

Effect of central compartment neck dissection on hypocalcaemia incidence after total thyroidectomy for carcinoma

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Abstract

Introduction: Central compartment neck dissection is increasingly performed as part of surgical management of differentiated thyroid carcinoma. However, elective central neck dissection remains controversial due to complications and lack of evidence of survival benefit.

Objective: To investigate and compare rates of transient and permanent hypocalcaemia following total thyroidectomy alone, compared with total thyroidectomy with central neck dissection, for differentiated thyroid carcinoma.

Methods: Retrospective study of 127 consecutive patients referred with differentiated thyroid carcinoma, 2004–2006; 78 patients had undergone total thyroidectomy (group one) and 49 total thyroidectomy with central compartment node dissection (group two). Surgery was performed in various hospitals by both otolaryngologists and endocrine surgeons.

Results: In groups one and two, the incidence of transient hypocalcaemia was 18 per cent (14/78) and 51 per cent (25/49) ($p < 0.001$), and the incidence of permanent hypocalcaemia 1 per cent (one of 77) and 12 per cent (six of 49) ($p < 0.01$), respectively. Most patients undergoing central neck dissection had evidence of pathological level six lymphadenopathy (29/49).

Conclusion: Total thyroidectomy combined with central neck dissection for the treatment of differentiated thyroid carcinoma is more likely to result in transient (51 per cent) and permanent (12 per cent) hypocalcaemia. Elective neck dissection should be performed selectively, with a high expectation of post-operative hypocalcaemia.

Key words: Thyroid Carcinoma; Neck Dissection; Surgery; Hypocalcemia

Introduction

Most patients with differentiated thyroid carcinoma undergo total thyroidectomy as part of definitive treatment. Neck dissection involving the lateral compartment (usually levels two to four, with or without level five) and central compartment (level six) is standard treatment for patients presenting with palpable or radiological evidence of metastatic lymphadenopathy.¹ However, the role of central compartment neck dissection for clinically staged node 0 disease is still unclear. The British Thyroid Association recommends that total thyroidectomy and central neck dissection be performed for patients who have papillary carcinoma and uninvolved nodes but who are deemed at high risk (i.e. male, aged more than 45 years, tumour larger than 4 cm in diameter, and extracapsular or extrathyroidal disease).²

The aim of combined total thyroidectomy and limited lymphadenectomy is to remove all macroscopic

malignant cervical lymphadenopathy, while causing minimum associated co-morbidity.³ Despite these guidelines, elective neck dissection (whether central compartment or lateral) remains controversial, due to the lack of clear data regarding its survival benefit and the complications associated with the procedure.⁴

The principal additional morbidity risk arising from central neck dissection is hypocalcaemia (and perhaps increased risk of recurrent laryngeal nerve palsy).⁴ Hypocalcaemia arising from hypoparathyroidism constitutes significant morbidity. In some patients, hypocalcaemia is difficult to control and requires frequent monitoring and treatment adjustment, often more so than for patients requiring thyroxine replacement. It should also be borne in mind that many of these patients are relatively young, and that the burden of lifelong hypocalcaemia management is therefore significant.

The aim of this study was to ascertain the risk of hypocalcaemia in a series of consecutive patients undergoing total thyroidectomy for differentiated thyroid cancer, in order to analyse principally the effect of central neck dissection. Our study cohort comprised consecutive patients referred to the Christie Hospital thyroid multi-disciplinary team, whose surgery had been performed in referring cancer network hospitals which formed part of this team. This afforded a representative group of patients operated upon by both ENT and endocrine surgeons within a number of different units.

Methods

A retrospective case note review was undertaken. The study included all patients referred to the thyroid oncology multi-disciplinary team at Christie Hospital having undergone total thyroidectomy with or without neck dissection between 2004 and 2006. Data collected comprised age, gender, pre-operative diagnosis, type of operation, histopathology (i.e. diagnosis and nodal status), presence of post-operative hypocalcaemia, and calcium replacement type and duration. Hypocalcaemia was defined as an adjusted calcium level of less than 2 mmol/l, which necessitated calcium or vitamin D analogue replacement.

Post-operative hypocalcaemia was classified into two groups: transient hypocalcaemia (resolving within two years of surgery) and permanent hypocalcaemia (persisting for more than two years after surgery).

