0.5% permanent RLN.

In general, IONM can be extremely useful because it facilitates the identification and dissection of the nerve in a surgical field with distorted landmarks, and may be helpful in predicting nerve function after surgery (16). Indeed, it is possible to map, with IONM's probe, the area where the nerve might be located to avoid blind dissection. However, according to the results of a recent comparative analysis, the use of IONM in thyroid revision surgery does not seem to significantly reduce the risk of RLN palsy (31); careful dissection and visualization of the nerve remain of pivotal importance to minimize the risk of iatrogenic injury. The authors also stated that, in RCND, most problems are related to the difficult dissection of noble structures from scar tissue. In this sense, Alesina *et al.* (31) suggested that continuous monitoring could be very useful in minimizing the risk of injury.

Although in primary surgery preservation of the ITA does not seem, as already mentioned, to be great help in preventing postoperative HPT, Kim *et al.* (64) recommended preserving the artery in RCND to minimize the risk of devascularization of the parathyroid glands. However, great attention is commonly placed on the outcomes and usefulness of parathyroid autotransplantation. Indeed, to avoid postoperative HPT, several authors have recommended to carefully examine the specimen for parathyroid tissue by means of a histologic frozen section analysis (64,65,74). Reimplantation of the parathyroid gland(s) into the sternocleidomastoid muscle at the time of revision CND will decrease the risk of long-term permanent HPT (64). It is worth remembering that fibrosis and multiple positive lymph nodes in the dissected specimen can make identification and confirmation of parathyroid tissue very difficult. In patients with extensive extracapsular lymph node spread and multiple involved nodes, reimplantation can inadvertently lead to reimplantation of tumor along with parathyroid tissue (64). Notably, also in recurrent disease, in absence of bilateral central compartment involvement, it is preferable to avoid bilateral CND in order to minimize the risk of definitive HPT and bilateral RLN palsy (16).

As a last remark, the most important element in minimizing complications in thyroid surgery is the surgical volume of the surgeon, as widely reported in the literature (28,75,76). For this reason, Mazzaferri and colleagues (28) have properly stated that it is overall better, for the small minority of patients who subsequently develop central node metastasis to undergo therapeutic RCND by more experienced thyroid surgeons, than all patients undergo prophylactic dissection, with the majority being performed by less experienced surgeons.

Conclusions

Primary CND is associated with an acceptable rate of complications, since an increase of permanent HPT is reported when CND is performed bilaterally. Preservation of the vascular pedicle of the parathyroid glands, in particular the ITV, prevents ischemic damage. RCND for recurrent or persistent thyroid cancer is a challenging procedure even for the most experienced surgeon. Surgical dissection must be meticulous, with identification of the RLN and parathyroid glands. IONM may help in identifying the nerve in a fibrotic surgical field, thus minimizing the risk of iatrogenic damage. In both TTCND and RCND, parathyroid autotransplantation seems to contribute to prevention of postoperative HPT. Other complications, such as chyle leakage, are very rare and data in the current literature are scarce. Surgical volume remains the most important factor affecting the rate of complications in thyroidectomy and/or CND.

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Footnote

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