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MANAGEMENT OF THE LATERAL NECK IN WELL DIFFERENTIATED THYROID CANCER

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Abstract

Lateral neck lymph node metastases in well differentiated thyroid cancer are common, ranging from 30–60%, with the majority of these foci identifiable only as microscopic deposits. A skilled ultrasound evaluation of the lymph nodes in the lateral neck is recommended for all patients presenting with newly diagnosed thyroid cancer undergoing surgical management. Ultrasound guided fine needle aspiration biopsy may be used to cytologically confirm suspected lateral neck nodal metastases prior to surgery. For patients with large volume nodal disease, extranodal extension, or multiple nodal metastases, computed tomography (CT) scan of the neck with contrast is an important additional imaging modality to accurately localize disease prior to surgery. Primary surgical management for lateral neck disease typically includes lateral neck dissection in conjunction with total thyroidectomy. Postoperative adjuvant radioactive iodine is typically recommended for patients with clinically evident nodal metastases, or for those with over 5 micrometastatic nodes. In the recurrent or persisting disease setting, complete surgical resection of local and regional disease remains the main treatment approach. However, subcentimeter nodal disease may take an indolent course, and active surveillance may be a reasonable approach in selected clinical circumstances. Conversely, external beam radiation therapy (EBRT) may be considered for scenarios with unresectable disease, or microscopic residual disease following surgery in a clinically unfavorable setting. Two multi-kinase inhibitors (sorafenib and lenvatinib) are now FDA approved for treatment of RAI refractory thyroid cancer and now play an important role in the management of progressive, metastatic and surgically incurable disease.

Keywords

papillary thyroid cancer; lymph node; papillary; metastasis

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INTRODUCTION

The incidence of well differentiated thyroid cancer (WDTC) is rising, in part related to an increased diagnosis of small volume disease, with overall excellent outcomes.(1, 2) Lateral neck nodal metastases from WDTC is a relatively common finding, particularly with an increasing use of ultrasound and fine needle aspiration biopsy which now enables the detection of nodal disease at a subclinical state. Other patients presenting with high volume nodal metastases and extranodal spread are at clearly elevated risk for future recurrence and may require more extensive workup and treatment. The divergence between the high incidence of detectable metastatic disease and the low incidence of clinically meaningful neck metastasis represents the foundation of adopting a conservative approach towards managing the lateral neck. Increased use of imaging will inevitably lead to an increase in discovery of subclinical disease. Such a trend has the potential to cause stage migration and overtreatment. This review covers the incidence of metastatic nodal disease, patterns of spread, evaluation of the neck, clinical significance of lateral neck disease, therapeutic approaches, management of recurrent or persisting lateral nodal metastases, and provides the background necessary to adopt a balanced approach to the treatment of WDTC metastatic to the lateral neck.

INCIDENCE AND PATTERNS OF METASTATIC LYMPH NODE SPREAD IN THE LATERAL NECK

Involvement of the lateral neck lymph nodes (LNs) by foci of metastatic WDTC is common, with occult disease identified in 30–60 percent of cases (3–6). Up to 80% of these nodes harbor microscopic foci, that are being detected with increasing frequency due to the widespread use of ultrasound, fine needle aspiration biopsy, and improved experience of ultrasonographers. Importantly, micrometastases carry less clinical significance as compared with macrometastases. (7) By the 2015 American Thyroid Association (ATA) guidelines, patients harboring up to 5 micrometastatic nodes limited to up to 2 mm tumor foci remain at low risk for recurrence and do not necessarily require radioactive iodine administration. [13] In contrast, large metastatic nodes or nodes with extrathyroidal extension carry a significantly higher risk of recurrence.[13]

