



Sub-centimetric recurrent and persistent metastatic lymph nodes in well-differentiated thyroid cancer: Operate or observe?

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Abstract:

Differentiated thyroid carcinoma (DTC) constitutes > 90% of all thyroid cancers and is generally associated with a very good prognosis due to effective surgery and adjuvant therapies. The overall survival (OS) rate at 10 years is reported to be 80 to 94%. Despite an excellent prognosis, locoregional recurrences are common and warrant lifelong follow up. Locoregional recurrence is a significant cause of morbidity among DTC patients. Various studies have reported that mortality in DTC patients is directly related to loco-regional recurrence. Optimal treatment for the management of recurrent/persistent lymph nodes in DTC is still debatable, especially for low volume disease. Modalities available for treatment are either surgery/ and RAI or observation. Local ablative therapies like alcohol ablation and radiofrequency ablation are also being used by various groups. The contentious issue is recurrences of less than one centimeter. Follow up with Tg/ATg and USG neck is a reasonable alternative to surgery as finding subcentimetric lymph node in scarred tissue is particularly difficult even in expert hands.

Keywords: Differentiated thyroid cancer, Metastatic lymph node, lymph node dissection, recurrent lymph node, persistent lymph node

Core tip: There are several reviews in the literature on the management of persistent or recurrent central/ lateral compartment lymph nodes in a follow-up patient of differentiated thyroid carcinoma. However optimal management of sub-centimetric recurrent/persistent lymph nodes is still debatable due to lack of randomized controlled trials. In this mini-review, we have tried to summarize the most appropriate management strategy based on currently available literature.

Introduction:

Thyroid carcinoma is the most common endocrine malignancy [1]. Differentiated thyroid carcinoma (DTC) is the most common entity comprising > 90% of all thyroid cancers[2]. DTC has generally a very good prognosis due to effective surgery and radioactive iodine therapy [3]. Overall survival (OS) rate at 10 years in both low-risk and high-risk groups of papillary thyroid carcinoma (PTC) has been reported to be 94 and 62% respectively[3,4]. The OS is somewhat lower for follicular thyroid cancers (FTC) but still is 80 and 54% for low and high risk groups respectively. Mazafferri et al. have reported long term recurrence rates of DTC patients [5]. 40-yr recurrence rates were about 35%, two-thirds of which occurred within the first decade after initial therapy. Local (or locoregional?)disease comprised 68% of

the recurrences in their study and the 30-yr cancer mortality rate was twice as high with recurrence in the neck soft tissues (30%) compared with those in cervical lymph nodes or the contralateral thyroid (16%) [5]. The overall recurrence rate was reported to be 26% by Shaha et al [6]. The overall local, regional, and distant recurrences were 10%, 13%, and 13%, respectively. Recently Kim et al.[7] from Korea reviewed the recurrence pattern in 2250 patients with PTC larger than 1 cm who achieved complete remission after total thyroidectomy and/or radioactive iodine treatment. During 8.1 years of mean follow-up, 68 (3.0%) patients developed structural recurrences: 53 lymph node recurrences (LNR), 11 local soft tissue recurrences (LR), and 4 distant recurrences (DR). Locoregional recurrence was most common in 70.9%, distant in 16.5%, and both sites in 12.7% of patients with DTC recurrence in a study by Anjali Mishra et al. [8]. Various studies have reported that mortality in DTC patients is directly related to locoregional recurrence[9,10,11,12].

As we can see, locoregional recurrence is a significant cause of morbidity among DTC patients. The management of larger lymph node recurrences (>8-10 mm) is more or less standardized but the management of sub-centimetric central compartment lymph node(CCLN) and/or lateral compartment lymph node(LCLN) is contentious with a number of available therapeutic options, including observation. In this mini-review, we present an optimal management strategy based on currently available literature.

Predicting the recurrence:

AJCC staging system does not predict the risk of recurrence accurately. The overall recurrence rate in AJCC stage II is higher than AJCC stage III, 51% and 37% respectively[4]. American thyroid association's initial risk stratification system is more accurate in predicting recurrence. The rate of recurrence is 14% for low risk, 44% for intermediate-risk and 87% for high risk[13]. Apart from this, older age (>45 years), larger tumor (>2-4 cm), extrathyroidal extension, cervical node metastases, especially if extensive, distant (extracervical) metastases, aggressive histological subtypes (tall cell, insular, columnar cell, Hürthle cell carcinoma, follicular thyroid cancer and hobnail variant) and presence of BRAF mutation are associated with higher recurrence rates[14,15].

