Treatment of differentiated thyroid cancers

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ABSTRACT
Although several guidelines have been published for the management of differentiated thyroid cancers, there are still some controversies. Besides an effective initial therapy, long term follow-up of the patients with differentiated thyroid cancers is important for the optimum management and this can be best done by interdisciplinary approach. In this review, treatment strategies and the long term follow-up are summarized. [Turk J Cancer 2005;35(4):153-158].

KEY WORDS:
Differentiated thyroid cancer, treatment strategies, follow-up

INTRODUCTION
Differentiated thyroid cancers, derived from the thyroid follicular epithelial cells, include papillary and follicular thyroid cancers (1). Although the prognosis is very good in differentiated thyroid cancers, recurrence rates are high ranging from 20% to 40%. Also, distant metastases can occur and often discovered decades after initial treatment (2). Therefore besides the need of effective initial therapy, long term follow-up of the patients with differentiated thyroid cancers is important for the optimum management. Therapeutic goals can be achieved by interdisciplinary approach. Although several guidelines have been published for the management of the thyroid cancers, there are still some controversies in certain issues (3-5).

Surgery
The primary treatment for differentiated thyroid cancers is surgery. The extent of the initial surgery is one of the most widely debated issues. Total or near total thyroidectomy that leaves less than 2 grams of thyroid tissue is preferred for most of the patients. The reasons for the preference of total thyroidectomy are because of the higher recurrence rates in the contralateral lobes and high probability of multifocality of the papillary cancers (6). As it is known that radioiodine therapy is facilitated by resection of as much thyroid tissue as possible, maybe the most important of all reasons is to improve the effectiveness of radioiodine
treatment. Also, it should be remembered that total thyroidectomy allows better serum thyroglobulin evaluation as a tumor marker in the follow-up period. Significantly lower 20-year recurrence rates have been reported in an analysis of 1685 low-risk patients (stage I & II) when treated with bilateral than unilateral thyroidectomy (2% vs 14%) (7). However, cancer-specific mortality was not different between the groups. Studies indicate that the risk of recurrence of thyroid cancer within the thyroid bed is reduced with total thyroidectomy compared to lesser operations (6,8). Also, Mazzaferri et al. (6) found that bilateral lobectomy was an independent variable affecting cancer recurrence. Arguments in the favor of unilateral lobectomy include the absence of survival benefit with extensive surgery and the lower risk of complications with the unilateral lobectomy (1).

Consensus guidelines recommend total or near-total thyroidectomy by an experienced thyroid surgeon to minimize the risks of hypoparathyroidism and recurrent laryngeal nerve injury in patients who had tumors larger than 1 cm in size. Other than that, total thyroidectomy is suggested in multifocal tumors, tumors with extra-thyroidal spread, clinically involved nodes or familial disease (3-5). Also in these guidelines unilateral lobectomy has been reported to be appropriate for the tumors smaller than 1 cm in size. However, some recent publications indicate that near total or total thyroidectomy should be performed even in these tumors (9,10).

The extent of lymph node dissection is another topic of debate. Thyroid cancer frequently metastasizes to the central and the ipsilateral cervical lymph nodes. Prophylactic neck dissection is not recommended as it has been reported not to improve long-term outcome (11). During the operation, the lymph nodes should be inspected, and any suspected node containing carcinoma should be biopsied and sent to frozen evaluation. If diseased nodes are found in the central compartment, then all nodal groups in this area should be resected. The presence of affected nodes lateral to the jugular vein indicates a need for a modified radical neck dissection. Kouvaraki et al. (12) reported that preoperative ultrasonography may detect nodal metastases not detected by physical examination in 34% of patients with differentiated thyroid cancer. Therefore, preoperative ultrasonography may help to plan surgical strategy in some patients.

**Radioiodine therapy**

Radioiodine has three uses in the postoperative treatment of patients with differentiated thyroid cancers. First is to ablate the normal remnant thyroid tissue to increase the specificity of long term monitoring, second is for the diagnostic imaging of possible residual or recurrent disease, and third for the treatment of residual microscopic or gross tumor in remnant thyroid tissue or distant metastases.

**Ablation**

Many retrospective studies suggest that there is reduction in disease recurrence and disease-specific mortality with the use of postoperative radioiodine therapy (6,13). A recent meta-analysis found that remnant ablation reduced the 10 year risk of locoregional recurrence (RR: 0.31) and reduced the risk of distant metastases by 3 percent (14). Still, the benefit of postoperative radioiodine therapy, especially for patients with low-risk for disease recurrence and mortality, remains controversial. Hay et al. (15) reviewed the outcomes of nearly 2500 patients with papillary thyroid cancer treated over six decades and found no differences in mortality or recurrence rates in the decades when radioiodine was rarely given (1940 to 1969) and the decades (1980 to 1999) when half of the patients received radioiodine therapy.