The type of operation undertaken was determined from the surgical operative notes or the referral letter. It was assumed that all surgeons' operative notes were consistent with the standardised classification for neck dissection,⁵ whereby level six lies centrally, the superior border being the hyoid bone, the inferior border the suprasternal notch and the lateral borders the common carotid arteries.

Univariate analysis of variables, including the association between central neck dissection and hypocalcaemia, was carried out using categorical tables, performing Pearson's chi-square test, Fisher's exact test and the Mann-Whitney test as appropriate. Multivariate analysis was carried out using multiple regression. The Statistical Package for the Social Sciences version 16.0 software was used for analysis. All tests were two-tailed, and differences were considered significant at $p < 0.05$.

Results

A total of 127 patient case notes were reviewed. These patients had been referred to the Christie Hospital thyroid oncology multi-disciplinary team by 34 consultant surgeons, within the two cancer networks for which the Christie Hospital provides thyroid clinical oncology services. Overall, 39 patients (31 per cent) had transient hypocalcaemia and seven (6 per cent) had permanent hypocalcaemia. The most common relevant supplementation was calcium with or without

vitamin D (e.g. Calcichew or Calcichew D₃). As would be expected, those with transient hypocalcaemia were less likely to have been commenced on 1 α -calcidol (2.6 per cent) than those with permanent hypocalcaemia (14.3 per cent).

No cases of vocal fold palsy could be identified from the Christie Hospital notes. However, as the surgical information was based on the operative record, histopathology report and referral letter, it could not be confirmed that all patients had undergone post-operative laryngoscopy, or how many patients had suffered voice problems post-operatively.

Table I demonstrates the patients' clinicopathological characteristics. Pathology categorised as miscellaneous comprised muco-epidermoid carcinoma (one case) and Hürthle cell carcinoma (three cases). Overall, 78 patients underwent total thyroidectomy without central neck dissection and 49 underwent total thyroidectomy with central neck dissection. A comparison between these two groups is shown in Table I. The groups were similar except that, unsurprisingly, all patients undergoing lateral neck dissection (generally levels two to five) also received central neck dissection (i.e. there were no lateral dissections in the total thyroidectomy only group). Also, more of the total thyroidectomy only group received a two-stage thyroidectomy (i.e. lobectomy then completion) rather than a primary total thyroidectomy ($p = 0.03$).

Histopathological examination identified the presence of metastatic nodes in the central compartment in 18 of the 35 patients undergoing total thyroidectomy plus central neck dissection without lateral neck dissection; and in 11 of the 14 patients who also underwent a lateral selective neck dissection (i.e. a total of 29/49).

The effect of having a central neck dissection was significant both in terms of transient and permanent hypocalcaemia. The incidence of transient hypocalcaemia in the total thyroidectomy only group and the total thyroidectomy with level six neck dissection group were 18 per cent (14/78) and 51 per cent (25/49), respectively ($p < 0.001$). The corresponding rates of permanent hypocalcaemia were 1 per cent (one of 77) and 12 per cent (six of 49), respectively ($p < 0.01$).

The effects of various other parameters on the incidence of transient and permanent hypocalcaemia are shown in Table II. There was a weak association between lateral neck dissection and permanent hypocalcaemia ($p = 0.03$), perhaps a reflection of the fact that this group always had level 6 neck dissection (Table I). Upon multivariate analysis, only central neck dissection was significantly associated with transient hypocalcaemia ($p < 0.001$). No parameters were significantly associated with permanent hypocalcaemia, although this may reflect the low number of cases of permanent hypocalcaemia.

Discussion

These findings indicate that, in the collective experience of a representative group of surgeons in different

TABLE I
PATIENT CLINICOPATHOLOGICAL CHARACTERISTICS

Characteristic	Patients			<i>p</i>
	All	TT	TT + L6 ND	
Patients (<i>n</i> (%))	127 (100)	78 (61)	49 (39)	
Sex (<i>n</i>)				
– Male	24	16	8	0.56
– Female	103	62	41	
Age (median (IQR); <i>y</i>)	45 (28)	43.5 (29)	46 (29)	0.72
Pathology (<i>n</i>)				
– Papillary Ca	98	57	41	0.34
– Follicular Ca	25	19	6	
– Miscellaneous	4	2	2	
Thyroid operation				
– TT	57	29	28	0.03
– Lobectomy + completion	70	49	21	
Lateral ND?				
– No	113	78	35	<0.001
– Yes	14	0	14	
Transient HC?				
– No	88	64	24	<0.001
– Yes	39	14	25	
Permanent HC?				
– No	120	77	43	0.01
– Yes	7	1	6	

