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STATEMENT

Management of Recurrent/Persistent Nodal Disease in Patients with Differentiated Thyroid Cancer: A Critical Review of the Risks and Benefits of Surgical Intervention Versus Active Surveillance

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Background: The primary goals of this interdisciplinary consensus statement are to define the eligibility criteria for management of recurrent and persistent cervical nodal disease in patients with differentiated thyroid cancer (DTC) and to review the risks and benefits of surgical intervention versus active surveillance.
Methods: A writing group was convened by the Surgical Affairs Committee of the American Thyroid Association and was tasked with identifying the important clinical elements to consider when managing recurrent/persistent nodal disease in patients with DTC based on the available evidence in the literature and the group's collective experience.
Summary: The decision on how best to manage individual patients with suspected recurrent/persistent nodal disease is challenging and requires the consideration of a significant number of variables outlined by the members of the interdisciplinary team. Here we report on the consensus opinions that were reached by the writing group regarding the technical and clinical issues encountered in this patient population.
Conclusions: Identification of recurrent/persistent disease requires a team decision-making process that includes the patient and physicians as to what, if any, intervention should be performed to best control the disease while minimizing morbidity. Several management principles and variables involved in the decision making for surgery versus active surveillance were developed that should be taken into account when deciding how best to manage a patient with DTC and suspected recurrent or persistent cervical nodal disease.

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy. In 2014, it is estimated that 96% of all new endocrine organ cancers will originate from the thyroid gland, resulting in approximately 63,000 new cases and taking the lives of 1890 patients (1). Cervical lymph node metastases have been reported to occur in 12–81% of patients with papillary thyroid cancer (PTC), and in a smaller proportion of patients with other histotypes (i.e., follicular thyroid cancer and Hürthle cell carcinoma) (2–4). Gross lymph node metastases can be present in approximately 35% of patients with differentiated thyroid cancer (DTC) (5–7). The likelihood of nodal recurrence depends not only on the actual clinical stage of disease, but also on which diagnostic modalities are employed to assess for potential lymphatic metastases and the extent to which a therapeutic or prophylactic central lymph node dissection is performed for high-risk disease (8,9). Although lymph node metastases are common in DTC, death is not, and the lack of a clear prognostic indication has led to controversy in the management of cervical lymph nodes. What may be more significant from a prognostic standpoint are lymph node metastases that are larger than 3 cm, exhibit extranodal extension, or metastasis present in more

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than five lymph nodes. This has been reported to correlate significantly with both the recurrence and persistence of thyroid cancer and, arguably, survival (4,10,11).

Patients with DTC generally undergo life-long follow-up. This surveillance scheme is mainly implemented based on landmark studies published in the mid-1900s, which examined long-term outcomes in large cohorts of thyroid cancer patients treated during the latter half of the 20th century. In a study by Mazzaferri and Jhiang (12), it was estimated that the tumor recurrence rates were 30% during postoperative surveillance and that approximately 66% of these recurrences were detected within 10 years of the initial therapy.

Recently, however, the cost effectiveness of this prolonged surveillance has been challenged. Skepticism has been raised in part by the increase in the detection of small, subclinical disease by the routine implementation of ultrasonography in clinical practice, and the population being evaluated (13). The incidence of thyroid cancer has been increasing steadily since the 1970s (14). Over the last decade, data from the Surveillance, Epidemiology, and End Results (SEER) registries have shown a 6.4% average annual increase of thyroid cancer in the United States (15). For these reasons, distinguishing patients with negligible risks for disease recurrence from those with higher-risk tumors that require more prolonged follow-up should allow the treating physicians to provide increasingly cost-effective treatment and surveillance plans for both groups of patients.

The past 20 years have also witnessed a major paradigm shift in the methods used to detect postoperative recurrence, with a clear decline in the use of whole body scans and increasingly widespread reliance on high-resolution ultrasound with serum thyroglobulin (Tg) examination after initial or reoperative surgical intervention. Ultrasound has proved to be more accurate than whole body scanning for detecting recurrent/persistent disease in low-risk DTC patients (16–18). As for serum Tg assays, detection limits have markedly improved in recent years (19). Serum Tg is considered the most sensitive marker for the presence of DTC after total thyroidectomy and radioactive iodine (RAI) treatment, especially when thyrotropin (TSH) is elevated through thyroid hormone withdrawal or injection of recombinant human TSH (rhTSH) (20). However, its enhanced sensitivity is also associated with a high rate of false-positives, especially in the presence of benign thyroid remnants and when adjuvant RAI has not been administered (21–23). This may lead to additional surveillance and intervention with potential resultant morbidity for patients at very low risk of morbidity or mortality from their disease. A rising Tg, especially when rising rapidly, is much more specific for risk of disease progression, whereas long-standing, stable, Tg-positive disease recently localized to the cervical lymph nodes due to more sensitive imaging modalities may not require immediate surgical intervention (24).

