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Current controversies in the management of neck node metastasis in differentiated thyroid cancer

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Abstract

The incidence of nodal metastasis is quite common in well-differentiated thyroid cancer. However, its clinical significance is generally quite minimal. The adverse pathological features need to be recognized. The debate continues over prophylactic central compartment dissection. However, it needs to be re-evaluated in terms of complications of elective procedure. The extent of lateral neck dissection is standardized from level II through level V. Recurrent nodal disease is more likely to be persistent nodal disease. Appropriate preoperative imaging is very crucial. Surgery for recurrent disease needs to be considered based on nodal prognostic factors and location of the disease. The approach of using active surveillance and continuous monitoring is reasonable, especially for recurrence below 1 cm.

Keywords: Thyroid cancer, well-differentiated thyroid cancer, nodal metastasis, active surveillance, continuous monitoring, management

INTRODUCTION

The incidence of thyroid cancer has rapidly risen around the world, particularly in the United States and other countries where incidentalomas are commonly found during routine evaluation of the neck both with clinical examination and imaging studies such as ultrasound, computed tomography (CT) scan, and PET scan. For example, in South Korea, where ultrasound is part of routine oncologic screening evaluation, it



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has risen almost 15 times^[1] Neck node metastasis is fairly common in papillary thyroid carcinomas, with an incidence ranging between 40%-60%^[2,3], however, nodal metastasis does not significantly impact overall prognosis or long-term outcome. Nonetheless, it does have a direct impact on the identification of the disease, surgical procedure and repeated surgical procedures for multiply recurrent neck node metastasis leading to surgical complications rather than overall outcome difference. It should be noted that there is a difference between clinically palpable disease and radiologically identifiable disease or biochemically identifiable disease in the recurrent setup. Biochemically identifiable disease in the recurrent setup has no definite prognostic implication, and small-volume recurrent disease such as that documented on ultrasound or CT scan likewise has very little prognostic significance. Sonographic documentation of 1 cm or less nodal metastasis generally is not of major concern unless it is plastered against the trachea or in the tracheo-esophageal groove directly against the recurrent laryngeal nerve. Bulky nodal metastasis and further recurrences with extranodal spread that may involve the soft tissues in the neck significantly affect long-term outcomes. There are many controversial issues surrounding the management of neck node metastasis, as outlined in [Table 1](#).

In the past, the major controversy in thyroid cancer management revolved around the extent of thyroidectomy: lobectomy versus total thyroidectomy. The focus of debate has now shifted to prophylactic central compartment dissection and the extent of lateral neck node dissection. This controversy likely originated in 2006 when the American Thyroid Association (ATA) guidelines suggested elective prophylactic central compartment dissection in patients with papillary carcinoma^[4]. It was soon recognized that this resulted in an increased number of complications related to temporary or permanent hypoparathyroidism and recurrent laryngeal nerve injury with no definite outcome benefit. In 2009, the guidelines were revised to recommend elective central compartment dissection only in high-risk patients presenting with larger tumors, gross extrathyroidal extension, or aggressive histology^[5]. This is an important paradigm shift with practical implications for the management of neck node metastasis.

DIAGNOSTIC EVALUATION

Clinical examination, evaluating the primary tumor and neck from the high jugulodigastric area to the paratracheal region, is extremely critical. However, there is clearly a difference between clinically apparent disease and disease identified by imaging. The most important imaging studies are ultrasound, ultrasound-guided needle biopsy, CT scan with contrast, MRI, PET scan, and RAI ablative scan. The ultrasound is a key investigation in the evaluation of both primary and neck nodes. The characteristic features of neck nodes which will render the suspicious diagnosis of metastatic thyroid cancer include irregularity, hypervascularity, loss of fatty hilum, extranodal extension, and calcification. Prior to any definitive surgical intervention, it is appropriate to confirm the presence of metastatic disease with an ultrasound-guided needle biopsy. There is considerable interest in thyroglobulin wash in needle biopsy aspirants, high thyroglobulin levels are a clear indication of metastatic thyroid carcinoma. CT scan with contrast is extremely helpful to evaluate certain critical areas such as the jugulodigastric, supraclavicular, and posterior triangle regions, and more importantly, central compartment evaluation including levels VI and VII, retropharyngeal and parapharyngeal lymph node metastasis. Routine ultrasound is unlikely to identify these specific areas and the CT scan with contrast should be an important preoperative investigation. The CT scan will also give a better determination of the extent of the primary disease including the substernal extension and adherence to the surrounding structures such as larynx and trachea^[6,7]. This is more important to localize the extent of the disease in the tracheo-esophageal groove and its adherence to the trachea or the esophagus. While MRI is also an important investigation, the CT scan offers a better perception and clarity of the extent of the disease. CT scan should be performed with contrast and the