TT = total thyroidectomy; L6 = level 6; ND = neck dissection; IQR = interquartile range; *y* = years; Ca = carcinoma; HC = hypocalcaemia

hospitals, total thyroidectomy combined with central neck dissection for the treatment of differentiated thyroid cancer was more likely to result in transient (51 per cent) and permanent (12 per cent) hypocalcaemia, compared with total thyroidectomy alone. Our data were derived from an unselected, consecutive patient series involving surgery performed by both otolaryngology-head and neck surgeons and endocrine surgeons. Most similar studies have been based in single surgical units and have therefore possibly been prone to bias. Our study should constitute a more

representative reflection of contemporary practice within the UK.

Whilst this study had the advantage of being multi-institutional, this also brought disadvantages. For example, when analysing histopathological reports, we found a great degree of variance in the reporting of parathyroid gland and tissue inclusion and the total number of lymph nodes found. Even when the latter information was included, the number of lymph nodes was dependent on histopathological tissue sectioning. Similarly, there was variation in the technique

TABLE II
COMPARISON OF PATIENTS WITH TRANSIENT VS PERMANENT HYPOCALCAEMIA

Characteristic	No HC	Trans HC*	<i>p</i> [†]	Pers HC	<i>p</i> [‡]
Patients (<i>n</i> (%))	88 (69)	39 (31)		7 (6)	
Sex (<i>n</i>)					
– Male	17	7	0.86	2	0.62
– Female	71	32		5	
Age (median (IQR); <i>y</i>)	45 (29)	46 (24)	0.71	58 (14)	0.10
T stage (<i>n</i>)					
– T ₁	27	15	0.70	1	0.29
– T ₂	34	14		4	
– T ₃	15	4		0	
– T ₄	12	6		2	
Thyroid operation					
– Total thyroidectomy	33	24	0.12	5	0.24
– Lobectomy + completion	55	15		2	
Level 6 neck dissection?					
– No	64	14	<0.001	1	0.01
– Yes	24	25		6	
Lateral neck dissection?					
– No	80	33	0.36	4	0.03
– Yes	8	6		3	

*Includes permanent cases. [†]No hypocalcaemia (HC) vs transient (trans) HC; [‡]permanent (pers) HC vs trans HC. IQR = interquartile range; *y* = years; T = tumour

of central neck dissection. It was assumed that the operating surgeon defined central neck dissection as per the standardised definition.⁵ However, in practice central neck dissection could vary from sampling a few nodes to full dissection of tissue from right to left common carotid arteries and from hyoid to suprasternal notch. We were unable to analyse inter-surgeon variability because of the large number of surgeons and the small number of thyroidectomies per surgeon (an overall mean of approximately four per surgeon).

The criteria used to define hypocalcaemia in the literature vary widely.⁶ Our definition, i.e. adjusted calcium level of less than 2 mmol/l and calcium supplementation, has been used by many other studies.^{7–10} The demarcation point between transient and permanent hypocalcaemia varies, but most agree that it should be at least one year post-operatively.⁶

Other authors have also reported the relationship between central neck dissection and hypocalcaemia, with similar results. Roh *et al.*¹¹ reported that transient post-operative hypocalcaemia was higher in patients undergoing total thyroidectomy plus nodal dissection, compared with patients undergoing total thyroidectomy alone (30.5 vs 9.6 per cent, respectively; $p = 0.001$). Henry *et al.*⁴ reported hypocalcaemia incidences of 14 and 4 per cent following total thyroidectomy with central neck dissection and total thyroidectomy alone, respectively.⁴ Pereira *et al.*¹² reported a 60 per cent incidence of transient hypocalcaemia and a 5 per cent incidence of permanent hypocalcaemia following neck dissection.¹²

The British Thyroid Association states that, following total thyroidectomy, 30 per cent of patients will require calcium supplementation with or without 1 α -calcidol, but that, by three months, less than 10 per cent will continue to do so. There is no mention of increased hypocalcaemia as a result of central neck dissection.²