Diagnosis of Lymph Node Recurrence:

ATA guidelines for the management of DTC

recommends that thyroglobulin (Tg) should be measured every 6-12 months by an immunometric assay and ideally in the same lab, the same assay along with ATg antibodies [16]. Hyperthyroglobulinemia after initial treatment (surgery with or without RAI) is generally an indication of recurrent thyroid cancer. High-resolution ultrasonography of the neck (HRUSG Neck) is the most sensitive radiological investigation for anatomical evaluation of regional LN and the thyroid bed. High resolution 7.5-10 MHz transducer can detect tumor deposits of as small as 2 mm in bed and lymph nodes (LN) [17]. Any lymph node of size more than 7mm in shortest diameter with hyperechoic punctuations or microcalcifications in context of of DTC should be considered metastatic because they seldom exist in metastatic LNs from other cancers [17].Functional scanning with I-131 or I-123 is another option. With oral use of 2-5 mCi of I-131, the neck can be visualized in 24 hrs [18].

Cross-sectional imaging of the neck and upper chest (CT, MRI) with IV contrast should be considered if bulky and widely distributed recurrent nodal disease, potential aerodigestive tract invasion, when neck US is felt to be inadequately visualizing possible neck nodal disease (high Tg, negative neck US)[16].

The 18F-FDG PET scan appears to be a significant investigation tool in the follow-up of patients with raised serum TG and negative whole body RAI scan or aggressive histologies [19].If value of Tg is <10 ng/ml FDG-PET should not be performed due to low sensitivity (10%-30%) and high risk of false-positive results, however in an aggressive variant of DTC and increasing titer of anti-Tg Ab, cutoff may be lowered[20]. Tg values >100 ng/ml18F-FDG PET should be done and TSH stimulation is not necessary. Tg values 10-100 ng/ml, FDG-PET should be performed after adequate TSH stimulation (TSH > 20 U/L) for optimal response [20].18F-FDG PET should also read in conjunction with standard uptake value (SUVmax), higher the SUVmax more metabolically active the lesion.

Management of Lymph Node Recurrence:

Optimal treatment for the management of recurrent lymph nodes in DTC is still debatable, especially for low volume disease. Modalities available for treatment are either surgery, RAI or observation. Local ablative therapies like alcohol ablation, radiofrequency ablation are also in use by various groups. Contentious issue is recurrences less than one centimetre. After extensive search of literature we could not find any randomized controlled trials

on this subject. Studies on subcentimetric lymph nodes are very few. Robenshtok et al.[21] followed up 166 patients with low-risk thyroid cancer with an abnormal lateral compartment node with an average follow up of 3.5-year. 22% of these patients underwent biopsy prior to the decision to observe. They reported progression by 3 mm or more in 20%, by 5 mm or more in 9% and 14% spontaneously resolved without any treatment. One major limitation of their study is 78% of the patients not undergoing a biopsy, the exact number of patients who had lymph node metastases difficult to interpret. Similarly Rondeu G et al.[22] followed up 191 patients with at least one thyroid bed (TB) nodule (≤ 11 mm) on the first postoperative US performed with median clinical follow-up of 5 years. Only 9% (17/191) of patients had increase in size of at least one TB nodule. The rate of growth was 1.3 mm/year in those nodules showing an increase in size. According to ATA guidelines surgical resection ideally should be considered in case significant (shortest diameter in central neck compartment ≥ 8 mm and lateral ≥ 10 mm) large lymph node or increasing in size of more than 3-5 mm in any dimension [16]. Ito et al.[23] have evaluated the impact of recurrence on prognosis and they concluded that aggressive histology, the size of the primary lesion and of the lymph node metastasis, and age at recurrence independently affected the prognosis of patients showing initial recurrence to the lymph node. Hence sub-centimetric lymph node recurrence may not impact overall

survival but further studies are needed to confirm it. Osman al saif et al.[24] have reported a positive outcome on biochemical complete response (BCR) after lymphadenectomy in patients with recurrent metastatic lymph nodes. Surgical resection of persistent PTC in cervical lymph nodes achieved BCR in 27% of patients and in patients who do not achieve BCR, Tg levels were significantly reduced. This study makes a strong point in favour of surgery. Surgeon should always keep in mind the difficulty of finding sub-centimetric lymph and challenges due to scarring and fibrosis. Also there is high risk of RLN injury and parathyroid injury [25,26]. Incidence of transient vocal cord paralysis is reported to be around 0%-15% and permanent paralysis in 0%-6%. The incidence of permanent hypocalcemia is also high ranging between 0% and 10%, and of transient hypocalcemia between 10% and 60% [25,26]. All these facts should be kept in mind while planning reoperative surgery. A recurrence in CC/LC in a case where the same region was dissected is not the same as recurrence in an undissected space. Lamartina et al. [27] reported suspicious lesions located in neck areas not previously dissected in 66 patients (41%), in previously dissected areas in 70 (43%) patients, and in both dissected and not previously dissected areas in 25 patients (16%) in a series of 161 patients. Surgery in undissected space is comparatively easier and may be a better alternative to watchful observation as the cost of observation is significantly higher in addition to patient anxiety.

Flow chart below depicts the management strategy.

