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Differentiated and Medullary Thyroid Cancer: Surgical Management of Cervical Lymph Nodes

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Abstract

Thyroid cancer metastasises to the central and lateral compartments of the neck frequently and early. The impact of nodal metastases on outcome is affected by the histological subtype of the primary tumour and the patient's age, as well as the size, number and location of those metastases. The impact of extranodal extension has recently been highlighted as an important prognosticating factor. Although clinically evident nodal disease in the lateral neck compartments has a significant impact on both survival and recurrence, microscopic metastases to the central or the lateral neck in well-differentiated thyroid cancer do not significantly affect outcome. Here we discuss the surgical management of neck metastases in well-differentiated and medullary thyroid carcinoma.

Keywords

Lymphatic metastasis; surgery; thyroid gland; thyroid neoplasms

Statement of Search Strategies Used and Sources of Information

All evidence for this review article was drawn from PUBMED articles cross-referenced with international guideline statements.

Introduction

Thyroid cancer often metastasises to the central and lateral compartments of the neck. Papillary thyroid cancer (PTC) metastasises early, and in some series rates are as high as 80% after prophylactic neck surgery [1,2]. Features of the primary tumours associated with increased rates of nodal metastases include young patient age, increasing tumour size, histological type and specific genotypes (e.g. BRAF) (Table 1). Advancements in the

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resolution of imaging modalities and improvements in biochemical testing (e.g. calcitonin) have led to an increased rate of detection of previously occult nodal metastases. Appropriate recognition of the preoperative disease burden is critical to decision making and appropriate surgical planning.

Surgical excision of gross, clinically evident nodal disease in well-differentiated thyroid cancer (WDTC) is widely accepted to be associated with improved outcomes both in terms of recurrence and survival. The role of surgery in occult metastatic nodal disease is, however, controversial as there is no clear benefit in patients who undergo prophylactic neck dissection compared with patients who are managed conservatively with observation of their neck. Medullary thyroid carcinoma (MTC) is a more aggressive disease and therefore prophylactic surgical management of the neck is recommended. However, once lateral neck node metastases are detected, irrespective of the extent of node dissection carried out, biochemical cure is rarely achieved.

Here we review the lymphatic drainage of the thyroid gland and the frequency and clinical impact of regional metastases. We consider both prophylactic and therapeutic indications for neck surgery in DTC and MTC.

Discussion

Lymphatic Drainage of the Thyroid Gland

The first echelon lymph nodes of the thyroid gland are in the central compartment (level VI) of the neck with subsequent drainage to the lower jugular chain (level IV) and the upper mediastinum (level VII). The most commonly involved central compartment lymph nodes are the prelaryngeal (Delphian), pretracheal and the right and left paratracheal nodes. The only exception to this rule is the upper pole lesion, which can metastasise to the lateral neck in some cases without evidence of central neck disease [3]. Rates of metastasis to the regional nodes are related to the histological type of tumour, with papillary and medullary carcinoma being associated with high rates of metastasis in contrast to follicular and Hurthle cell carcinoma, which infrequently spread to lymph nodes.

Incidence and Clinical Significance of Lymph Node Metastases: Differentiated Thyroid Carcinoma

The clinical impact of lymph node metastases on overall survival of patients with WDTC is small [4]. Early cohorts, such as those reported by the Lahey clinic in the 1970s, suggested that nodal metastases might even exert a positive prognostic effect [5]. However, a matched-pair analysis from Memorial Sloan-Kettering Cancer Center subsequently showed that nodal involvement in patients older than 45 years of age was associated with a poor outcome [6]. It remains clear, however, that the impact of nodal metastases on outcome for younger patients is less significant. A recent analysis of the National Cancer Data Base and the Surveillance, Epidemiology and End Results (SEER) database showed that patients younger than 45 years with lymph node metastases have a significantly increased risk of death compared with younger patients without involved lymph nodes, and that having incrementally more metastatic lymph nodes (up to six involved nodes) confers additional mortality. However, it

took a cohort size of almost 50 000 patients to show this clinical effect [7]. The number of involved metastatic lymph nodes has recently been suggested as a more accurate prognostic factor than nodal traditional TNM staging alone [8]. The size of lymph nodes, particularly larger than 3 cm, has also been shown to negatively affect outcomes [9–12].