Table 1. Controversial issues in the management of neck node metastasis

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- Evaluation - clinical and imaging
 - FNA and thyroglobulin wash
 - When to operate
 - Management strategies
 - Observation and non-surgical approaches
 - Management of recurrence
 - Complications of surgery
 - Follow-up strategy and prognosis
-

concern about iodine in contrast dye is not a major issue as generally it is washed out within a few weeks, at which point radioactive ablation can be performed.

CONTROVERSIES RELATED TO CENTRAL COMPARTMENT

The central compartment has generated considerable debate over the last two decades [Tables 2 and 3]. There are strong supporters and opponents of the elective central compartment dissection when the imaging studies and the ultrasound do not show any obvious metastasis^[8]. It should be recognized that elective central compartment evaluation is extremely important from carotid to carotid area, including the superior mediastinal and thymic region, to see if there is any obvious metastatic disease. Proponents of routine elective central compartment dissection recommend this based on high incidence of central compartment nodal disease (50%-60%), difficulties in the second surgical procedure when patients recur in the central compartment, decisions regarding radioactive iodine when the central compartment nodes are positive, and upstaging of some of these patients. Opponents hold strong contrasting views mainly related to a higher incidence of complications and low overall recurrence rate (2%-3%), which is unlikely to have any major implication with elective central compartment dissection. Proponents also recommend that procedures be performed by experienced surgeons, as the risk of complication is likely to be lower. However, the majority of thyroid surgeries in the United States are still performed by surgeons with limited experience and low-volume surgical practice. Clearly, we are always going to find the difference in the outcome between low- and high-volume surgeons^[9]. It also depends upon the practice of individual thyroid surgeons and individual institutions^[10-13].

EXTENT OF NECK DISSECTION FOR LATERAL DISEASE

The old “berry-picking” operation is no longer advocated, as it removes only gross disease and patients may recur with additional neck node metastasis. The incidence of nodal metastasis at levels Ia,b and Va is rare, so a standard neck dissection which is generally advocated includes levels IIa, III, IV, and Vb. The dissection above the accessory nerve (IIb) is rarely indicated unless there is bulky nodal disease at level IIa^[14]. The reasoning for these modifications in the surgical procedures is to minimize the risk of complications such as accessory nerve injury, phrenic injury, and Horner’s syndrome^[14]. These complications need to be kept in mind prior to considering any aggressive surgical intervention. The classical description of lateral neck node metastasis is modified neck dissection preserving important and vital structures such as accessory nerve, jugular vein, and sternocleidomastoid muscle. A variety of other names are also considered, such as functional neck dissection, selective nodal dissection, jugular node dissection, and compartment-oriented neck dissection. The basic concept of these neck dissections is akin to the removal of lymph nodes from level II-V. Levels VI and VII are already discussed in the central compartment. The risk of thoracic duct injury and chyle leak is mainly much more pronounced on the left side (however, it does also occur on the right side). Chyle leak can be a major complication of neck dissection leading to prolonged hospitalization and continuous wound problems. No firm guidelines are available as to re-exploration for control of chyle leak, however, it may be considered in the early or late postoperative period, especially if the chyle leak is more than 500 cc per day^[15,16]. There now appears to be considerable interest in thoracic duct embolization or transthoracic video-assisted thoracic duct ligation under the expertise of thoracic surgeons.

