

Evaluation of the response levels of non-metastatic thyroid cancer patients in the postoperative twelfth month

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Abstract

Objective: Radioactive iodine (RAI) is used to ablate residual thyroid tissue after total thyroidectomy. The aim of this study was to evaluate the response according to the 12th-month results of thyroid cancer patients and to investigate the changes in response level during follow-up.

Materials and Methods: The study included 97 patients, comprising 88 (90.7%) females and 9 (9.3%) males, with a mean age of 41.68 ± 13.25 years. None of the patients had lymph node or distant metastasis and all received RAI therapy. Thyroid-stimulating hormone (TSH), thyroglobulin (TG), and anti-TG levels and neck USG were examined in the 12th-month. Response to therapy was evaluated as an excellent response, biochemical incomplete response, structural incomplete response, or indeterminate response.

Results: In the 12th month, 80 patients (82.47%) had excellent response, 13 patients (13.40%) had an indeterminate response, 3 patients (3.09%) had structural incomplete response and 1 patient (1.03 %) had biochemical incomplete response. Of the 80 patients with excellent response, 15 had no follow-up after the 12th month. The remaining 65 patients were followed up for 31.11 ± 9.58 months. The response changed to indeterminate in the 18th month in 1 (1.54%) patient, and to structural incomplete response in the 35th month in 1 (1.54%) patient. The 13 patients with indeterminate responses were followed up for 20.61 ± 6.28 months.

Conclusion: The TG level at 12th months provides accurate data about the course of the disease especially in patients with excellent response. Patients with excellent response in the 12th month may be followed up less often and those with indeterminate or incomplete response should be followed up more often.

Keywords: thyroid cancer, iodine radioisotopes, thyroglobulin

Introduction

Thyroid cancer is the most common endocrine malignancy. Differentiated thyroid cancers, papillary and follicular thyroid cancers, account for more than 90% of all thyroid cancers (1). Surgery is the cornerstone in the management of thyroid cancer with ablative RAI as an adjuvant treatment in selected cases based on the risk of recurrence and disease-specific mortality. In recent years, the rate of total thyroidectomy has increased. Preoperative investigation of patients with thyroid cancer with high-resolution ultrasound imaging has led to an increase in the detection of contralateral nodules identified preoperatively, resulting in total thyroidectomy instead of lobectomy, regardless of the histological status of the contralateral thyroid nodule (2).

Radioactive iodine-131 (RAI-131) is used in the treatment of differentiated thyroid cancer.

RAI and thyroid hormone suppression are complementary to surgery as the primary treatment modality (3).

Thyroid cancer does not accumulate iodine to the same degree as functional thyroid cells do. Serum TSH levels are increased to maximize RAI uptake in thyroid remnants and to ablate malignant cells with postoperative ablative therapy (4). RAI whole-body scan and serum thyroglobulin measurements are used to detect local recurrences and distant metastases. Therefore, the ablation of thyroid remnants after total thyroidectomy increases the sensitivity and specificity of RAI whole-body scan and thyroglobulin measurements (5).

The aim of this study was to evaluate the response, by examining neck USG, TG, and anti-TG levels after surgery and RAI therapy during a 12-month follow-up period.



Materials and Methods

The study included a total of 97 patients, comprising 88 (90.7 %) females, and 9 (9.3%) males, with a mean age of 41.68±13.25 years (range, 15-75 years). All the patients received RAI therapy after surgery and none of the patients had lymph node or distant metastases. Surgery was applied as total thyroidectomy, and RAI therapy was given one month postoperatively. Multicentric tumors were determined in 23 patients. The diameter of the tumors was 15±0.64mm (7-40 mm). Seven patients had 50 mCi, 13 patients 75 mCi, and 77 patients 100 mCi. The patients were followed up at 1, 3, 6 and 12 months, with the 12-month results of serum thyroid-stimulating hormone (TSH), thyroglobulin (TG), and anti-TG levels analysed in this study together with neck USG examination.

Response to therapy was classified as an excellent response (negative imaging and either suppressed TG <0.2 ng/mL or TSH-stimulated TG <1 ng/mL), biochemical incomplete response (negative imaging and suppressed TG ≥1 ng/mL or stimulated TG ≥10 ng/mL or rising anti-TG antibody levels), structural incomplete response (structural or functional evidence of disease with any TG level with or without anti-TG antibodies) or indeterminate response (non-specific findings on imaging studies, faint uptake in the thyroid bed on RAI scanning, non-stimulated TG detectable but <1ng/mL or anti-TG antibodies stable or declining in the absence of structural or functional disease). These criteria can be used at any point during the follow-up of patients (6, 7).

