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Current Status and Future Perspectives in Differentiated Thyroid Cancer

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Thyroid cancer is increasing all over the world. The exact cause of this increase is still debated and there are conflicting reports. Sophisticated molecular studies suggest that environmental chemicals may have effects of thyroid carcinogenesis. The development of powerful molecular biology techniques has enabled targeted next-generation sequencing for detection of mutations in thyroid cancer, and this technique can make a specific diagnosis of thyroid cancer in cytologically indeterminate cases. The initial treatment of well-differentiated thyroid cancer (DTC) is surgery followed by radioiodine remnant ablation. However, further studies are needed to determine the optimal dosage of radioactive iodine for DTC patients with lateral neck metastasis. DTC is an indolent tumor and may cause death even decades later. Thus, long-term follow-up is mandatory. Recently, dynamic risk stratification (DRS) has begun to use stimulated thyroglobulin level at 1 year after the initial treatment and restratified the risk in accordance with the response to the initial treatment. This DRS strategy accurately predicts disease free survival and can be widely used in daily clinical settings. For the iodine refractory metastatic disease, redifferentiation therapy and targeted therapy are two promising alternative treatments. Sorafenib is the first approved agent for the treatment of progressive iodine refractory advanced thyroid cancer in Korea and may be very helpful for radioactive-refractory locally advanced or metastatic DTC. Selumetinib may be an effective redifferentiating agent and could be used within several years.

Keywords: Thyroid; Thyroid neoplasms; Diagnosis; Therapy; Prognosis

INTRODUCTION

Thyroid cancer is increasing all over the world. The exact cause of this increase is still debated and there are conflicting reports [1]. The widespread use of ultrasonography (US) which can detect small-sized thyroid cancer is a likely factor. Some researchers insist that the increased incidence of thyroid cancer is not real, but just reflects increased detection of small indolent cancers from large asymptomatic reservoirs since the cancer specific mortality rate is stationary [2]. The increased use of US and guided aspirations have contributed to increased detection of small impalpable thyroid cancers in asymptomatic patients. Routine check-up procedures have been blamed for the widespread use of US. Recently, an elegant epidemiological study in the United States revealed that only about half of this increase is due to the increased use of US, while the remaining half may be a true increase in cancer [3,4]. Also noteworthy is the finding that thyroid cancer incidence is sharply increasing in children, adolescents and young adults. Not only small-sized cancers, but also large-sized cancers (over 2 cm) have sharply increased, and this increasing trend for larger tumors rules out diagnostic scrutiny as the only explanation for

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the observed results [5].

ETIOLOGY

While we still do not know the exact cause of cancer, carcinogenesis depends on genetic predisposition and environmental stimuli. It is highly unlikely that human genetic trait changes over the last several decades are responsible for the increased incidence of cancer, which may be due to some unknown environmental changes, including radiation, chemical carcinogens, and dietary changes. Chronic inflammation may also cause cancer in general. Hashimoto thyroiditis is associated with increased incidence of papillary thyroid carcinoma (PTC), but may have a protective role [6]. Many groups including ours have provided observational data on the association of obesity and thyroid cancers [7,8]. A recent comprehensive review suggested that there are five important issues in explaining this connection, including thyroid hormones, insulin resistance, adipokines, inflammation, and sexual hormones [9].

PATHOGENESIS

Through a sophisticated molecular study, it has been documented that increases in thyroid cancer over the last four decade were accompanied by a high frequency of *BRAF* mutations and a sharp increase in Ras mutations. *RET/PTC* rearrangement is decreasing slowly [10]. These studies showed that there was a decrease in classic PTC and an increase in the follicular variant PTC. The proportion of tumors with a *BRAF* mutation was stable, but increased from 50% to 77% within classic PTCs. The proportion of tumors with a Ras mutation increased sharply, especially within follicular pattern tumors. Most radiation induced thyroid tumors are PTC and they are characterized by *RET/PTC* rearrangement. Sporadic PTC has a *BRAF* point mutation [11]. The decreasing frequency of *RET/PTC* rearrangement suggests that recent increases in thyroid cancer are likely not due to ionizing radiation exposure. The increase in frequency of the Ras mutation in follicular patterned tumors suggests that environmental chemicals may have carcinogenic effects. It is interesting that the *BRAF* mutation in classic PTC increased. The *BRAF* mutation is associated with high iodine intake [12] and with volcanic areas where many elements such as boron, iron, manganese, and vanadium in drinking water exceed the maximum admissible concentrations [13]. Whether the recent increase in iodine intake is related is an open question.