Depending on the initial therapy and prognostic variables (detectable or elevated Tg vs. structurally identifiable recurrent disease), it is estimated that approximately 31–46% of DTC patients will have persistent disease and 1.2–6.8% will have structural tumor recurrences during postoperative surveillance (25). Although not usually fatal, disease recurrence can be serious and is sometimes the first sign of a potentially poor outcome (26,27). However, it has been suggested that small, stable cervical lymph nodes, even when suspicious in character, can be observed (28,29). In addition, a low level of serum Tg, in the absence of structural disease, is now gaining acceptance as not being harmful to the patient (30).

The development of metastatic disease in the cervical and mediastinal lymph nodes represents the most common location (74%) for recurrent/persistent DTC, followed by the thyroid remnant (20%), and the trachea and adjacent muscle (6%). In 21% of cases, the site for recurrence is distant metastases, most often (63%) in the lungs alone (12).

Clinicians involved in the care of patients with recurrent/persistent DTC nodal metastases must determine the most appropriate management approach, which may include compartmental lymph node dissection, active surveillance (watchful waiting with serial cervical ultrasound evaluations), RAI ablation therapy, external beam radiation therapy, and/or nonsurgical, image-guided, minimally invasive ablative approaches. Guidelines from the American Thyroid Association (ATA) and the National Comprehensive Cancer Network (NCCN) provide valuable parameters for the management of recurrent/persistent nodal disease, but fail to guide the physician as to the myriad of factors that should be taken into account in each individual case (31,32).

A writing group was convened by the Surgical Affairs Committee of the American Thyroid Association and was tasked with identifying the important clinical elements to consider when managing recurrent/persistent nodal disease in patients with DTC. This consensus statement was developed within the framework of the current ATA Management Guidelines and the NCCN Clinical Practice Guidelines to aid the decision-making process in patients with recurrent/persistent nodal metastases based on the literature available at the time of writing (31,32). Additional input and recommendations were developed by the writing group to address gray areas that guidelines do not address and where existing evidence is insufficient. The present position statement paper was then submitted to the leadership council of the ATA who made further edits and endorsed it in its current form.

REVIEW

Definition of Recurrent/Persistent Disease, Local and Regional Recurrences

The primary treatment for locally advanced DTC should consist of total thyroidectomy, with both a therapeutic neck dissection and thyroid remnant ablation as indicated (31). The goal is to sustain a disease-free status and minimize the recurrence rates and need for reoperation. The intraoperative and histopathology findings of R_0 (no residual tumor) or R_1 (microscopic residual tumor) resections are important to distinguish between recurrent and persistent disease. A distinction must be made between *local recurrence* in the thyroid bed or the residual thyroid tissue and *regional recurrence* in the lymph nodes of the central or lateral compartments of the neck. Recurrent thyroid cancer should be divided into central compartment recurrence (primary or nodal recurrence), lateral neck recurrence (nodal lesions), and distant recurrence. Disease recurrence is defined as biochemical or structural identification of disease in a patient previously thought to have no evidence of disease (undetectable stimulated or highly sensitive Tg and negative cross-sectional imaging). Biochemically detectable disease is defined by serum testing of Tg using various thresholds. Patients who present with an increased serum Tg level are most likely to have disease in the nodal groups, which may be in the central compartment (level VI), in the lateral neck commonly at levels II, III, IV and V, or level VII (upper mediastinal nodes) (33). All structural and biochemical disease identified before a patient is classified as having no evidence of disease is considered persistent disease (25,34).

Considerations for Surgery Versus Active Surveillance

Follow-up standards for patients with DTC have changed considerably in the last decade. Recent studies have shifted their focus to accurate risk-group stratification for predicting locoregional recurrence in patients with thyroid cancer (31,34–37). These ongoing risk estimates provide the basis for new recommendations regarding the need for either additional therapy versus active surveillance and should guide the intensity and modalities of our long-term follow-up paradigm. Once the risk of recurrence is established for an individual patient, the treating physicians can then plan an initial treatment and follow-up strategy that matches this initial risk estimate. Patients at high risk of recurrence will be considered for adjuvant therapy with RAI ablation, external beam radiation, thyroid hormone suppressive therapy, and/or systemic therapy depending on the RAI avidity of the tumor. Patients at intermediate risk of recurrence will need individualized assessments of the risk/benefit ratio of any suggested adjuvant therapies. Patients at low risk of recurrence can be followed without aggressive TSH suppression and without the need for additional adjuvant therapy.

Overall, long-term survival is 100% in patients with only biochemical evidence of persistent disease and 85% in patients with structural evidence of persistent disease, whereas the long-term survival in patients with distant metastatic lesions is less than 50% (38). The time interval between detection of recurrence in patients with distant metastases and cancer death is less than 5 years in 49% of cases, 5–9 years in 38%, 10–14 years in 20%, and 15 years or more in 8% (12). Generally, cancer mortality rates are lowest in patients younger than 40 years and increase with each subsequent decade of life (12).