The occurrence of transient hypocalcaemia following total thyroidectomy and central neck dissection is a concern, not least because it usually presents late (typically the second post-operative day) and therefore results in prolonged patient hospitalisation.¹¹ A recent study found that routine post-operative treatment of patients undergoing total thyroidectomy and central neck dissection with calcium and vitamin D reduced the risk of transient hypocalcaemia without causing parathyroid hormone inhibition.¹³ Taken together with our findings, this information supports the role of prophylactic treatment of all patients undergoing total thyroidectomy and central neck dissection with calcium and vitamin D. Such treatment should not only prevent hypocalcaemia but also reduce in-patient stay.

Permanent hypocalcaemia is a troublesome complication requiring lifelong medication and frequent blood test monitoring. It is not uncommon to find a fluctuating response to a stable therapeutic regime of calcium and vitamin D. This necessitates closer

monitoring of calcium levels in patients receiving long-term treatment. The goals of therapy are to maintain a serum ionised calcium level within the normal range and to avoid hypercalcaemia.¹⁴ Studies have also found that long-term hypoparathyroidism may result in increased bone mineral density in the lumbar spine, the significance of which is not entirely clear.^{15,16} Chronic hypocalcaemia due to poor compliance may be associated with cataract formation, ectopic calcification (of the basal ganglia), and, less commonly, parkinsonism and dementia. Thus, permanent hypocalcaemia is not a trivial complication.

Much controversy remains regarding the oncological advantage of elective central neck dissection in the treatment of differentiated thyroid carcinoma,¹⁷ irrespective of the undoubted high incidence of pathologically detectable lymph node metastases in all levels of the neck.¹⁸

- **Elective central compartment neck dissection is increasingly performed as part of surgical management of differentiated thyroid cancer**
- **There is no conclusive evidence of the oncological advantage of elective central neck dissection in differentiated thyroid cancer**
- **In this study, the incidence of transient and permanent hypocalcaemia following total thyroidectomy with central neck dissection was 51 and 12 per cent, respectively; that following total thyroidectomy alone was 18 and 1 per cent, respectively**
- **Systematic implementation of central neck dissection, in the absence of clinical nodal involvement or other high risk factors, should be avoided unless a survival benefit can be demonstrated, particularly in units administering post-operative radio-iodine to most patients**

The British Thyroid Association recommends that total thyroidectomy and central neck dissection should be carried out in patients deemed to be at high risk.² The revised (2009) American Thyroid Association guidelines recommend that 'routine central-compartment (level VI) neck dissection should be considered for patients with papillary thyroid carcinoma and suspected Hürthle carcinoma'. This recommendation does go on to state that central neck dissection may be omitted if surgery is followed by radio-iodine therapy.¹⁹ The European Thyroid Cancer Taskforce argue that central neck dissection is advantageous for staging of the disease, to guide subsequent treatment.³ There seems to be a general and on-going trend towards increasing use of elective central neck dissection in the treatment of thyroid carcinoma.²⁰

However, there is a significant difference between the UK and many parts of Europe, and certainly the

US (and even more so Japan), in that, in the UK, most patients with differentiated thyroid cancer undergoing total thyroidectomy are also treated with post-operative radio-iodine.² Hence, the need to stage metastatic disease to help determine the need for post-operative radio-iodine is not nearly so relevant.

Given the above controversies surrounding elective central neck dissection, our findings of increased transient and permanent hypocalcaemia after central neck dissection suggest that the systematic implementation of such dissection in the absence of pathological disease needs reassessment, particularly in the setting of post-operative radio-iodine therapy administered almost by default. Alternative approaches include simple intra-operative exploration of the central compartment to determine central neck dissection,¹² and ipsilateral central neck dissection only.²¹

Conclusion

The collective experience of a representative group of UK thyroid surgeons is that total thyroidectomy combined with central neck dissection is more likely to result in transient (51 per cent) and permanent (12 per cent) hypocalcaemia (the latter requiring long-term medication and monitoring), compared with total thyroidectomy alone. Whilst most of our patients did have evidence of pathological lymphadenopathy, there remained no evidence of any survival benefit following central neck dissection. There appears to be an increasing prevalence of systematic implementation of central neck dissection in the absence of clinical nodal involvement or other high risk factors; however, this should be avoided unless a survival benefit can be demonstrated, particularly in units where post-operative radio-iodine therapy is administered to most patients. In patients who do undergo central neck dissection, consideration should be given to routine post-operative calcium and vitamin D supplementation.