The location of LN metastases follows patterns based on the location of the primary thyroid cancer. Nodal metastasis of WDTC typically first involves the central compartment (level VI) before spreading to the lateral compartments of neck (Figure 1) (6, 8). A meta-analysis to investigate the value of central neck involvement as a predictor of lateral compartment metastasis showed central neck metastasis resulted in a 7.64 increase risk of lateral LN involvement.(9) Early work from Japan and Germany reported on LN distribution in WDTC(6, 10), and Sivanandan and Soo characterized LN distribution by neck levels.(11) In neck dissection specimens performed for therapeutic indications, the majority of patients had multiple levels of LN metastasis present (82%), with levels III and IV most commonly involved. Levels I and V were rarely involved and metastases here were observed only in the context of multi-level disease. Upper pole carcinomas have a higher propensity to metastasize directly to levels II and III.(12)

EVALUATION OF THE LATERAL NECK COMPARTMENT

Before surgical treatment, preoperative imaging and sometimes laboratory tests are used to stage patients with WDTC. Preoperative evaluation for lymph node metastasis may alter surgical planning. Ultrasound (US) evaluation of the lateral neck of all patients undergoing thyroid cancer surgery is strongly recommended by the ATA.(13) Utilizing US preoperatively detects non-palpable LN metastases in about one third of patients. (14) Ultrasound findings suggestive of metastatic LNs include: enlarged size, loss of a fatty hilum, a round shape, taller than wide shape, hyperechogenicity, cystic change, calcifications, and peripheral vascularity. When suspicious LNs are identified, the ATA recommends US-guided FNA of suspicious lymph nodes > 8–10 mm. Lymph nodes 8–10 mm in size that can be localized on anatomic imaging may be considered targets for surgical removal. Although metastatic foci as small as 2–3 mm in size can sometimes be identified on imaging, the clinical benefit of treating such foci has not been clearly demonstrated. Thyroglobulin washout of the FNA sample can also be useful in some cases to establish a diagnosis of metastatic thyroid cancer, particularly for cystic LNs when cytologic evaluation of the FNA is equivocal, or when cytologic and sonographic evaluations are conflicting.

In patients with clinical suspicion for advanced disease including an invasive primary tumor, bulky lymph node involvement, extranodal extension of disease, or multiple nodal metastases, cross sectional imaging with a neck CT or MRI scan with contrast is recommended and may convey critical information that is not demonstrated on the US. The use of intravenous contrast helps to delineate the anatomic relationship between metastatic disease and other structures. Nodal disease in the retropharynx, superior mediastinum, and deep tracheo-esophageal groove is often not detectable by US. In addition, the identification and assessment of extranodal disease, and its relationship with the great vessels, trachea, larynx, esophagus, and neural structures, is more accurately conveyed with cross sectional imaging than US. It is now accepted that the added information gained from the use of iodinated contrast with a neck CT scan far outweighs historical concerns about iodine burden from IV contrast causing a delay in subsequent radioactive iodine administration. Iodine is generally cleared within 4–8 weeks of the contrast administration and does not incur a significant delay. Contrast neck CT scans provide high quality preoperative imaging which may enhance the likelihood of achieving a complete surgical resection of disease, a critical initial objective in the successful management of thyroid cancer.(15)

CLINICAL SIGNIFICANCE OF METASTIC DISEASE IN THE LATERAL NECK

Prior retrospective studies suggested that regional LN metastases do not adversely impact on survival after surgical management in patients with WDTC.(16, 17) This is reflected in older prognostic risk stratification systems such as GAMES(16), MACIS(18) and AMES(17) which do not incorporate nodal status as a prognostic variable. However, more recent work has shown metastatic disease in the lateral compartment predicts for poorer outcomes, particularly in older patients. (19) The American Joint Commission for Cancer staging system incorporates the presence of lateral nodal disease by upstaging patients to stage IV in those over 45 years old. Importantly, this only takes into account nodal status as a positive or negative binary variable. Other characteristics such as size, number of LNs and extranodal

extension have also been reported to be prognostic. (7, 9, 20, 21) Clinically occult LNs have little prognostic value in contrast to macroscopic LN metastases. In contrast, patients with macroscopic LN metastases are at increased risk of additional regional nodes and distant disease.(19, 22) LNs greater than 3 centimeters in size are associated with a decrease in recurrence free survival (RFS) (20), and are predictive of decreased disease specific survival (DSS) in patients older than 50.(21) Adam et al showed cervical lymph node metastases were associated with compromised survival in patients younger than 45 years old in two national datasets.(23) However, in this study the LN characteristics including size, location and features such as extranodal spread were not analyzed. Ito reported that five or more LNs in the lateral neck is predictive of worse RFS.(20) Extracapsular spread is also associated with worse survival in older patients.[20, 21] The recently published 2015 ATA guidelines for management of WDTC now incorporate such nodal variables (size, number, extracapsular spread) into a new graded scale of risk assessment of structural recurrence of disease.[13]