In a large series of patients with PTC, Yamashita *et al.* [13] showed that extranodal extension is associated with a higher recurrence rate and a poor overall prognosis. In 2012, the American Thyroid Association (ATA)'s Surgical Affairs Committee's Taskforce on Thyroid Cancer Nodal Surgery reported that the presence of extranodal extension was associated with a 24% median risk of recurrence [14]. Extranodal extension as a prognosticating factor has been recently examined in a review by Urken *et al.* [15]. In this paper, the authors were critical of using clinical evidence of metastatic nodes as a prognosticating factor as accuracy of preoperative ultrasound, clinical examination and perioperative assessment all lack sufficient diagnostic accuracy. They also criticised the number of involved lymph nodes as a prognosticating factor due to a potential lack of completeness in comprehensive compartmental dissection, inexperience of pathology residents processing specimens and errors in identifying micrometastatic foci during sectioning before staining. Urken *et al.* [15] supported the finding that extranodal extension confers a negative prognosis and should be incorporated into staging and risk stratification systems. The size of lymph nodes (in contrast to the size of the metastasis confined within) should not confer prognosticating value as a small focus of thyroid cancer [AQ1] does not need to fill the entire node before it breaks out into the surrounding soft tissues. However, the authors highlighted the wide variation in pathological criteria currently used to report extranodal extension, calling for a more standardised approach.

Although it is now well accepted that macroscopic nodal metastases affects prognosis, the effect of occult regional disease is far more limited. Such low volume disease has no impact on survival and, at most, a limited impact on rates of recurrence [14,16]. It is critical when appraising the literature that the reader confirms the surgical approach of the clinical team reporting their results. Those groups who favour prophylactic neck dissection report high rates of nodal disease (cN0pN1) with generally favourable outcomes in contrast to those groups who practice only therapeutic neck dissection. Such groups have lower rates of nodal disease (cN1pN1) and those patients with metastases tend to have poorer outcomes.

In relation to the neck, the current staging model relies solely on the presence or absence of metastatic disease in the central (N1a) or lateral (N1b) compartment. This system will probably be superseded by a system that takes into consideration not only the presence of disease but the size, position, number of nodes and presence of extracapsular extension.

Incidence and Clinical Significance of Lymph Node Metastases: Medullary Thyroid Carcinoma—Patients with MTC have relatively high rates of nodal metastases and once disease has escaped the thyroid gland, 'cure' rates drop considerably. This is particularly true if disease is present in the lateral compartment. In fact if there is contralateral lateral neck disease, patients are considered incurable irrespective of treatment approach. Therefore, a balance has to be made between the aggressiveness of treatment versus long-term benefit. Patients with MTC and evidence of nodal metastasis or high

calcitonin levels at presentation have low rates of biochemical cure, regardless of the extent of surgery. Despite the difficulty in achieving cure, long-term survival in these patients can be expected with 10 year survival over 70% despite evidence of nodal disease. In a large series of patients with MTC published by the French Calcitonin Tumors Study Group, the 10 year survival rate was reported to be over 70% despite the presence of nodal metastases [17].

Surgical Management of the Neck: Differentiated Thyroid Carcinoma

A summarised approach to management of the neck in PTC is presented in Fig. 1.

Therapeutic Neck Dissection in Differentiated Thyroid Carcinoma

Regional lymph node dissection is widely accepted practice in all patients with clinically evident central or lateral metastatic nodal disease [4,18]. The aim of an oncologically complete surgical resection is to remove all gross metastatic disease while preserving vital neurovascular structures and reducing the chance of requiring to operate again on exposed neck levels. The old fashioned 'berry-picking' approach of removing only grossly involved lymph nodes results in unacceptably high rates of recurrence and has now been abandoned.

In a consensus statement published in 2009, the ATA defined that a central neck dissection includes comprehensive, compartment-oriented removal of the prelaryngeal and pretracheal nodes and at least one paratracheal lymph node basin [19]. A therapeutic central compartment neck dissection implies that nodal metastasis is apparent clinically (preoperatively or intraoperatively) or by imaging (clinically N1a). The cephalo-caudad borders of the dissection should include the thyroid notch and the innominate artery. The lateral borders of the dissection are the carotid arteries (levels VI and VII). Ideally this operation should be carried out by high volume surgeons, as complication rates can be high in inexperienced hands.