Results

The mean TSH level was 0.55±1.41 µIU/mL at 12 months. The TG level was unmeasurable in 82 patients, and mean 1.13±1.79 ng/mL (min:0.26, max:7.53) in the other 15 patients. The anti-TG level was unmeasurable in 95 patients, and 30.30 and 30.50 IU/ml, respectively in the other 2 patients. After 15 months, the anti-TG level became unmeasurable in 1 of these 2, and in the other, the neck USG and RAI whole-body scintigraphy were clear for residue, recurrence or metastases in the 12th month. In the 20th month when the TSH level was 0.05, the TG level was 1.97 ve anti-TG level was unmeasurable and the patient was evaluated as biochemical incomplete response. In the 12th month, 80 patients (82.47%) had excellent response, 13 patients (13.40%) had indeterminate response, 3 patients (3.09%) had structural incomplete response and 1 patient (1.03 %) had biochemical incomplete response. Of the 80 patients with excellent response, 15 did not have follow-up after the 12th month. The remaining 65 patients were followed up for 31.11±9.58 (min: 18, max: 54) months. In 1 patient (1.54 %) the response was evaluated as indeterminate response in the 18th month and in 1 (1.54%) as structural incomplete response in the 35th month. The 13 patients with indeterminate response were followed up for an extra 20.61±6.28 (min:15, max:40) months. During this follow-up period, 5 (38.46%) patients still had indeterminate response, 5 (38.46%) became biochemical incomplete response, and 3 (23.08%) became excellent response. One patient with biochemical incomplete response was evaluated with structural incomplete response in the 20th month (Figure 1).

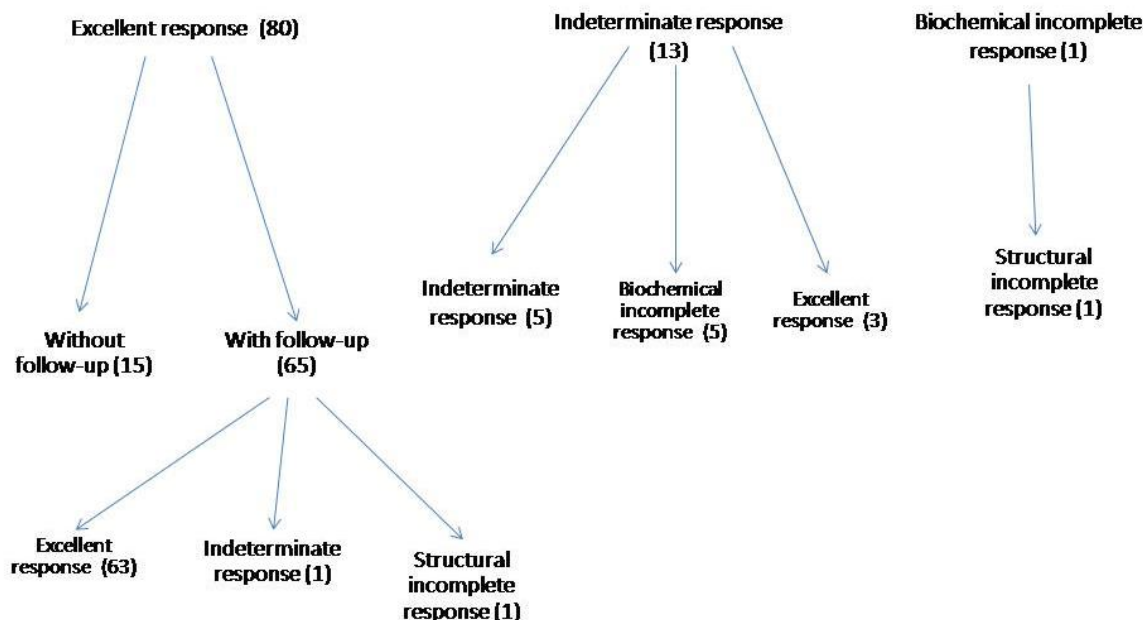


Figure 1. Level of response at 12 months and follow-up after the 12th month

Discussion

Although advancements in diagnostic techniques and increased medical attention to small thyroid nodules has resulted in the early detection of cancers in small nodules, increasing exposure to diagnostic X-rays and environmental hormone disruptors may also explain part of the observed increase (8). The increase does not only include micro-cancers (<1 cm), but significant increases have also been observed of tumors ≥ 4 cm. This shows that diagnostic scrutiny is not the only explanation (9).

Although the outcome of thyroid cancer after effective treatment is generally excellent, some cases have a poorer prognosis. The prognosis is negatively influenced by age, distant metastasis, and lymphadenectomy (10). The initial therapeutic approach is very important in differentiated thyroid cancer because a rigorous initial approach leads to better survival and very low morbidity. RAI refractory cancer has a worse prognosis (11). Papillary thyroid cancer with a low or intermediate risk has an excellent response to initial therapy, and can be defined as non-stimulated TG < 0.2 ng/ml. Long-term follow up with clinical examination and periodic non-stimulated TG measurement is sufficient in low or intermediate-risk groups (12). Rigorous follow up enables early detection and treatment of persistent or recurrent locoregional or distant disease. Most recurrences develop in the first 5 years after the first diagnosis, but in a few cases, recurrence may develop even after 20 years (1). Amin et al showed an increasing prevalence of papillary carcinoma and greater prevalence of intermediate risk, and although the likelihood of cancer-related deaths was low, it was not negligible. The magnitude of the RAI ablation dose was found to be the single significant factor affecting the initial ablation success rate and remote metastasis was found to be the single significant prognostic factor in predicting future morbidity (13). Rosario et al reported that non-stimulated TG ≤ 0.25 ng/ml with negative anti-TG antibodies and no metastases seen on US after thyroidectomy rules out the presence of persistent disease in low-risk papillary thyroid carcinoma patients. This weakens the indication for RAI ablation in this patient group (14).