With the goal of achieving a disease-free status, it is helpful to review the contemporary literature on surgical management for recurrent/persistent nodal disease to determine the likelihood of disease progression. Table 1 summarizes the published series of DTC patients who underwent surgery for recurrent/persistent nodal disease. Articles that did not provide information about the length of follow-up or criteria used to measure surgical success were excluded from the review. While surgery seems very effective in the treatment of patients with recurrent/persistent nodal disease from DTC, data about long-term disease-specific outcomes remain limited. Moreover, a comprehensive review of the literature cannot determine the true value of surgery due to the short follow-up intervals and the lack of homogeneity in reporting findings.

Critical Factors Involved in the Decision Making for Surgery Versus Active Surveillance for Recurrent/Persistent Nodal Disease in the Central and Lateral Neck Compartments

There are a number of basic principles that the treating physician should take into account in deciding what the best form of therapy should be for any given patient with recurrent/persistent DTC in the lymph nodes. The management of thyroid cancer is often best conducted as a joint decision-making process between the patient and the disease management team that strives to strike the best balance between likely effective therapy and the likely side effects of that therapy. Often, the optimal therapeutic decision is not so clear and straightforward. Thus, it is vital to educate the patient about the options relating to their individual circumstance when selecting an intervention (39). The disease management team often includes a surgeon, endocrinologist, nuclear medicine specialist, dedicated pathologist, medical oncologist, and possibly a radiation oncologist, who have a keen interest and experience in the management of thyroid cancer. The decision on how best to manage an individual patient requires the consideration of a significant number of variables that cannot be simply placed into a formula in order to determine the best paradigm of therapy. The most important principles that should be considered are:

Likelihood and clinical significance of structural disease progression

Clinically evident lymph node metastases may be followed in select circumstances to document growth before proceeding with therapeutic intervention. Small, postoperative thyroid bed nodules (defined as <11 mm) occur in as many as a third of patients undergoing surgery, with or without adjuvant therapy (28,29). Only a small percent ($<10\%$) of these nodules will prove to be malignant lymph nodes, and even fewer will progress over time (28). Furthermore, lateral neck lymph nodes with ultrasonographic features that were very suspicious for malignancy also demonstrated a low potential for structural disease progression (over a median of 3.5 years, only 9% increased by more than 5 mm in size) (29). In both of these studies, surgical resection at the time of structural disease progression was very successful without evidence of local invasion or distant metastases. These data suggest that properly selected patients can be offered a strategy for close monitoring with serial Tg measurements and ultrasonography of suspicious cervical lymph nodes.

The decision to biopsy suspicious lymph nodes or utilize the measurement of Tg in the washout fluid from the fine needle aspiration (FNA) biopsy should be made based on the determination as to whether the results of the biopsy will lead to an appropriate and reasonable therapeutic intervention. The size of the lymph node, in any dimension, deemed to be 8 mm or greater in the central compartment and 10 mm or greater in the lateral compartment represents reasonable guidelines for a FNA biopsy for cytology and/or the measurement of Tg in the aspirate when surgery is being considered. These cutoffs were extracted from the upcoming third edition of the ATA guidelines that have revised the 2009 guidelines recommending FNA biopsy for smaller nodes.

In nearly all circumstances before surgery, as outlined by the current ATA guidelines (31), confirmation of the presence of metastatic thyroid cancer should be performed through a FNA biopsy of the suspicious lymph node for cytology and/or Tg analysis. However, FNA confirmation may not always be technically possible due to the anatomic location of the nodal mass, and in these situations where the radiologic features are particularly suspicious for metastatic disease, surgery may still be considered if thought to be beneficial.

Table 1. The Outcomes of Surgical Management for Recurrent and Persistent Thyroid Cancer

Author (reference #)	*Year*	*Adjuvant RAI after primary surgery (%)*	*Average length of follow-up (months)*	*Biochemical remission (%)*	*No evidence of structural disease (%)*
Rubello (85)	2007	100	33.6	*	81
McCoy (81)	2007	*	17	50[a]	*
Lee (68)	2008	*	(7–109.2)	64[a]	100
Schuff (41)	2008	92	(> 6)	41[a]	72
Al-Saif (115)	2010	100	60	27[b]	*
Roh (119)	2011	60	61	*	91
Clayman (118)	2011	72	87	66	74
Hariri (120)	2012	*	(2–24)	42[a]	51
Hughes (113)	2012	89	15.5	21[a]	72
Shah (117)	2012	85	28	56[c]	80
Tufano (114)	2012	*	41.5	*	100
Lang (121)	2013	100	42	32[a]	72

*Studies did not comment on specific variables.
[a]Biochemical remission based on an achieved Tg level < 2 ng/mL.
[b]Biochemical remission based on an achieved Tg level < 0.9 ng/mL.
[c]Biochemical remission based on an achieved Tg level < 1 ng/mL.
RAI, radioactive iodine; Tg, thyroglobulin.

The widely accepted American Joint Committee on Cancer (AJCC) staging system simply characterizes lymph nodes on the basis of location in the central, lateral, or mediastinal compartments. This system does not take into account the size, number of involved nodes, histology, and presence or absence of extranodal extension. Recent emerging evidence related to these additional findings recommends distinguishing between different types of lymph nodes in the decision-making process, along with whether the nodes are identified in a previously dissected compartment (4). Nonetheless, the proximity of vital structures to the involved nodes will impact on the decision-making process. In addition, the function of the vocal folds and the position of the documented disease as it relates to the recurrent laryngeal nerve (RLN) and/or the vagus nerve must be taken into account.

