Residual lymph-node metastases are relatively common in patients with high-risk PTC, who often have non-avid ^{131}I metastases

Kaneko K, Abe K, Baba S, Isoda T, Yabuuchi H, Sasaki M, Hatakenaka M, Honda H. Detection of residual lymph node metastases in high-risk papillary thyroid cancer patients receiving adjuvant I-131 therapy: the usefulness of F-18 FDG PET/CT. Clin Nucl Med 2010;35:6-11.

SUMMARY

BACKGROUND

This is a retrospective study aimed at evaluating the incidence of residual lymph-node metastases in patients with high-risk papillary thyroid cancer (PTC).

METHODS

The study subjects comprise a total of 37 patients who were treated with adjuvant radioiodine (^{131}I) therapy in the Department of Clinical Radiology in Kyushu University in Japan from 2006 through 2008. Excluded from the study were patients with tumor recurrence, distant metastases, or any other uncontrolled malignancy. Of the 37 patients, 13 were men (35%) and 24 were women (65%). The mean age was 52 years (range, 21 to 72); 10 patients were <45 years (27%) and 27 (73%) were ≥45 years. All patients had one- or two-stage total thyroidectomy, and neck-lymph-node dissection was performed in all patients. The lymph-node dissections included the central compartment (level VI) in 10 patients (27%), the lateral neck compartment in 25 patients (68%), the bilateral lateral compartment in 2 patients (5%), and the mediastinal lymph node in 2 patients (5%). A total of 23 patients (62%) were treated with ^{131}I (first treatment) and the remaining 14 (38%) had ^{131}I therapy 1 year after initial ^{131}I therapy (second treatment) to eliminate the thyroid remnant or malignant tissue. Patients were prepared for ^{131}I therapy with thyroid hormone withdrawal, which increased the mean (±SD) thyrotropin (TSH) to 151±79.8 mIU/L. Patients were treated with 100 to 122 mCi of ^{131}I. The initial ^{131}I therapy was given within 6 months of surgery (range, 1 to 6; mean, 3) to all patients.

RESULTS

Study Patient Characteristics (Figure 1)

A total of 33 residual lymph-node metastases (range, 1 to 14 per patient) were found in 9 patients (24%). Metastases were diagnosed by histology in 18 lesions (55%), by computed tomography (CT) in 6 (18%),, and by positive ^{131}I whole-body scan (WBS) in 14 (42%). (Some lymph-node metastases were identified by more than one imaging method). Of the 9 patients with lymph-node metastases, 7 (78%) were in the initial ^{131}I therapy group and 2 (22%) had second ^{131}I therapy. Five lesions were diagnosed by CT and also had positive ^{131}I WBS and one lesion was identified only by CT, showing an increase in size on the CT obtained 11 months after the initial ^{131}I therapy (Figure 1).

Characteristics of Lymph-Node Metastases (Figure 2)

Of the 33 residual lymph-node node metastases, 22 (67%) were located in the lateral neck (13 in the ipsilateral neck (33%)and 9 in the ipsilateral contralateral area(27%, 1 in the contralateral retropharyngeal region, 5 in the supraclavicular region, and 5 in the upper mediastinum.

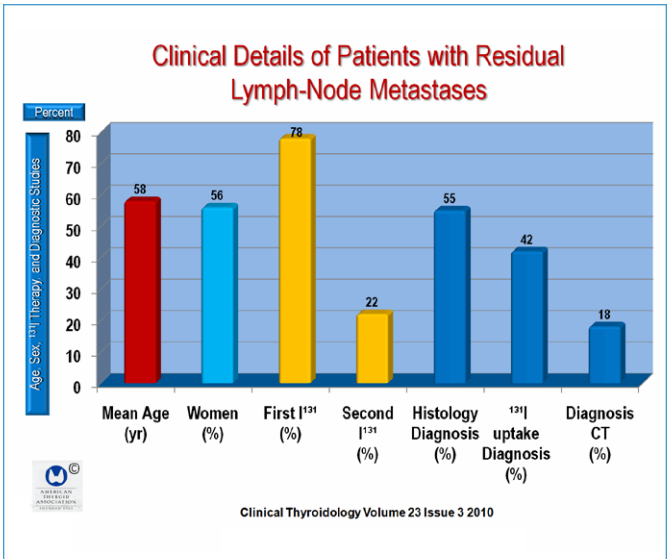

Figure 1. This figure shows the clinical details of patients with residual lymph-node metastases treated with adjuvant ^{131}I therapy. The most sensitive imaging studies in this setting is FDG CT/PET scans.