Table 2. Arguments for elective central neck dissection

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- High incidence of central node metastasis
 - Imaging studies may not be very helpful for the central compartment
 - Future recurrence may be difficult to handle surgically
 - Restaging of the thyroid cancer (stage migration)
 - Consideration of radioactive iodine in some patients with multiple positive nodes
 - Disease-free interval?
 - Decreased recurrence rate
 - Upstaging in patients above 55
 - Safe procedure in experienced hands
-

Table 3. Arguments against elective central neck dissection

-
- Most of these are micrometastasis with no major impact on the outcome or prognosis
 - Intraoperative evaluation is more important than elective nodal dissection
 - Generous frozen section will help to select the patients who will be benefited from central compartment dissection
 - High incidence of temporary and permanent hypoparathyroidism and nerve injury
 - No benefit to survival
 - Unless there are multiple positive nodes (more than 5) no need for radioactive iodine
 - Even if patient recurs, surgical dissection is amenable with similar risks
 - No clear evidence regarding unilateral or bilateral elective central node dissection
 - Most thyroid surgery is not done by high-volume surgeons
 - Conflicting data on survival and decreased recurrence
 - The risk may outweigh the benefit
 - "Primum non nocere" - first, do no harm
-

NON-SURGICAL MANAGEMENT OF NECK NODE METASTASIS

Decisions regarding the management of neck nodes in thyroid cancer are quite complex and, as mentioned earlier, depend upon the extent of disease. It is not uncommon to find a suspicious but unproven small lymph node in the neck. The metastatic disease may be quite small, and it may be very difficult to find. Non-surgical approaches are available, including alcohol injection, as popularized at the Mayo Clinic^[17]. The overall experience with alcohol injection is quite small, however, it has shown some remarkable results in isolated low-risk metastatic thyroid cancers. It remains to be seen what the long-term follow-up of these patients will evidence and whether it has any impact on subsequent surgical procedures. Other modalities which are used anecdotally include radiofrequency ablation, microwave ablation, and laser ablation, although these techniques are used more for benign thyroid pathologies, there appears to be some interest in using them for primary malignant tumors of the thyroid or even metastatic disease, but the experience remains limited around the world. A non-surgical approach is advised in small lymph nodes, which may be difficult to find during surgery, and if not in close proximity to vital structures, could be monitored, as per active surveillance. This requires detailed imaging studies with ultrasound and cross-sectional imaging with continuous monitoring and repeat imaging in 9-12 months.

PROGNOSTIC INDICATORS IN THE NECK NODE METASTASIS FROM THYROID CANCER

The publication by Randolph *et al.* has described the risk of recurrence and prognostic factors in nodal metastasis, starting from the lowest risk of recurrence to the highest risk of recurrence^[18]. One of the most important prognostic factors is the number of lymph nodes removed and the number of positive nodes - lymph node density or lymph node ratio. The metastatic number of lymph nodes of more than 10 is considered to be at high risk for future recurrence. The ATA in the 2015 guidelines used 5 as a cut-off between low- and intermediate-risk nodal metastasis^[19]. The size of the metastatic focus is also important and again ATA used 2 mm as a cut-off. The size of the nodal metastasis is also important [Table 4]. Nodal metastasis greater than 3 cm is considered to be prognostically concerning, as is extranodal extension. Patients with major extranodal extension will have soft tissue extension into the surrounding tissues, which has a high risk of future recurrence. Aggressive histology (e.g., tall cell, insular, hobnail, columnar, and

Table 4. Extent of metastatic disease in neck nodes from papillary cancer of the thyroid

| Type | Import on outcome |
|--------------------------------|--|
| Micrometastasis | None |
| Mini metastasis (by U/S of Tg) | None |
| Minivolume metastasis | None |
| Large volume metastasis | Maybe (regional or distant) |
| Major metastasis | Yes, in older patients (regional or distant) |

poorly differentiated) is another important prognostic factor. These patients generally do not respond very well to radioactive iodine and there may be a high incidence of recurrent disease. If in the central compartment, more than 11 lymph nodes are removed, that is a satisfactory surgical procedure, and if the positivity rate is between 20%-50%, it is also considered to be satisfactory. A positive ratio of more than 65% is considered to be a high risk for future recurrence. There are compelling recent reports about BRAF positivity in the lymph nodes and a high risk of future recurrences^[20]. Again, the data is quite limited, and further studies are needed to determine which molecular markers are of high risk, however, at this time, BRAF and TERT mutation are considered to be of high risk.