Potential benefits of lymph node resection

The rationale for, and the potential benefit from, intervention for recurrent/persistent metastatic lymph nodes should be discussed in detail with the patient. Preventing local disease progression in areas of vital structures may be the most rational reason for surgery. Theoretically, there may be benefit derived from removing these nodes to prevent *de novo* distant metastases as well, although this has not been proven. It should be made clear that the surgical removal of metastatic cervical nodes may not produce undetectable Tg levels in as many as 50% of patients, and may have no impact on overall survival (24,40,41).

Age and comorbidities

There are a number of factors that have to be considered for each individual patient related to their comorbidities and overall health. The decision on how to treat recurrent/persistent lymph node metastases may be influenced by these factors and the impact that they have on the patient's life expectancy unrelated to their thyroid condition. Conversely, chronological age should not be factored into the decision to reoperate or not for recurrent or persistent nodal disease, especially since most patients who are at high risk of recurrent/persistent disease tend to be older in age.

Patient motivation and emotional concerns

Patient motivation and emotional concerns related to recurrent/persistent metastatic lymph nodes may critically impact the treatment decision-making process.

Lack of prospective randomized studies

There is a wide range of clinicopathologic presentations that often make for very difficult decisions regarding the management of recurrent/persistent lymph node metastases. This is further complicated by the lack of prospective and randomized clinical trials with long-term follow-up (> 10–20 years) of clinically evident recurrent/persistent lymph nodes that have assessed the outcome of early surgical management versus active surveillance that would provide the best level of evidence upon which to base these clinical decisions.

Biologic factors impacting virulence and likelihood for progression of metastatic nodes

There are a number of biologic factors that are unique to an individual patient's tumor that may affect the responsiveness to various treatments, and the potential aggressiveness and likelihood for progression of recurrent lymph nodes over time. These factors include the following:

(a) Primary tumor factors
- Adverse histology of the primary tumor (tall cell variant, insular, poorly differentiated) is associated with a more aggressive growth pattern and possibility of invasion to adjacent structures.
- The change in Tg levels in the blood, namely a rapid Tg level doubling time (< 1 year and possibly < 3 years) represents a dynamic measure of a tumor's virulence and rate of growth in the absence of other disease (21,42,43).
- The inability of the tumor to concentrate radioactive iodine or produce thyroglobulin.
- The presence of markedly ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)-avid disease.
- Molecular markers for aggressive behavior:

  - ○ The presence of a BRAF (p.V600E) mutation has been associated in many studies with the aggressiveness of PTC (extrathyroidal invasion, lymph node metastasis, and advanced stage) and also with disease-specific mortality when associated with other aggressive features, such as extrathyroidal growth (44,45). BRAF mutation analysis offers a very low positive predictive value (28%) and a high negative predictive value (87%) for disease recurrence, therefore suggesting that BRAF mutation analysis should be used with caution in the clinical management of PTC (46). Positivity for a BRAF mutation also has been associated with the loss of radioactive iodine avidity of recurrent PTC (47–50). RAS mutations are associated with a thyroid neoplasm with a follicular pattern, and have also been reported in poorly DTC (51). The clinical significance of RAS mutations in thyroid cancer is controversial. Some reports show that RAS mutations are associated with tumor aggressive phenotypes and poor prognosis (52,53), while others could not confirm this association (54). Similarly, RET/PTC rearrangements were associated in some reports with lymph node metastasis and extrathyroidal extension (55), and with a better prognosis in other studies (56,57). PAX8-PPARG rearrangements have been associated with multifocality of the tumors and vascular invasion, conferring an invasive potential (5860). Despite this, the consistent detection of PAX8-PPARG rearrangements in benign tumors hinders its value as a diagnostic molecular marker (61).
  - ○ To date, none of these markers have been demonstrated to be clear, independent prognostic indicators, thus preventing their widespread acceptance and utilization in clinical practice.
- Presence of lymphocytic infiltration has been associated with decreased tumor aggressiveness, such as small tumor size and low stage. DTC in the presence of chronic lymphocytic infiltration in the thyroid gland has been associated with better locoregional control, lesser rates of recurrence, and greater overall and disease-free survival (62–66).

(b) Lymph node factors
- Documented stability or change in the size of lymph node(s) on serial imaging studies.
- Presence of direct extranodal extension to the trachea, esophagus, or carotid artery with loss of tissue planes between structures in a previously dissected lymph node compartment on imaging.

(c) Patient factors
- Significant comorbidities that are likely to affect quality of life and life expectancy of the patient independent of the recurrent/persistent DTC at the time of the work-up for recurrent/persistent disease.
- Vocal fold paralysis contralateral to the side of central nodal recurrence (location of node near the only working RLN).
- High-risk surgical comorbidities such as history of extensive neck surgery or external radiation therapy of the neck.