The lateral neck is assessed preoperatively, and if metastatic nodal disease is identified, surgery should be carried out at the same time as the procedure for primary disease. Again, a compartment-orientated approach is now considered mandatory. The extent of a resection in the lateral neck is mainly guided by preoperative assessment, but most of the involved lymph nodes are found in levels IIa–Vb and, therefore, all of these should be included in the surgical specimen [20]. Thyroid cancer rarely metastasises to level I or regions of the neck above the accessory nerve. For this reason, levels I, IIb and Va are not routinely included in a 'comprehensive' neck dissection. Such an approach minimises risk to the marginal mandibular and accessory nerves.

Prophylactic Central Neck Dissection in Differentiated Thyroid Cancer

A prophylactic central neck dissection is carried out in the absence of evidence of nodal metastasis (cN0). Prophylactic neck dissection in follicular thyroid carcinoma is not indicated as only 1–8% of patients will have lymph node metastases [21]. Prophylactic central lymph node dissection with total thyroidectomy for the treatment of PTC in the clinical absence of neck metastases is controversial because of the possibility of increased morbidity with uncertain benefit in clinical outcomes.

Arguments Supporting Prophylactic Central Neck Dissection in Differentiated Thyroid Cancer

One of the arguments for carrying out prophylactic central neck dissection is the high rate of occult disease found in the clinically uninvolved central neck in patients with PTC [1,2]. In addition, the central compartment can be relatively easily accessed during total thyroidectomy without a significant increase in incision length. Both pre-and intraoperative assessment of the central compartment have been shown to be unreliable in detecting microscopic nodal metastases [22] and, therefore, pathological analysis of a central neck dissection specimen can be used to refine the staging of PTC. Up to 60% of patients undergoing prophylactic central neck dissection will have pathological evidence of subclinical nodal metastases [21]. As the current staging system stands, this finding will subsequently upstage those patients aged 45 years or older [21,23]. This information has been used by some groups to target patients for adjuvant radioactive iodine (RAI) or for administration of higher RAI doses in centres that use adjuvant RAI routinely [23].

An additional argument for prophylactic central neck dissection is that it may result in lower postoperative thyroglobulin levels. Sywak *et al.* [24] showed lower thyroglobulin in patients who underwent prophylactic neck dissection but this effect lost significance with time. In addition, Barczynski *et al.* [25] are one of the few groups to show that prophylactic central neck dissection was associated with improvements in disease-specific survival and locoregional control. However, these results have not been widely reproduced [22] and the validity of this argument is therefore questionable.

Arguments Against Prophylactic Central Neck Dissection in Differentiated Thyroid Cancer

Despite some arguments for the use of prophylactic central neck dissection at the time of thyroidectomy, it is not routinely supported by the most recent ATA guidelines [4]. Most studies report no meaningful impact on outcome after prophylactic central neck dissection [23,26]. Zetoune *et al.* [27], in a meta-analysis of 1264 patients, showed that prophylactic central neck dissection in WDTC does not significantly reduce locoregional recurrence and therefore has no effect on survival.

The lack of benefit in patients undergoing prophylactic central neck dissection is explained by the excellent outcomes experienced by those patients without clinical evidence of nodal disease (cN0) [14]. Monchik *et al.* [28] showed that for low-risk patients selected not to undergo prophylactic central neck dissection at the time of total thyroidectomy, less than 2% develop clinically evident disease during follow-up. Similarly, Ito *et al.* [29] reported a 1% 5 year and 3% 10 year recurrence rate in those who did not undergo prophylactic neck dissection. Nixon *et al.* [30] reported a 5 year disease-specific survival rate of 100% and 5 year recurrence-free survival and central neck recurrence-free survival of 97% and 99%, respectively, in a large cohort of PTC patients who underwent observation of their central neck. With such excellent outcomes experienced by those patients who do not undergo prophylactic central neck dissection, it is hardly surprising that it has been difficult to show a significant benefit to this more aggressive approach to therapy. In addition, the concept that such low-risk patients should be upstaged to further intensify treatment with RAI is questionable.

In addition to the lack of benefit patients receive from prophylactic central neck dissection, additional surgery can expose patients to surgical complications. Although experienced surgeons working in high volume units report low rates of surgical complications from central neck dissection [23,31], national database studies of postsurgical complication rates are not in agreement with this. The Scandinavian Quality Register for Thyroid and Parathyroid Surgery reported higher rates of wound infection and hypocalcaemia in patients undergoing additional neck dissection compared with patients undergoing thyroid surgery alone [32]. Data from the UK suggest that in multivariate analysis, nodal dissection roughly doubles the rate of late hypocalcaemia in comparison with total thyroidectomy alone. Interestingly, this group found that inter-surgeon variability had an even greater effect than nodal dissection, highlighting the difficulty in tailoring surgical guidelines to individual surgeons' practice.