EXTENT OF LATERAL NECK DISSECTION REQUIRED IN WDTC

Therapeutic lateral neck compartment lymph node dissection should be performed for patients with biopsy-proven metastatic lateral cervical LNs.(13) “Lymph node plucking” or “berry picking” techniques removing only distinct foci of metastatic disease is discouraged at initial surgery secondary to the high risk of recurrence(24), in favor of compartmental lymphadenectomy. The jugular nodes in levels II, III, and IV are the most commonly involved lateral neck compartments for WDTC(11, 25) and should be included in all therapeutic lateral neck lymph node dissections. Level V, representing the posterior triangle of the neck, is less commonly involved, but level Vb should be assessed carefully, in the region inferior to the course of the spinal accessory nerve. Level V may be approached either by a limited exposure anterior approach by retracting the sternocleidomastoid muscle posteriorly, or more comprehensively by dissecting the posterior triangle behind the sternocleidomastoid muscle back to the trapezius muscle. Level I is only at very low risk for harboring metastatic thyroid cancer, and is not dissected in the absence of clinically involved LNs. The precise extent of neck dissection is a decision made based on the volume and location of disease. Comprehensive lymph node dissection (CLND) including levels II-V is recommended by the ATA for most patients with clinically evident lateral neck metastatic disease, although the nuances regarding the extent of the level V dissection are not clarified. Special attention should be paid to the retrocartoid area, low in the neck between levels 4 and 6, as this often can harbor metastatic disease. The need to resect extranodal structures such as the sternocleidomastoid, internal jugular vein, and the spinal accessory nerve in WDTC is rare. However, the extent of the disease should dictate the need to resect these structures with the goal of achieving a negative margin resection.

Prophylactic central neck dissection may be considered in patients with clinically involved lateral neck nodes even in the absence of radiographic central compartment disease.(13) In 319 patients who underwent both central and lateral node dissection, Ito et al observed that 70% of patients with positive lateral neck disease also had central neck LN metastases.(26) For patients with clinically evident metastatic lateral LNs, a compartmental lymph node dissection is associated with a reduced risk of future recurrence.(27–29) For patients with

upper pole carcinomas, the first echelon draining LN level may be II rather than VI, which brings into question the need for prophylactic central neck dissection in these patients with only clinically involved level II lateral neck nodes. Each patient's extent of nodal dissection may be individualized, and the risks and benefits of prophylactic central neck dissection in the setting of lateral neck metastases should be discussed with the patient. Preoperative imaging may also guide extent of surgery in these cases.

Elective lateral neck dissection for WDTC without evidence of nodal metastasis on clinical exam or by imaging is not recommended. While some authors report prognostic value in elective neck dissection in the N0 neck, this has not been shown to translate into improved survival.(30, 31) Despite the high prevalence of occult metastasis, this disease rarely becomes clinically relevant and if it does it can safely be salvaged at a later date if it becomes clinically significant.