Completeness of index procedure

Every effort should be made from an oncologic standpoint to resect all gross tumor at the initial surgery. The extent of surgery required for recurrent/persistent nodal disease remains uncertain and involves a balance of risk of morbidity from intervention with risk of disease left untreated. The general consensus is that secondary nodal surgery, if performed, should be reserved for therapeutic resection of clinically evident nodal disease. In general, secondary surgery in the central compartment is always reoperative, given prior thyroidectomy, regardless of whether central compartment dissection has been previously performed. Secondary nodal surgery in a previously undissected lateral neck should include levels II–V to maximize nodal yield and possibly reduce recurrence while limiting morbidity to the regional nerve structures (33,67). In reoperative settings, it is recommended that the surgeon dissect only the compartments with clinically identifiable disease (68–70), and adjacent previously undissected compartments (33). However, some authors favor a more extensive approach to include the compartments immediately adjacent to the clinically identifiable disease on oncological grounds, even if previously dissected (41). Regardless, once a nodal compartment level is entered, it should be cleared of any nodal disease to reduce the risk from subsequent dissection in that compartment. Node plucking or berry picking of only the involved nodes is discouraged unless extensive scar prevents otherwise, due to higher rates of persistent disease and morbidity from reoperative surgery (31).

DISCUSSION

The above-delineated principles should be taken into account in deciding how best to manage a patient who has been identified with recurrent/persistent metastatic cervical nodal disease. The following variables (Table 2), derived from these principles, have been identified with the intent of providing a framework for the physician to make thoughtful decisions as to when to consider an operation and when to consider active surveillance. This decision requires a careful consideration of multiple factors, rather than a single one, to formulate the most appropriate and tailored management plan for the patient. There will always be clinical situations that will confound the care, regardless of consideration of the variables proposed in this statement (e.g., patient with RAI-avid nodal disease that otherwise meets criteria for surgery or with FDG-PET-avid nodal disease that meets criteria for observation; metastatic nodal disease in the presence of stable systemic metastases; surgery considered in a compartment previously dissected multiple times, etc.). Nonetheless, the foundation for the management plan in these situations will continue to consist of candid interdisciplinary communication that involves the patient.

Technical Considerations

Reoperative surgery for recurrent/persistent nodal disease has been reported by some to be associated with higher risks of major complications in certain circumstances, including vocal fold paralysis, temporary or permanent hypoparathyroidism, and injury to major neural structures, such as the marginal mandibular branch of the facial nerve, the spinal accessory nerve, the sympathetic trunk, or phrenic nerve. This is mostly due to the technically more demanding

Table 2. Variables to Consider When Deciding How Best to Manage a Differentiated Thyroid Cancer Patient with Recurrent/Persistent Nodal Disease

Variables	*Active surveillance*	*Surgery*
Key considerations		
Absolute size of lymph nodes (any dimension)[a]	≤ 0.8 cm (central compartment) < 1 cm (lateral compartment)	> 0.8 cm (central compartment) ≥ 1 cm (lateral compartment)
Rate of lymph node growth on serial imaging	Minimal/slow (< 3–5 mm/year)	Progressive (> 3–5 mm/year)
Vocal cord paralysis contralateral to the paratracheal nodal basin where the positive lymph node is located (next to only working RLN)	Strongly consider observation if node is stable	Consider surgery if node is increasing in size and expertise for reoperative surgery available
Known systemic metastases	Progressive distant disease outpacing nodal metastasis	Stable distant metastasis, but nodal disease threatens vital structures
Comorbidities for surgery	Yes	No
Invasion into/proximity to critical anatomic structures	No	Yes
Good long-term prognosis	No	Yes
Patient wishes to undergo surgery	No	Yes
Disease likely to be identified intraoperatively	No	Yes
Biological considerations		
RAI-avid[c]	Yes	No (unless other criteria for surgery met)
FDG-PET-avid	No	Yes
Aggressive histology	No	Yes
Extrathyroidal extension of primary tumor	No	Yes
More advanced initial T stage (> 4 cm) and more advanced nodal disease	No	Yes
Extranodal extension (features of nodes at initial surgery)	No	Yes
Molecular prognosticator for aggressive biology (see text)	No	Yes
Surgical technical considerations		
First recurrence in that compartment?	No	Yes
Recurrent or persistent disease in previously formally dissected compartment or multiple dissections in same compartment[b]	Stable disease	Limited/focused dissection if progressive disease and threatening important structures

Each situation refers to one or more overarching principles delineated in the text. We have elected to divide these situations into those in which surgery should be considered and ones in which active surveillance should be considered.

[a]Most authors agree that nodes < 1 cm can usually be observed. However, depending on the unique situation of each patient, it may be reasonable to avoid surgery on nodes as large as 1.5–2 cm in carefully selected patients.

[b]Initial intervention was a formal attempt at central or lateral neck dissection and not just a node plucking or limited retrieval of nodes.

[c]Active surveillance or RAI therapy are both reasonable options if the lymph node metastasis is RAI avid.