References

- Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K *et al*. Preoperative ultrasonographic examination for lymph node metastasis: usefulness when designing lymph node dissection for papillary microcarcinoma of the thyroid. *World J Surg* 2004;**28**:498–501
- British Thyroid Association. *Guidelines for the Management of Thyroid Cancer*. London: Royal College of Physicians, 2007
- Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur J Endocrinol* 2006;**154**:787–803
- Henry JF, Gramatica L, Denizot A, Kvachenyuk A, Puccini M, Defechereux T. Morbidity of prophylactic lymph node dissection in the central neck area in patients with papillary thyroid carcinoma. *Langenbecks Arch Surg* 1998;**383**:167–9
- Robbins KT, Clayman G, Levine PA, Medina J, Sessions R, Shaha A *et al*. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology–Head and Neck Surgery. *Arch Otolaryngol Head Neck Surg* 2002;**128**:751–8
- Mehanna HM, Jain A, Randeve H, Watkinson J, Shaha A. Postoperative hypocalcemia – the difference a definition makes. *Head Neck* 2010;**32**:279–83
- Abboud B, Sargi Z, Akkam M, Sleilaty F. Risk factors for post-thyroidectomy hypocalcemia. *J Am Coll Surg* 2002;**195**:456–61
- Ramus NI. Hypocalcaemia after subtotal thyroidectomy for thyrotoxicosis. *Br J Surg* 1984;**71**:589–90
- Demeester-Mirkine N, Hooghe L, Van Geertruyden J, De Maertelaer V. Hypocalcemia after thyroidectomy. *Arch Surg* 1992;**127**:854–8
- Lindblom P, Westerdahl J, Bergenfelz A. Low parathyroid hormone levels after thyroid surgery: a feasible predictor of hypocalcemia. *Surgery* 2002;**131**:515–20
- Roh JL, Park JY, Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and post-operative levels of serum parathyroid hormone. *Ann Surg* 2007;**245**:604–10
- Pereira JA, Jimeno J, Miquel J, Iglesias M, Munne A, Sancho JJ *et al*. Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. *Surgery* 2005;**138**:1095–100, 100–1
- Roh JL, Park JY, Park CI. Prevention of postoperative hypocalcemia with routine oral calcium and vitamin D supplements in patients with differentiated papillary thyroid carcinoma undergoing total thyroidectomy plus central neck dissection. *Cancer* 2009;**115**:251–8
- Litvak J, Moldawer MP, Forbes AP, Henneman PH. Hypocalcemic hypercalciuria during vitamin D and dihydrotyrosol therapy of hypoparathyroidism. *J Clin Endocrinol Metab* 1958;**18**:246–52
- Chan FK, Tiu SC, Choi KL, Choi CH, Kong AP, Shek CC. Increased bone mineral density in patients with chronic hypoparathyroidism. *J Clin Endocrinol Metab* 2003;**88**:3155–9
- Laway BA, Goswami R, Singh N, Gupta N, Seith A. Pattern of bone mineral density in patients with sporadic idiopathic hypoparathyroidism. *Clin Endocrinol (Oxf)* 2006;**64**:405–9
- Mazzaferrri EL, Doherty GM, Steward DL. The pros and cons of prophylactic central compartment lymph node dissection for papillary thyroid carcinoma. *Thyroid* 2009;**19**:683–9
- Mazzaferrri EL, Young RL, Oertel JE, Kemmerer WT, Page CP. Papillary thyroid carcinoma: the impact of therapy in 576 patients. *Medicine (Baltimore)* 1977;**56**:171–96
- Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ *et al*. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009;**19**:1167–214
- Hartl DM, Travagli JP. The updated American Thyroid Association Guidelines for management of thyroid nodules and differentiated thyroid cancer: a surgical perspective. *Thyroid* 2009;**19**:1149–51
- Lim YC, Choi EC, Yoon YH, Kim EH, Koo BS. Central lymph node metastases in unilateral papillary thyroid microcarcinoma. *Br J Surg* 2009;**96**:253–7

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