Another interesting finding that questions routine prophylactic central neck dissection is the experience of those groups involved in surgery for recurrent or persistent central neck disease. Clayman *et al.* [33] analysed a retrospective cohort of patients with PTC with confirmed metastatic disease by fine needle aspiration cytology in the central neck compartment and reported that 60% will have recurrent disease in a position dorsal to the recurrent laryngeal nerve and at the level of the thoracic inlet. In the prophylactic setting, such high-risk areas are not routinely explored due to potential injury to the recurrent laryngeal nerve and, therefore, any microscopic disease in this area will be overlooked.

Prophylactic Central Neck Dissection in Differentiated Thyroid Cancer: National Guidelines

As prophylactic central neck dissection in WDTC increases the risk of morbidity without significantly improving clinical outcomes in appropriately selected patients, both the American and British national guidelines are moving away from the recommendation that the procedure is considered in all cases towards a more risk-adapted approach. With small, low-risk primary tumours, routine prophylactic central neck dissection is now not recommended, reserving consideration of prophylactic surgery for large tumours and those cases with evidence of extrathyroidal extension [4,34].

The 2015 ATA guidelines suggest (weak recommendation) that prophylactic central neck node dissection should be considered in patients with PTC with advanced primary tumours (T3 or T4) or clinically involved lateral neck nodes (cN1b) or if the information will be used to plan further management in these patients. Thyroidectomy without prophylactic central neck dissection is strongly recommended for small (T1 or T2), non-invasive, PTC and for most follicular cancers [4]. This is a subtle but significant shift from the 2009 ATA guidelines that recommended that prophylactic central compartment neck dissection (ipsilateral or bilateral) may be carried out in patients with PTC with clinically uninvolved central neck lymph nodes, especially for advanced primary tumours (T3 or T4) [35]. This change in national guidelines reflects a gradual move away from prophylactic central neck dissection internationally, as reflected in the recent British Thyroid Association guidelines [34].

The ATA examined the design and feasibility of a multi-institutional prospective randomised controlled trial of prophylactic central lymph node dissection in patients without any clinical

evidence of neck disease. They concluded that 5840 patients would have to be enrolled in the study to show significant differences in outcomes, which would make it not readily feasible [36]. Given that these are prohibitively large sample sizes, the debate over the benefit of prophylactic central neck dissection in WDTC will probably continue.

Prophylactic Lateral Neck Dissection in Differentiated Thyroid Cancer

In comparison with the central neck, the lateral neck compartment contains lower rates (23%) of occult metastasis [23] and prophylactic surgery in that area of the neck results in higher postoperative complication rates. This does not discourage a few expert groups from advocating selective prophylactic lateral neck dissection as they report an optimisation of disease staging with low complication rates in their hands [23].

Other expert groups report an overall complication rate ranging from 25 to 50% after total thyroidectomy and lateral neck dissection [10,37]. Complications reported include hypocalcaemia, chronic neck pain, chyle leak and recurrent laryngeal nerve palsy [37]. Even groups who advocate routine use of prophylactic central neck dissection accept that it does not confer any significant benefit in terms of survival and has minimal impact on disease recurrence [23]. The 2009 ATA guidelines recognised the potential for involvement of lateral neck nodes in WDTC, but only supported therapeutic, not prophylactic, node dissection, an approach that was unchanged in the 2015 revisions [4].

Surgical Management of the Neck: Medullary Thyroid Carcinoma

A summarised approach to the management of the neck in PTC is presented in Fig. 2.

Therapeutic Neck Dissection: Medullary Thyroid Carcinoma

Similar to the previous version, the latest 2015 ATA guidelines recommend that patients with MTC confined to the neck and cervical lymph nodes should undergo dissection of the central (levels VI–VII) and the involved lateral neck compartment (levels II–V). However, in recognition of the use of calcitonin in predicting patterns of disease, the most recent guidelines now also recommend that in those patients, contralateral ‘prophylactic’ lateral neck dissection should also be considered if the basal serum calcitonin level is greater than 200 pg/ml [38]. In such cases without ultrasound evidence of disease, high rates of pathological disease are reported after prophylactic surgery. Although this approach is recommended by some authors, rates of biochemical cure are low with bilateral neck disease and surgeons must carefully weigh the increased rates of complication associated with bilateral neck dissection against the potential to improve clinical outcome.