RECCURENT OR PERSISTENT LATERAL NECK DISEEASE

Recurrent or persistent WDTC may be broadly classified as either biochemical or structural. In a patient that has undergone prior total thyroidectomy, serum thyroglobulin (Tg) in the absence of Tg antibodies is very useful tool to monitor for recurrent and persistent disease. For patients with thyroglobulin antibodies, the serum antibody levels may indirectly reflect disease burden, and may be used as a surrogate for serum thyroglobulin level. Rising Tg levels in the absence of radiographic disease represents biochemical recurrence, while new radiographic disease represents structural recurrence. Follow-up with cervical US to evaluate the lateral neck, the thyroid bed, and the central neck should be performed from 6–12 months after surgery and then periodically thereafter to assess for structural disease, depending on the patient's risk stratification and Tg status.(13)

Incidence of LN recurrence ranges from 1.5–34%.(32–35) Patients who initially do not present with metastatic nodal disease by imaging recur in less than 10% of cases (34, 35), while patients with positive LNs in the central neck or lateral neck at the time of initial management are more likely to have a recurrence in the lateral neck.(35) In patients without lymph node metastasis at the time of initial surgery, regional recurrences in levels II–IV of ipsilateral neck are more common. When LNs are present at clinical presentation, recurrences are more commonly seen in IV–VI of ipsilateral side and level II of the contralateral side.(34) The identification of recurrent or persisting lateral neck disease is most often an indication for compartmental lymphadenectomy. The decision to proceed with surgery should be made in the context of assessing the relative risks and benefits of revision surgery, the clinical significance of the identified disease, assessment of other sites of disease, patient preference, patient comorbidities, as well as the availability of surgical expertise. Preoperative structural imaging utilizing CT with contrast is an important component of assessing the extent of disease and in planning revision surgery. PET/CT scans are useful for patients with RAI refractory disease, or in patients with a rising TG level with a negative RAI scan. The proximity of LNs to vital structures which can be invaded should be assessed. This issue is more common with central LNs and thyroid bed recurrences rather than lateral neck recurrence. High volume recurrent disease in the lateral neck is best treated surgically. Cytologic confirmation of malignancy by fine

needle aspiration biopsy is appropriate for abnormal appearing lymph nodes before surgical intervention. Surgical management remains the mainstay of treatment for the majority of disease the recurrent setting. Therapeutic compartmental lateral neck dissection including levels II-V, sparing uninvolved structures, is the most common operation for lateral neck disease. However, in cases where lateral neck surgery has been previously performed, a more targeted approach towards excision of recurrent disease may be appropriate.

ACTIVE SURVEILLANCE OR PERCUTANEOUS ETHANOL INJECTION FOR SMALL VOLUME NODAL DISEASE

While surgery is the gold standard of treatment for recurrent or persisting lateral neck nodal disease, in some cases small volume, indolent nodal disease will be identified with questionable clinical significance. The American Thyroid Association Surgical Affairs Committee Writing Task Force issued guidelines recently (36), regarding the judicious adoption of an active surveillance approach for lateral neck nodes <1 cm in dimension that have appropriate clinical characteristics such as slow growth rate and well differentiated histology. Interestingly, a recent observational study of recurrent or persisting low volume nodal disease following prior surgery suggests that the majority of nodal disease progresses slowly, with a median progression of 1.4 mm/year. The majority of patients were safely followed by ultrasound.(37, 38) Only a minority (20.5%) of patients with a growth rate exceeding 3 mm/year exhibited worse survival.

For patients with small volume nodal disease who are not appropriate for observation, and who may be poor surgical candidates (multiple prior surgeries or medical co-morbidities), percutaneous ethanol injection (PEI) may be used for control of local metastatic lymph nodes. One study of 109 metastatic lymph nodes treated with PEI and a mean follow-up of 38 months demonstrated that 84% were successfully ablated after one to three treatment sessions, without any major complications.(39) Hay and colleagues similarly reported that 95% of metastatic LNs treated with PEI decreased in size, and 46% disappearing on rescan in a cohort of 37 biopsy proven metastatic LNs.(40) The authors also reported a cost benefit to this technique. However, many of the lesions treated in these two studies were subcentimeter LNs. In some cases, low-volume recurrent nodal disease may be indolent and may not necessarily impact on patient outcomes. Future research is needed to determine which of these LNs may be safely observed, alleviating the need for invasive intervention in carefully selected patients.(37)