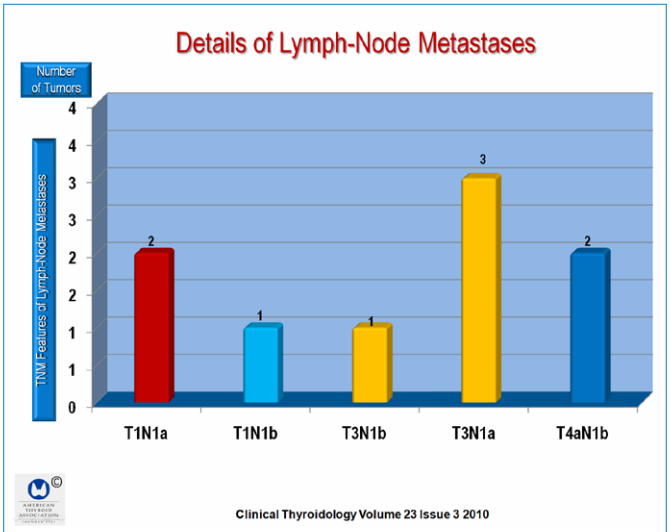

Figure 2. This figure shows the tumor–node–metastases (TNM) staging of residual tumors in this study. A T1N1a is a tumor ≤2 cm with metastases to level IV and prelaryngeal/Delphian lymph nodes. A T1N1b is a similar tumor that has metastases to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph-node metastases. A T3N1b is a tumor >4 cm that is limited to the thyroid or any tumor with minimal extrathyroid extension to sternothyroid muscle or perithyroid soft tissues. A T3N1a tumor is the same size and level of lymph-node metastases as noted above. A T4aN1b tumor is a primary tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.

Abnormal fluorodeoxyglucose (FDG) accumulation was found in 100% of the 33 lymph-node metastases, and the standardized uptake value was significantly higher in lesions without ^{131}I accumulation as compared with lesions that had ^{131}I uptake (6.6±2.8 vs. 4.2±1.8; P = 0.007). Serum thyroglobulin (Tg) levels were significantly higher in patients with residual lymph-node metastases, as compared with patients without lymph-node metastases (709±1470 vs. 25.6±37.1 ng/ml, P = 0.005). Serum Tg concentrations were significantly higher among patients with residual lymph-node metastases as compared with patients without lymph-node metastases (35% vs. 0%, P = 0.03)

CONCLUSION

Residual lymph-node metastases are relatively common in patients with high-risk PTC, despite being treated with adjuvant ^{131}I therapy, which is often caused by metastases that do not accumulate^{131}I. Non–iodide-avid tumors usually accumulate FDG, making CT/positron-emission tomography (PET) scans a highly sensitive means of identifying residual tumors that do not concentrate ^{131}I.

COMMENTARY

Residual lymph-node metastases are relatively common in patients with high-risk PTCs that often do not respond to adjuvant ^{131}I therapy because the tumors have a pattern of non-avid ^{131}I uptake and aggressive tumor recurrences. These tumors often harbor a BRAF mutation, which is most common in tall-cell PTÇs, is second most prevalent in classic PTC, and is least common in follicular variant PTC (1,2).

A comprehensive series of studies by Xing et al. (2,3) found a significant association between BRAF mutation and extrathyroidal tumor invasion (P<0.001), lymph-node metastasis (P<0.001), and advanced tumor stage (P = 0.007) at the time of initial surgery. They found that during a 15-year follow-up, BRAF mutation is significantly associated with tumor recurrence rates, with 25% recurrence with BRAF mutation versus 9% without BRAF mutation (P = 0.004). Xing et al. found on multivariate analysis that conventional predictors of recurrence, including the PTC subtype (odds ratio, 4.0; 95% confidence interval, 1.1 to 14.1; P = 0.03), are significant independent predictors of recurrence. BRAF mutation was even an independent predictor of recurrence in patients with stage I or II tumors (22% with vs. 5% without BRAF mutation; P = 0.002). BRAF mutation was also more commonly associated with non-avid ^{131}I tumors and treatment failure with recurrent disease. Thus, BRAF mutation in PTC is associated with poorer outcomes and independently predicts recurrence. It is likely that what Kaneko et al. are describing are BRAF-positive tumors.

Kaneko et al. report that many of the lymph-node metastases in their series were not recognized on ^{131}I whole-body scans, but were uniformly identified by 18FDG-CT/PET. This is in accord with the ATA thyroid cancer guidelines suggesting that 18FDG-CT/PET studies are particularly useful in the initial staging and follow-up of high-risk patients with poorly differentiated or metastatic tumors, which may be missed with ^{131}I scanning and conventional imaging. This approach is widely accepted and is especially well suited in patients with high-risk PTCs (4-6). Levothyroxine therapy does not influence 18FDG-CT/PET studies, and the positive results often correlate with high Tg levels. The 18FDG-CT/PET results are even more sensitive when recombinant human TSH is given prior to the scan (5).

The observations by Kaneko et al. are in accord with many studies that find that lymph-node metastases are relatively common in patients with high-risk PTC, despite receiving adjuvant ^{131}I therapy, especially when serum Tg levels are high after surgery and ^{131}I therapy has been performed. Also, the finding by Kaneko et al. that high-risk PTCs often have lymph-node metastases that fail to concentrate ^{131}I despite adequate preparation is also in accord with most studies. PTCs that display aggressive growth and resistance to initial therapy are often the sign of a BRAF mutation.

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