Postoperative remnant ablation is performed for several reasons in addition to destroying occult microscopic cancer. It facilitates follow-up with whole body radioiodine scans and TSH-stimulated serum thyroglobulin measurements, which both can be affected from residual thyroid tissue. Also, persistent disease cannot be identified after surgery when there is a large thyroid remnant (16,17). Radioiodine remnant ablation seems to be not beneficial for patients with tumors smaller than 1 cm without evidence of metastatic disease (18).

Main problems caused by radioiodine remnant ablation are usually transient and include loss of taste, nausea, sialadenitis, radiation thyroiditis (18). There are also potential risks of bone marrow suppression, diminished reproductive function, and secondary malignancies (19). To some extent, these risks can be reduced or eliminated by using smaller amounts of radioiodine.

Once more there isn’t any consensus for the dosing of the radioiodine ablation and the treatment regimens are variable. Many centers use a standard fixed dose for all patients, given between 30-150 mCi of radioiodine.
recent study concluded that any activity of radioiodine between 25 and 50 mCi appears to be adequate for remnant ablation (20). Until consensus about the radioiodine therapy has been reached, the therapy should be individualized and the lowest effective doses of radioiodine should be used.

**Imaging**

Residual or metastatic tumor imaging can be performed 4-6 weeks after surgery with whole-body radioiodine scans. A low dose (2-5 mCi) $^{131}$I scan is usually performed with whole body imaging 48-72 hours later. However, these low doses of radioiodine have been reported to reduce uptake of the subsequent ablative or treatment dose which is known as stunning (21). This effect may be minimized by using $^{123}$I or $^{99m}$Tc for scanning (4).

Serum TSH levels should be at least 25 mU/L before imaging is done for maximum radioiodine uptake. To obtain these levels of TSH, either thyroxine (L-T4) treatment should not be started after surgery for 4-6 weeks or the treatment should be withdrawn for 4-6 weeks before the scan. Triiodothyronine (T3) has shorter half-life (8-12 hrs) than thyroxine (approximately 7 days); so T3 may be given for the first 4 weeks after the withdrawal of thyroxine to minimize the symptoms of hypothyroidism. But it should be held for 2 weeks prior to radioiodine scan (18). Also patients should be warned about not to take high iodine content foods for at least 2 weeks before the scan.

Administering recombinant human TSH (rhTSH) increases serum TSH levels sufficiently to stimulate radioiodine uptake and thyroglobulin release without need of thyroxine withdrawal (22). This avoids the temporary hypothyroidism; so it helps to avoid the negative effects of acute hypothyroidism on cardiovascular, hepatic and neurologic function. It has been shown that the accuracy of radioiodine scanning after two injections of rhTSH (0.9 mg on two consecutive days) is almost equivalent to the scan done with thyroxine withdrawal (1).

**Residual disease**

Third use of radioiodine is for the treatment of residual or metastatic disease. Patients with residual postoperative disease in the thyroid bed are usually treated with 100 mCi, and in cervical lymph nodes 150 mCi of radioiodine (18). However, if extensive locoregional disease or a remnant is detected by scan (radioiodine uptake > 5-10%), additional surgery before radioiodine therapy should be considered (1). A dose of not less than 175 mCi is administered for distant metastases (18).

Several days after the therapeutic radioiodine dose, a post-treatment whole body scan is often performed which has a greater sensitivity to detect metastatic disease than the low dose diagnostic scan (21,23).

**Thyroid hormone suppression**

After initial surgery of differentiated thyroid cancers, all patients should receive thyroxine (L-T4) to prevent hypothyroidism and to minimize potential TSH stimulation of tumor growth. It has been reported that disease free survival can be improved by 2-3 fold with thyroxine therapy especially in high-risk patients (24,25). However, controversies remain regarding the optimal TSH concentration required. In British Association guidelines, it is recommended that TSH suppression of <0.1 mU/L may be sufficient (4); whereas in AACE guidelines, TSH suppression is recommended as 0.01 mU/L to < 0.1 mU/L for patients who are at high-risk for recurrence and mortality. For low-risk patients TSH suppression of 0.1 mU/L < to <0.4 mU/L may be adequate (5).

It should be remembered that aggressive suppression of TSH may worsen osteoporosis in postmenopausal women, may lead to cardiac hypertrophy and atrial fibrillation (1,26). Because of these risks and the unproven benefits of TSH suppression, thyroxine dose can be varied according to the extent of the disease and the likelihood of recurrence.

**External radiation therapy**

External radiation therapy may be useful in patients with differentiated thyroid cancers whose tumors do not concentrate radioiodine, or who have residual or recurrent disease that is not amenable to further surgery and radioiodine therapy. It has been also used for the palliative therapy of distant metastases (4,5).