Prophylactic Neck Dissection: Medullary Thyroid Carcinoma

The indications for prophylactic neck dissection in MTC are significantly different to DTC. Prophylactic central neck dissection is advised in all cN0 cases as the rates of occult disease are high and metastatic nodal disease is known to be an accurate predictor of outcome [38].

In the presence of central neck node metastases (cN1a), prophylactic lateral neck dissection is an area of controversy. The number of involved lymph nodes in the clinically cN0 neck can be used to predict the likelihood of lateral neck disease. Machens *et al.* [39] showed that

in patients with one to three positive central lymph nodes, involvement of the ipsilateral lateral neck increases from 10% (with negative central neck nodes) to 77%. The risk is even higher at 98% in patients with four or more positive central nodes [39]. Therefore, in the presence of multiple involved central neck nodes one should consider prophylactic lateral neck dissection.

The preoperative calcitonin levels are also important in determining the extent of lymphatic metastases. In a study by Machens *et al.* [40] of 300 patients with MTC treated by total thyroidectomy and compartment-oriented lymph node dissections, there was only minimal risk of nodal disease when the preoperative calcitonin level was less than 20 pg/ml. With rising calcitonin levels, >20, >50, >200 and >500 pg/ml, the burden of disease increases to involve the ipsilateral central then lateral followed by contralateral central then lateral and mediastinal compartments. This biochemical data can be used to guide the extent of surgery. However, one should also consider that although bilateral neck dissection can achieve biochemical cure in more than half of patients when preoperative calcitonin levels are less than 1000 pg/ml (in experienced hands), for patients with preoperative levels exceeding 10 000 pg/ml, cure is unrealistic irrespective of surgical extent [40].

The 2015 ATA guidelines now state that in patients with no clinical evidence of neck metastases, and no distant metastases, dissection of lymph nodes in the lateral compartments (levels II–V) may be considered based on serum calcitonin levels (>200 pg/ml) [38]. The ATA task force, however, states that their members did not achieve consensus on this recommendation. This is a significant shift from the 2009 guidelines that recommended that prophylactic lateral neck dissection in the absence of clinically evident nodal metastasis was not indicated and lateral neck dissection was reserved for clinically evident disease [41].

Patients with normal (<10 pg/ml) serum calcitonin level after attempted complete lymph node dissection are considered ‘biochemically cured’ and have a 97.7% survival at 10 years [17]. However, one should consider that 3% of patients with normal baseline serum calcitonin level after thyroidectomy will have a biochemical recurrence within 7.5 years [42].

Conclusions

Thyroid cancer has a propensity to metastasise to regional lymph nodes. Recent advances in our understanding of the impact of regional metastases, particularly in DTC, highlight the importance of the size, number and extent of metastases, rather than simply their presence, as recognised in current staging systems.

The modern thyroid surgeon has to be familiar with the indications and techniques of regional lymph node dissection. Overt nodal metastasis is associated with worse outcomes in all types of thyroid cancer, and should be excised with minimum morbidity in order to reduce rates of regional recurrence and improve survival. Although complication rates of neck dissection are low in experienced hands, there is considerable inter-surgeon variability in this regard. As such, those patients considered for neck dissection should be referred, wherever possible, to high volume units in order to optimise clinical outcome.

Understanding the biology of regional disease is critical in surgical decision making. The role of therapeutic neck dissection is now well defined, and the place of prophylactic neck dissection is more controversial. International guidelines are currently moving away from prophylactic central neck dissection in PTC and towards biochemically targeted prophylactic lateral neck dissection in MTC.

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Fig 1.
Surgical management of the neck in papillary thyroid cancer.

Fig 2.
Surgical management of the neck in medullary thyroid cancer.

Table 1

Factors associated with nodal spread in well-differentiated thyroid carcinoma

Tumour/patient factors	Impact on nodal metastases
Patient age	More common in younger patients
Primary tumour size	More common in larger tumours
Histology	More common in papillary > medullary > follicular carcinoma
Genotype	More common in papillary thyroid cancer with BRAF mutations