FOLLOW-UP OF PATIENTS WITH NODAL METASTASIS

Patients who have undergone previous surgery for multiple positive nodes need to be monitored very carefully. Appropriate follow-up comprises blood tests (including thyroglobulin, which is a good tumor marker for well-differentiated papillary cancer), ultrasound performed on a serial basis, and cross-sectional imaging with CT scan. As mentioned previously, cross-sectional imaging is quite helpful for the evaluation of paratracheal, superior mediastinal, retropharyngeal, and parapharyngeal lymph nodes. The areas where lymph nodes are generally missed during initial surgical procedure are jugulodigastric, retropharyngeal, and parapharyngeal areas, as well as superior mediastinal lymph nodes in the deep paratracheal region below level VI and VII or retro jugular lymph nodes. These patients would be best followed on a regular basis both by the endocrinologist who is monitoring the long-term outcome of patients with thyroid cancer and the surgeon who has performed the initial surgical procedure and neck dissection. In patients presenting with rising thyroglobulin and no obvious structural disease, FDG PET scan will be helpful to highlight any obvious recurrent disease.

COMPLICATIONS OF NECK DISSECTION

Even though neck dissection is quite safe in thyroid cancer, there are certain complications specifically related to neck dissection [Table 5]. These complications can be disturbing to the patient. The main complications are related to accessory nerve injury leading to shoulder disability. This is the main reason to avoid skeletonizing the entire accessory nerve. The dissection above the accessory nerve at level IIb is generally not indicated unless there is bulky disease at level IIa. Postoperative minor disability related to stretching of the nerve may be improved with appropriate physiotherapy. Injury to the phrenic nerve may lead to diaphragmatic dysfunction, and in older patients, it may lead to respiratory issues. The risk of recurrent laryngeal nerve injury and hypoparathyroidism is much higher in patients undergoing thyroidectomy with neck dissection. If the jugular vein is directly involved, resecting the jugular vein on one side does not have a major impact. However, simultaneous resection of both jugular veins is best avoided, as the morbidity and mortality can be quite high. The major risk of neck dissection revolves around the injury to the thoracic duct or its tributaries. At the conclusion of the procedure, the surgeons should check for any chyle leak with Valsalva maneuver along with pressure on the abdomen to increase intrathoracic pressure^[15]. If the chyle leak could be identified, it would be important to tie these lymphatics or use hemoclips to avoid further tearing of the lymphatics. If the chyle leak is identified with a large volume

Table 5. Tips and tricks for neck dissection in thyroid cancer

-
- Review preoperative imaging very carefully - CT/MRI/Ultrasound
 - Review thyroid bed and paratracheal area
 - Preoperative status of vocal cords and calcium levels
 - Necklace incision
 - Identify accessory nerve, but no need to skeletonize or dissect above the accessory nerve
 - Look for jugulodigastric nodes
 - Avoid dissection on the surface of submandibular salivary gland
 - Look for supraclavicular and retrojugular node
 - Look for pre- and paratracheal nodes
 - Avoid lymphatic injury - chyle leak, chyloma
-

Table 6. Recurrent thyroid cancer - decision octagon

-
- Undetectable
 - Detectable
 - Actionable
 - Prognosticating
 - Critical location
 - Complications of surgery
 - Opportune time for surgery
 - Close monitoring - recurrence may lead to further detection of recurrence
-

drainage on day 1 or 2, the patient may be returned to the operating room to control the chyle leak. However, the majority of the leaks may not be identified and early and surgical exploration after a few days may be difficult due to intense inflammatory response. Patients may be treated with low-fat diets and rarely by total parenteral nutrition. Sandostatin may be of some help to reduce the amount of chyle leak. If the chyle leak continues for an extended period of time, one may consider transthoracic video-assisted thoracic duct ligation with expertise from the thoracic surgeon. One may consider thoracic duct embolization with the help of an interventional radiologist. However, such expertise may not be available in every center. One may consider the use of vascular sealants in the operating room. However, the experience appears to be quite limited at this time.