Tumor initiation and tumor progression may be separate events. If we can find the exact mechanism for tumor progression, we may treat patients with thyroid cancer only in cases of higher risk, especially patients with thyroid papillary microcarcinoma. Several groups of researchers have found that telomerase reverse transcriptase (*TERT*) promoter mutations are associated with aggressive, advanced metastatic thyroid cancer [14-16]. The *TERT* mutation is found in about 10% of PTCs and is associated with advanced stage, distant metastases and poor outcomes, indicating it may be one of the factors related to thyroid cancer progression, as opposed to cancer initiation. If we can get sufficient information about thyroid cancer progression and initiation, we can provide tailored treatments according to gene profiles. Several new factors have recently been suggested, such as an X-linked inhibitor of the apoptosis protein and *CPSF2* [17,18].

DIAGNOSIS

Fine needle aspiration cytology will remain the cornerstone of the diagnosis of thyroid nodules. However, there is substantial variability in pathologists' cytopathologic evaluation, even after widespread adoption of the Bethesda standardized reporting system [19].

The molecular biology of development and the progression of thyroid neoplasia have been extensively studied [20]. A variety of aberrant signaling in thyroid cancer has been reported and explains much about thyroid carcinogenesis [21-23]. The development of powerful molecular biology techniques enabled targeted next-generation sequencing for detection of mutations in thyroid cancer [24]. Almost all the mutations are found with this method and the technique is applied for fine needle aspiration samples and can detect cancers even with indeterminate cytology. This technique may render the sophisticated gene expression profile using RNA obsolete [25] and can make a specific diagnosis of thyroid cancer in cytologically indeterminate cases.

Molecular studies using DNA mutation profiles (specific) may replace the former gene expression profiles using RNA (sensitive). US-guided core needle biopsy was re-introduced by several group for diagnosis and management of thyroid nodules with indeterminate cytology [26]. Core needle biopsy may be useful in some indeterminate cases without much expense.

TREATMENT FOCUSED ON INITIAL RADIOACTIVE IODINE TREATMENT

The initial treatment of well-differentiated thyroid carcinoma (DTC) has been surgery followed by radioiodine remnant ablation. Improvement in surgical techniques and the use of radioiodine for intermediate to high-risk thyroid cancer patients has further improved survival rates. There are many controversies regarding surgical extent, indication for radioactive iodine remnant ablation (RRA), and the appropriate amount and preparation of RRA. Debates for the extent of surgery are above this review and we will focus on radioiodine administration.

Well-known poor prognostic factors for DTC are old age, large primary tumor size, extrathyroidal extension, nodal metastasis, and distant metastases [27]. Some reports have suggested that male sex and certain subcategorical pathologies could be other poor prognostic parameters [28]. Various tumor staging systems including the pTNM system are based upon the clinical and pathological findings at the initial treatment. They can predict patients' outcome and further therapy is usually based on the stage of the tumor. Most experts recommend using the pTNM staging system [29], but this system was developed to predict survival, not persistent and/or recurrent disease. The American Thyroid Association (ATA) has proposed the following ATA risk classification for predicting recurrence [29]: high: patients with distant metastasis, gross invasion into surrounding tissue, or gross remnants after surgery; and intermediate: neck node metastasis, extracervical uptake after radioiodine treatment, or aggressive pathology (tall cells, columnar cells, insular cancer, Hürthle cell carcinoma, follicular carcinoma, or vascular invasion). Patients with lateral neck metastasis have a greater chance of distant metastasis [30,31] and/or death [27,32] than those with central neck metastasis. The limitation of the ATA risk classification is that both patients with only central neck lymph node metastasis and those with lateral neck lymph node metastasis are regarded as same intermediate risk.