The benefit of adjuvant radiotherapy after surgery is controversial. Several reports have described no benefit; whereas some studies have suggested an improvement in local control with radiotherapy (8, 26-28). External radiation therapy might be effective in selected patients.
Chemotherapy

Chemotherapy for differentiated thyroid cancers has been studied inadequately. It is mostly restricted to progressive and symptomatic thyroid cancer uncontrolled by surgery, radioiodine therapy, or external radiotherapy. Doxorubicin is associated with up to 40% response rate. The recommended dose is 60 to 75 mg/m² every three weeks; however, the duration of response is usually short (1). The results of combination chemotherapy have been disappointing. Pamidronate, may reduce bone pain and improve quality of life in bone metastases, and in one study resulted in partial radiologic improvement in 2 of 10 patients (29).

Long-term follow-up

Although most recurrences or distant metastases of differentiated thyroid cancers occur within the first five years after initial treatment, they can occur even decades later. Therefore all the patients should have periodic evaluations of the presence of the disease. The most effective follow-up is also up to debate. However, it is usually recommended that for the first two years patients should be evaluated every 3-6 months, then for the next three years every 6 months and then annually if disease-free (3,4).

When total thyroidectomy and radioiodine ablation have been performed as an initial treatment in patients with differentiated thyroid cancer, measurement of basal and TSH-stimulated thyroglobulin (either with L-T4 withdrawal or rhTSH), whole-body radioiodine scans and neck ultrasonography are the three most valuable tests for follow-up assessments (2).

Serum thyroglobulin level is the most sensitive and specific marker of differentiated thyroid cancer. Serum thyroglobulin levels should be very low (<1 to 2 ng/mL) in most patients who are disease free, whereas increased serum thyroglobulin levels (a value of 5 ng/mL or higher) suggests the presence of functional thyroid tissue or tumor, and more extensive evaluation is indicated. Undetectable serum thyroglobulin during TSH suppressive therapy with L-T4 does not exclude persistent disease; therefore serum thyroglobulin should be measured after TSH stimulation. Persistent tumor is rarely found when the serum thyroglobulin levels are less than 5 ng/mL after L-T4 withdrawal or less than 2 ng/mL after rhTSH stimulation (30,31). Also, after unilateral lobectomy and under L-T4 therapy, serum thyroglobulin levels should be usually less than 10 ng/mL in the absence of metastases (5). Antithyroglobulin antibodies, present in about 25% of patients with thyroid cancer, interfere with all assays for thyroglobulin, invalidating the thyroglobulin result (32). So, the laboratory should test for antithyroglobulin antibodies when measuring serum thyroglobulin. Moreover, serum thyroglobulin measurements can’t be used to monitor patients who have these antibodies.

When increased level of thyroglobulin is obtained, whole-body radioiodine scans and neck ultrasonography are the most informative tests to detect local recurrence or distant metastases.

Whole-body radioiodine scans should be performed 6-12 months after initial ablation. Grigsby et al. (33) reported that the predictive value for relapse free survival of one and two annual negative radioiodine studies were 91% and 97% respectively. They suggested that annual radioiodine imaging is necessary until two consecutive negative studies are obtained, after which repeat imaging at 3-5 years appears to be satisfactory. However, some studies suggest that whole body scanning is unnecessary if rhTSH-stimulated serum thyroglobulin concentrations are less than 2 ng/mL or are undetectable after L-T4 withdrawal; prompting a more recent consensus recommendation to rely upon rhTSH-stimulated thyroglobulin testing instead of radioiodine scanning in all low-risk patients (34-36). However, periodic scanning beyond this 6-12 month follow-up is necessary for high-risk patients and also for patients in whom recurrence is suspected (3-5).

Besides clinical examination or rising serum thyroglobulin concentrations, the most sensitive technique is ultrasonography for the detection of the recurrent tumor in the thyroid bed and the neck region (37,38). For this reason, ultrasonography should be considered in the routine follow-up of patients especially with extrathyroidal invasion. A recent study by Pacini et al. (39) reported that a combination of rhTSH-stimulated thyroglobulin and neck ultrasonography has a better predictive value than either rhTSH-stimulated thyroglobulin alone or in combination with radioiodine scanning.

Other radiographic studies like chest X-rays, computerized tomograms (CT), magnetic resonance imaging (MRI), skeletal x-rays, and skeletal radionuclide imaging may also be used in the routine follow-up. [18F] Fluorodeoxyglucose positron-emission tomography imaging can detect recur-
ence or metastases; however, its use should be limited to the patients with increased thyroglobulin levels and negative radiiodine scan, CT or MRI (40).

Primary therapy of the recurrence in lymph nodes is surgery and then radiiodine therapy, if possible. If the recurrence within the thyroid bed is associated with soft tissue, tracheal or esophageal invasion it may require more extensive resection. After surgery, radiiodine therapy or external radiotherapy should be given. Patients who develop distant metastases are treated like those with metastases found at the time of initial treatment. However, radiiodine therapy may be less effective in these patients (41). Surgery may be considered for patients with single distant metastases, like single brain or bone metastasis (42). Systemic chemotherapy or palliative external radiotherapy may be considered for patients with either local or distant recurrence, or when radiiodine fails to control local growth and spread of disease.

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