DTC, differentiated thyroid cancer; RLN, recurrent laryngeal nerve; FDG, ^{18}F-Fluorodeoxyglucose; PET, positron emission tomography.

dissection of scarred and fibrotic tissue and the disruption of the normal tissue planes and anatomy left by the initial surgery, and in some cases due to the aggressiveness of recurrent/persistent disease (71).

Parapharyngeal/retropharyngeal nodal disease

Of special consideration is the involvement of the parapharyngeal and retropharyngeal lymph nodes. These nodes are rarely involved in DTC recurrences or, even more rarely, upon the initial presentation of disease (72–74). The retropharyngeal space communicates with the parapharyngeal space through a dehiscence of the superior constrictor muscle fascia, thus potentially permitting the spread of metastatic tumor from the retropharyngeal space into the parapharyngeal space, especially in patients with tumors in the superior pole of the thyroid (75). Surgical resection of metastases to the parapharyngeal space is challenging due to the proximity of major vascular and neural structures within the carotid sheath in this region. Dissection of the parapharyngeal/retropharyngeal space carries the risk of injury to a number of neurovascular structures and can lead to profound long-term morbidity in this patient population. These include facial nerve paralysis and hypoglossal and spinal accessory nerve injuries, among others. The decision to operate in this region for nodal metastases must be made in conjunction with surgeons who possess the surgical skill and experience to manage this area. Confirmation of disease in these areas should be attempted when considering surgical resection. Diagnosis is made mainly on the basis of CT (computed tomography) and/or magnetic resonance imaging (MRI), as these studies might suggest the histologic nature of the lesion based on characteristic imaging features (73). CT-guided FNA may also be helpful when trying to determine a management plan for lymphadenopathy in this area (76). Parapharyngeal space nodal metastases from DTC are usually cystic which may cause false negative results on cytology assessment. Therefore, Tg measurement in the FNA biopsy may be a useful technique for examining the presence of nodal disease (77).

Preoperative assessment

When evaluating a patient in the reoperative setting for recurrent/persistent DTC, a comprehensive preoperative assessment is necessary to counsel the patients appropriately, decrease the operative risks associated with these procedures, and reduce the need for further revision surgeries. A detailed history and physical examination should be performed. It is also important to review the previous operative reports to determine the extent of the initial surgery performed and to ascertain if there were any complications associated with the previous surgeries. The pathology report can provide additional information regarding the extent of disease, status of the surgical margins, and preservation of the parathyroid glands. The surgical pathology slides should also be reviewed by a pathologist with experience and expertise in endocrine pathology.

A detailed cranial nerve assessment should be performed including an analysis of vocal fold function before any reoperative surgery. Laboratory testing should include a serum calcium level and an intact parathyroid hormone level, in addition to a serum Tg, anti-Tg antibodies, and TSH level if not previously obtained.

Confirmation of disease

High-resolution ultrasound is the recommended initial imaging modality for the detection of recurrent/persistent nodal disease. Ultrasound-guided FNA biopsy can then be used to confirm the presence of malignancy if an operative intervention is to be planned. It should be recognized that ultrasound is far more operator dependent than cross-sectional imaging studies such as CT and MRI (78), and furthermore these modalities have advantages over ultrasonography in specific anatomic locations (e.g., retrotracheal, retropharyngeal, mediastinal) and clinical scenarios (e.g., invasion into the aerodigestive tract) (33). CT scans with intravenous contrast are better than MRI for evaluation of the central compartment, and lateral neck compartments that were not addressed at the time of the initial lateral neck dissection (41). The presence of fatty tissue harboring lymph nodes can easily be visualized in axial cuts of the CT scan, whereas a lack of a plane between the great vessels and the sternocleidomastoid muscle can suggest previous dissection in that area. Ultrasound and MRI with gadolinium are feasible alternatives to CT for cystic lateral nodes and avoid the potential impact of this study in delaying postsurgical adjuvant RAI scans or therapy if thought to be useful. Fused PET-CT scans are sensitive and specific for radioiodine scan-negative disease and higher Tg levels, especially with TSH stimulation (79). Moreover, PET-positive nodes may portend a worse prognosis (80).

If a nodal dissection is indicated, the recommendation is always to attempt performing a compartmental nodal dissection if possible. Such an approach helps to minimize the chances of nodal persistence and missing the target disease (33). Intraoperative localization of small volume nodal disease may be challenging for the surgeon, especially in previously dissected nodal basins when removing only the metastatic node may be most prudent. Surgeon-performed ultrasound (68), immediate preoperative ultrasound (81), preoperative or intraoperative ultrasound-guided dye (e.g., lymphazurin blue, indigo carmine, methylene blue) (82,83), technetium-99m injection (84), needle localization, preoperative FDG, and ^{131}I treatment with gamma-probe assistance or ultrasound-guided tattooing with a charcoal suspension are strategies that have been reported to help identify nodal metastasis intraoperatively (24,85–88). The value of operating on such small volume disease warranting these localization studies has to be carefully considered.