TG is produced by normal and pathologically altered thyroid follicular cells and plays an important role in well-differentiated thyroid cancers after thyroidectomy and ablative RAI therapy when TG-Ab levels are negative. TG level identifies patients with residual tumor and prevents unnecessary tests in patients who are in remission (15).

TG is generally measured during T4 replacement therapy and elevated values indicate suspicion of cancer relapse with 1 $\mu\text{g/L}$ TG corresponding to 1 g thyroid tissue (16). Pre-RAI TG is a significant risk factor for disease recurrence in patients with differentiated thyroid cancer (17). Postoperative TG levels >10 ng/mL increase the probability of persistent or recurrent disease, failing RAI ablation, and the presence of distant metastases. TG levels may fail to identify patients with a small metastatic volume which are usually located in the neck region and US is the method of choice for nodal disease (18). Non-stimulated TG measurement has predictive value and can be used as a

general indicator in the follow up of differentiated thyroid cancer. An increase of TG levels during hormone replacement therapy is a highly suspicious finding and needs further investigation (19). Anti-TG antibodies can be used as an important marker during the follow-up period. A trend of increasing anti-TG antibodies should be investigated for recurrent disease, whereas stable or declining levels do not seem to reflect a risk for recurrence (20). Serum anti-TG levels are present in 25% of differentiated thyroid carcinoma and 10% of the general population. This is important because anti-TG antibodies may interfere with TG measurements (21). As anti-TG antibodies appear against TG emanating from residual benign or malignant thyroid tissue, the evaluation of anti-TG levels has become used as a tumor marker in the follow-up (22). Patients with a progressive increase in TG or anti-TG levels and a negative RAI diagnostic whole-body scintigraphy are evaluated as TENIS syndrome. Carrillo et al reported that intermediate and high-risk differentiated thyroid cancer patients with TG elevation during follow up should probably receive RAI therapy without diagnostic whole-body scintigraphy to prevent treatment delays, increased costs, and TENIS syndrome. The accuracy of diagnostic whole-body scintigraphy was reported to be low and may cause stunning and treatment delay (23).

USG is useful for evaluation of the thyroid bed and cervical lymph nodes because the neck is the most common and treatable site of recurrence. Kim et al stated that in patients with positive TG and negative USG/FDG PET/CT, suppression of hormone replacement and more intensive follow up with neck USG should be applied, because of potential side-effects and discomfort. Empirical RAI therapy should be applied to patients with definite clinical evidence of disease (24).

Schlumberger et al proposed a treatment algorithm for the management of thyroid cancer and distant metastases. According to this algorithm, patients with metastatic differentiated thyroid cancer are managed with appropriate focal treatment (surgery, radiotherapy or thermoablation) RAI, or both, based on the RAI avidity. If one or more metastatic lesions are RAI refractory, RAI treatment should be abandoned (25). Chow et al reported that hemithyroidectomy with central compartment dissection can achieve excellent prognosis in selected cases, and reduces surgical complications and spares patients from undergoing RAI treatment (26).

Patients with low-risk micropapillary thyroid carcinoma treated with thyroidectomy and a low dose of 50 mCi RAI have been shown to have excellent long-term prognosis (27). The rate of successful ablation is higher with intermediate-high RAI therapy (1.85-3.7 GBq) compared with low activity (81.1 GBq) reaching a complete response in most cases. In a study of 277 patients, Albona et al showed extrathyroidal uptake in 27 with post-RAI imaging, 17 laterocervical nodal, and 10 distant metastases (28).

The four response to therapy categories used in this study were first described by Tuttle et al (29) and later modified by Vaisman et al (7, 30). Tuttle et al. stated that the

American Thyroid Association recurrence staging system predicted the risk of recurrence and persistent disease, therefore more effective dynamic risk assessment could be made with this recurrence staging system (29).

Conclusion

The results of this study showed that most of the patients had excellent response after total thyroidectomy and RAI therapy at the 12-month follow-up. After 12 months, an excellent response rarely becomes an indeterminate, structural incomplete or biochemical incomplete response. Of the patients without excellent response, approximately one-sixth (17.65%) showed an excellent response after the 12th month. Patients with an excellent response at 12 months may be followed up less often and those with an indeterminate or incomplete response should be followed up more often.

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