RECURRENT THYROID CANCER

The majority of recurrences in the neck are truly persistent diseases primarily related to underestimation of the extent of the disease during the first surgery [Tables 6 and 7]. This is directly related to the lack of thorough preoperative evaluation with ultrasound and CT scan. There is always a concern about the extent of central compartment dissection if the surgeon notices an obvious metastatic disease in this area. The contralateral central compartment is routinely not dissected but should be evaluated thoroughly with appropriate frozen sections if indicated. Recurrent disease is fairly common in patients presenting with bulky nodal disease. Even though radioactive iodine is expected to help microscopic metastatic disease, its role in gross metastatic disease remains unclear and surgical intervention would be the best undertaking. The diagnosis of recurrent disease is made by rising thyroglobulin and a good ultrasound. The exact location and extent of the disease are best determined with cross-sectional imaging by CT scan. If the lesion appears to be less than 1 cm and not plastered against the trachea, it would be best to monitor such patients and only intervene if there is a major increase. A fine-needle aspiration is best avoided below 1 cm, as finding such disease may be quite difficult during re-operative surgery and clearly at higher risk of nerve injury. If the disease continues to grow, a targeted surgical resection with appropriate neuromonitoring should be considered. Patients should be informed that there is always a risk of future recurrence even with excellent surgical procedures, either in the same neck, central compartment, or opposite neck. There may be some use of intraoperative ultrasound if the disease cannot be localized. The commonest areas where the disease is left behind are the high jugulodigastric region, retrojugular area, or deep in the superior

Table 7. Risk of recurrence

| Modified 2009 risks | Risk of recurrence |
|---|---------------------------------|
| High risk Gross extrathyroidal extension, incomplete tumor resection, distant metastases, or lymph node >3 cm | High risk 50% |
| Intermediate risk Aggressive histology, minor extrathyroidal extension, vascular invasion, or > 5 involved lymph nodes (0.2-3 cm) | Intermediate risk 20% |
| Low risk Intrathyroidal DTC ≤ 5 LN micrometastases (< 0.2 cm) | Low risk 5% |

Table 8. Factors affecting management of recurrent nodal disease

| |
|---|
| <ul style="list-style-type: none"> • Time of recurrence • Location of recurrent disease • Size of recurrent disease • Doubling time • Surgical complications • Patients' wishes and anxieties |
|---|

Table 9. Localization of recurrent thyroid cancer

| |
|--|
| Preoperative imaging - Ultrasound, ultrasound-guided fine-needle aspiration - Cytology - thyroglobulin wash - CT with contrast - MRI - PET scan - RAI Preoperative - Ultrasound on the operating table Intra-operative - Charcoal - Methylene blue - Guide wire - I 131 probe - PET probe - Intraoperative ultrasound - Radio guidance Postoperative - Follow-up U/S & imaging studies |
|--|

Table 10. Ten commandments in the management of recurrent thyroid cancer

| |
|---|
| <ol style="list-style-type: none"> 1. Evaluate the initial surgical procedure and the reasons for recurrence 2. Evaluate the extent of the disease, biology of the disease, and vocal cord evaluation 3. If possible, discuss with the previous surgeon about first operation- timing of recurrence. 4. Appropriate imaging- US localization, CT with contrast, and PET scan 5. Be prepared to manage the patient now from A to Z 6. Observation for small tumors is a good choice 7. Work in a multidisciplinary group-may need adjuvant RT 8. Intraoperative monitoring of recurrent laryngeal nerve-parathyroids 9. Start the surgery from a non-dissected area- altered anatomy due to scarring and fibrosis 10. Monitor the patient for future recurrence and appropriate treatment <ul style="list-style-type: none"> • Don't miss the boat • Avoid multiple operations, second, third, and fourth-make it one complete operation |
|---|

mediastinum. Finding small-volume disease in the supraclavicular area may be quite difficult due to extensive vascularity and fear of injuring the pleura. Certain alternate non-surgical approaches may be considered in selected patients, such as continuous monitoring, active surveillance, and ethanol injection. The experience with radiofrequency ablation appears to be limited at this time for nodal metastasis. There is a sizeable experience from Mayo Clinic with alcohol injection. However, it does require sonographic expertise. [See [Tables 5-10](#)].

CONCLUSION

Management of neck node metastasis in thyroid cancer is quite controversial and depends on the individual practice of the surgeon and the institution. Even though nodal metastasis has minimal impact on the long-term outcome, certain features of nodal metastasis are important, such as the size of the nodal metastasis, number of positive nodes, and lymph node ratio. It is very important to avoid complications during appropriate neck dissection.

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