Technique

Technical surgical considerations for reoperative central compartment dissection include optimal visualization of the entire compartment. Horizontal transection of the sternothyroid and, although rarely necessary, the sternohyoid muscles may assist in exposure if the patient has had multiple surgeries or has a medical condition precluding full neck extension. The sternothyroid muscle can then be transected at its midpoint first medially from the trachea or laterally after identification and protection of the carotid sheath structures with preservation of the ansa cervicalis branch if possible. When elevating the superior and inferior limbs of the sternothyroid muscle from the paratracheal lymph nodes, the surgeon must be sure that all fibroadipose tissue that may lie immediately posterior to the strap muscle is included as part of the central compartment specimen, as metastatic lymph nodes can be adherent to the strap muscles and inadvertently left behind. The surgery can then proceed in a systematic approach to the central compartment (89). Re-approximation of the sternothyroid and sternohyoid muscles would be performed, if possible, at the end of neck dissection as part of the closure.

Because the right RLN loops around the subclavian artery and enters the central compartment away from the tracheoesophageal groove, the right paratracheal lymph nodes can be divided into an anterior and posterior compartment that is separated by the nerve. Recurrent/persistent disease is often localized to the posterior compartment on the right side. Therefore, it is important when performing a reoperation for recurrent/persistent disease in the right central compartment that the right RLN is mobilized and the posterior lymph node compartment removed as part of the dissection. Because the left RLN travels along the tracheoesophageal groove and the esophagus is present immediately posterior to the RLN, dissection of the lymph nodes along the prevertebral fascia and anterior to the left RLN is usually sufficient for the left side.

Preservation of the inferior thyroid artery is also recommended during reoperative thyroid surgery for recurrent/persistent DTC to prevent devascularization of the superior parathyroid glands. Furthermore, some authors have recommended that the superior border of the central lymph node dissection be defined by the inferior thyroid artery and a plane at the level of the cricoid cartilage because metastatic lymph nodes are rarely found cephalad to the artery and this approach minimizes risk of injury to the superior parathyroid glands (90). If recurrent/persistent lymph nodes are present above the inferior thyroid artery, high-resolution ultrasonography is particularly helpful in the reoperative scenario in localizing these metastatic lymph nodes in the absence of a thyroid shadow. Fibrosis and multiple positive lymph nodes in the reoperative central compartment specimen can make identification and confirmation of parathyroid tissue difficult *in situ*. Therefore, after dissection of the central compartment packet, the specimen should be carefully examined for the presence of parathyroid tissue. If a candidate parathyroid gland is identified, a biopsy of the tissue should be performed for histologic confirmation by frozen section histopathologic analysis before reimplantation into muscle. Therefore, in patients with extensive extracapsular lymph node spread and multiple involved lymph nodes, reimplantation must be performed with caution such that the surgeon does not inadvertently reimplant tumor with parathyroid tissue (90). Reimplantation of the parathyroid glands of questionable viability into the sternocleidomastoid muscle at the time of the revision surgery also diminishes the risk of long-term permanent hypoparathyroidism.

In the last two decades, there have been reports of the development of several nonsurgical, image-guided, minimally invasive approaches for the treatment of recurrent thyroid cancer. Percutaneous ethanol injection therapy (91–94), radiofrequency ablation, and laser ablation have each been reported as effective for locoregional control of cancer or for improving tumor-related symptoms in selected patients (94–99). However, these techniques are not without complications and morbidity. When ethanol leaks out of the desired cervical node site, it can be associated with neck pain and, rarely, hoarseness and hypoparathyroidism. One potential complication that is of concern to the authors but has not been discussed in the literature is the potential for significant tissue fibrosis and sclerosis should subsequent surgery become necessary. This is an issue that may need further clarification in the literature prior to widespread adoption of this technique. Thermal injury to surrounding structures has also been reported with ablative techniques (94). Nonsurgical ablation seems likely to have some role in managing recurrent/persistent thyroid cancer. Its specific indications, however, remain to be determined. At present, due to small series reports from single centers, the use of these techniques should be relegated to an alternative therapy category rendered at large medical centers with the most significant experience with these techniques (100).

Recurrent laryngeal nerve invasion

The RLN is one of the most frequently involved structures in patients with locally invasive DTC (101–103). The RLN is most susceptible to invasion along the course of the inferior thyroid artery and near its entrance to the larynx at the cricothyroid junction because of its relative fixation at these positions (104).

Management of the RLN found to be invaded by thyroid cancer at the time of surgery in part depends on the functional status of both the ipsilateral and contralateral vocal fold, the relationship of the tumor to the nerve (adherent vs. encasing), tumor histology, and the overall disease status (presence of distant metastasis or other local-regional disease). Intraoperative electromyographic data may also be helpful in neural management decision making when nerve monitoring is employed.