EXTERNAL BEAM RADIATION THERAPY FOR THE LATERAL NECK

External beam radiation therapy (EBRT) is a potent adjuvant treatment that may be applied for cases with gross residual nodal disease, or for microscopic residual disease in a clinically unfavorable setting such as high grade or RAI refractory disease. Routine use of EBRT for nodal disease is not recommended in the absence of high risk features.(41) Assessing the true value of EBRT for recurrent lateral neck disease in WDTC is limited by the lack of randomized control trials. In a retrospective, single institution review of histologically heterogeneous patients with persistent or recurrent disease, a locoregional control rate of 72% at 4 years was observed in patients treated with EBRT.(42) In the setting of

recurrence disease with significant extracapsular spread and high likelihood of residual microscopic disease, EBRT may be considered, although evidence to support the benefits of this approach are more limited. The American Head and Neck Society recently issued general guidelines on these approaches.(41)

Systemic Targeted Therapy in Thyroid Cancer

In patients with RAI refractory disease that is symptomatic and progressive, two tyrosine kinase inhibitors have been approved by the FDA and should be considered in the management of patients with WDTC with unresectable disease or metastatic disease. Sorafenib(43) and lenvatinib (44) have shown significant efficacy in this cohort. Sorafenib was approved based on the phase III DECISION trial, which found that the median progression-free survival (PFS) was significantly longer in the sorafenib treated group (10.8 months) as compared to the placebo group (5.8 months) in patients with recurrent and/or metastatic differentiated thyroid cancer. In a similar patient population, the SELECT trial demonstrated a median PFS in the treatment group of 18.3 months as compared with 3.6 months in the placebo group with an overall objective response rate of 64.8%. No overall survival benefit was observed with either of these two multi-kinase inhibitors, which reflect the study design which allowed for patient crossover while on trial. These drugs are hypothesized to exert their actions by targeting tumor angiogenesis by inhibiting vascular endothelial growth factor receptors, VEGFR- 1, VEGFR-2 and VEGFR-3. In addition, these agents also inhibit other kinases. Sorafenib inhibits RET, BRAF, and the platelet-derived growth factor receptor (PDGFR) β while lenvatinib inhibits PDGFR α , RET, the mast/stem cell growth factor receptor Kit and the fibroblast growth factor receptors; FGFR-1, FGFR-2, FGFR-3 and FGFR-4. These different molecular mechanisms of activity may contribute to the differences in clinical efficacy observed between these two compounds. Both kinase inhibitors are associated with significant toxicity with 82% of patients requiring a dose interruption in the SELECT trial. The duration of treatment, quality of life and strict selection criteria were not addressed in these clinical trials. Patient counseling with a discussion of risks and benefits of systemic therapy in this setting should be part of clinical decision making along with input from the disease management team including the endocrinologist and medical oncologist.

CONCLUSIONS

Nodal metastases to the lateral neck LNs from WDTC are common. Ultrasound should be used to assess the cervical lymph nodes for all patients preoperatively. Surgical management with compartmental lymphadenectomy is the gold standard therapy for structurally evident lateral neck nodal disease. Elective neck dissection is not recommended in patients without structurally identifiable disease. For patients with large volume nodal disease, multiple nodal metastases, or a concern about extracapsular nodal disease, imaging using CT scan with contrast will help localize disease and its relationship with critical structures, allowing for optimal preoperative planning. In the recurrent or persistent setting, subcentimeter nodal disease with favorable clinical characteristics may remain indolent, and active surveillance for carefully selected patients may be an alternative to revision surgery. The surgical management of nodal recurrence with compartmental lymphadenectomy remains the gold

standard of treatment, although more targeted surgical resection may be appropriate in a revision surgical setting. Percutaneous ethanol ablation may be used selectively for low volume nodal disease in patients who are poor surgical candidates. EBRT is recommended as postoperative adjuvant treatment for patients with gross residual disease, or microscopic residual in high risk setting. Two multi-kinase inhibitors (sorafenib and lenvatinib) have recently been FDA approved for treatment of RAI refractory thyroid cancer. For patients with unresectable and progressive metastases that are not amenable to surgery or radiation, these novel agents represent an additional therapeutic option.

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Figure 1:
Levels of the neck.