Generally, if the vocal fold is paralyzed preoperatively and the nerve is suspected to be involved with cancer, en bloc resection of the nerve with the thyroid cancer is indicated. If preoperative vocal fold function is intact, there should be an attempt at preserving the nerve during tumor resection, except if unequivocal nerve invasion is found and the tumor completely encases the nerve. Leaving microscopic disease does not lead to decreased survival or increased loco-regional recurrence as compared to resection of the nerve (105,106). Therefore, a near-complete removal or shaving the tumor off of the nerve is reasonable, when possible. Additionally, in the recent thyroid cancer series by Kihara *et al*. (107), 83% of patients who underwent partial layer resection of the RLN (thickness of the preserved nerve is $<50\%$ of its original size) achieved functioning vocal folds and nearly normal phonation postoperatively. In rare cases of known preoperative paralysis of the contralateral vocal fold, the potential morbidity from sacrificing the ipsilateral nerve with the subsequent need for tracheostomy may justify dissection of tumor off the nerve and then treating with adjuvant therapy rather than resection (108).

Bilateral vocal fold paralysis is a devastating complication that usually requires a tracheostomy to maintain a patent airway. Therefore, it is crucial to preserve at least one functioning RLN if possible. It has been shown that the use of intraoperative nerve monitoring in reoperative settings and during the management of thyroid cancer provides prognostic information regarding the functional status of the nerve during and after resection (109–112). Electrophysiological feedback may also be helpful in making real-time decisions as to whether to preserve a nerve (108).

Table 3. Complications Encountered During Central Compartment Reoperations for DTC Nodal Metastases

		Hypoparathyroidism (%)		*Unexpected vocal fold paralysis (%)*	
Author (reference #)	*Year*	*Temporary*	*Permanent*	*Temporary*	*Permanent*
Farrag (69)	2007	6	0	0	0
Schuff (41)	2008	16	7	1	0
Ondik (122)	2009	11.9	9.5	2.1	6.4
Clayman (116)	2009	22	6	1.5	0
Alvarado (123)	2009	9	0	4	0
Shen (124)	2010	23.6	0.9	4.7	1.9
Erbil (84)	2010	6.5	0	4.3	0
Al-Saif (115)	2010	*	0	0	0
Roh (119)	2011	46.3	4.9	22.2	2.2
Tufano (114)	2012	10	3	0	0
Shah (117)	2012	20	7	2	2
Hughes (113)	2012	9.8	0	0	0
Harari (120)	2012	5.7	1.9	1.9	3.8
Lang (121)	2013	14	0	6	1

*Studies did not comment on specific variables.

Morbidity and Efficacy of Reoperation

The morbidity encountered from reoperative surgery relates directly to the anatomy of the region undergoing dissection, the degree of fibrosis and scarring from prior surgery, the extent of disease requiring resection, and the experience of the operating surgeon. The primary risks of reoperative central compartment dissection include injury to the laryngeal nerves and parathyroid glands, which some authors have demonstrated can be performed without significant increases in risk when compared to primary surgery (113,114). Furthermore, bilateral reoperative central compartment dissection is associated with higher risks of temporary and permanent laryngeal nerve and parathyroid injury than unilateral reoperative dissection (70).

To be able to advise patients on the safety of performing reoperative lymph node dissection in the central compartment and to help physicians formulate their own risk–benefit analysis when considering observation versus reoperation, we have summarized the contemporary series in the literature that have reported the incidence of hypoparathyroidism and vocal fold paralysis (Table 3). The incidence of permanent hypoparathyroidism following reoperative central compartment neck dissection has been reported to range between 0% and 9.5%, with a considerably higher incidence of temporary hypoparathyroidism (up to 46.3%). The rate of transient, unexpected vocal fold paralysis ranged from 0% to 22.2% (average 3.6%). The rate of permanent, unexpected vocal fold paralysis ranged from 0% to 6.4% (average 1.2%). Nonetheless, recent reports have shown that in experienced hands, reoperative central compartment neck dissection can be performed without significant increases in the risk when compared to primary surgery (113,114).

With regard to biochemical absence of disease, recent studies of reoperative surgery for recurrent/persistent DTC have reported a 27% rate of biochemical disease-free status using an undetectable stimulated Tg of less than 0.5 ng/mL criterion, compared with 30–51% and 59–71% using a low (< 1 or 2 ng/mL) stimulated Tg level and a low basal Tg respectively (24,40,41,84,85, 115–118). With regard to absence of clinically detectable disease, regardless of biochemical status, the majority of the studies reported clinically detectable disease-free status rates approaching or exceeding 90% (24,41,68,69,84,115,118). Furthermore, the pre-reoperative Tg status was found to be a significant predictor of the likelihood of post-reoperative disease-free status. Lower pre-reoperative Tg values were associated with a greater chance of disease-free status post-reoperation (40). Nonetheless, appropriate patient counseling regarding reoperative surgery should include a discussion of both biochemical and clinically detectable disease outcome possibilities, in addition to the risks of reoperation.

SUMMARY

The decision on how best to manage individual patients with suspected recurrent or persistent nodal DTC is challenging and requires the consideration of a significant number of variables by members of the interdisciplinary team. This manuscript presents the management principles and variables that should be taken into account when deciding how best to manage a patient with DTC and suspected recurrent or persistent cervical nodal disease.

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