RRA after thyroidectomy is known to be very useful to eliminate microscopic residual disease after operation [29,33]. RRAs are recommended to those patients with intermediate to high-risk. The role of RRA for those with low-risk is questionable, because most of those patients can be cured by surgery alone. Thus, in low-risk patients, low-dose iodine may be enough for ablate remnant [34-36]. Moreover, recombinant human thyrotropin may be used as well as thyroid hormone withdrawal, with comparable efficacy for preparation of the patients [37,38]. In low-risk patients, recombinant human thyrotropin aided low-dose ablation might be enough to avoid various complications from high-dose radioiodine.

The dosage of radioiodine used for remnant ablation after surgery might impact the prognosis of patients. However, many reports have showed that there were no significant differences between a low-dose (30 mCi) and a high-dose (100 mCi) for patients with intermediate risk [39,40]. Two large scaled prospective trials, one from France (the ESTIMABL study) and the other from UK (the HiLo trial), were performed to compare two different dosages of RRA for DTC patients with low- to intermediate-risk [37,38], and concluded that a low-dose is not inferior to a high-dose to achieve successful ablation. The ESTIMABL study was a multi-center large-scale randomized study recruiting a large number of low-risk DTC patients [37]. Thirty percent of patients enrolled were pathological T2N0 and another 10% were pathological T2N0. Thus, almost forty percent of patients had intrathyroidal DTC without any pathological evidence of neck node metastasis, and could be cured by surgery alone. Another 40% of patients had pT1Nx disease, and these patients did not receive prophylactic neck dissection. The most striking finding was that 43% of patients with negative thyroglobulin (Tg) antibody at the time of ablation showed Tg levels less than 1 ng/mL just before RRA. This finding suggests that 43% of total patients were already cured by surgery alone. Only 15% to 20% of total patients had N1 disease, but there was no data regarding sub-classification of neck node according to location, such as N1a (central neck only) or N1b (lateral neck). Thus, this study is not sufficient to conclude that low-dose radioiodine is noninferior to high-dose radioiodine for intermediate risk patients, such as DTC patients with lateral neck metastasis. The HiLo trial was also a prospective multicenter study with slightly fewer patients enrolled and showed similar results to the ESTIMABL study [38]. The spectrum of the recruited patients was wider in the HiLo trial. The ESTIMABL study recruited DTC patients with T1/T2 and N0/Nx/N1. The HiLo trial included same staged patients plus additional patients with T3 disease. Seventy-five percent of the study subjects had T1, T2 and 60% of patients had N0 disease. These low-risk patients can be cured by surgery alone, and the effect of ablation was questionable for this group. Similar to the ESTIMABL study, only 15% of patients had N1 disease and 25% of patients had Nx disease. Also, there were no differences between central and lateral neck metastasis. A meta-analysis covering nine prospectively designed

papers including the ESTIMABL and HiLo trial was recently published [41]. This analysis showed that there was no significant difference between the low and high dosage regimen. Thus, they recommend using the low-dose regimen, because there is less chance of side effects. However, some studies enrolled a very limited number of patients with neck node metastases [37-39], and another did not describe the neck node metastasis status [42,43]. Thus, we could not obtain information regarding the optimal dosage of RRA for DTC patients with lateral neck metastasis from these pre-existing prospective studies.

Recently, postsurgical ablation with low radioactive iodine activity was shown to be comparable to high dosage in thyroid cancer patients with intermediate risk [40]. In a selected intermediate risk group of patients, a low-dose may be also enough. Sabra et al. [44] showed that a higher dosage of radioactive iodine might be required for older patients with lateral neck node metastasis. Bartenstein et al. [45] reported that high-risk DTC patients with T4 primary tumors achieve successful remnant ablation equally well using recombinant human thyroid stimulating hormone (rhTSH) or thyroid hormone withdrawal. In high-risk patients, a high-dose radioiodine is still necessary.

FOLLOW-UP STRATEGIES BASED ON DYNAMIC RISK STRATIFICATION

Thyroid cancer is an indolent tumor. Sometimes, widespread thyroid cancer may cause death even decades later. The cumulative death rate increases 5 years after initial diagnosis and continues to gradually increase for 30 years [46]. Long-term follow-up for 10 to 15 years after surgery is mandatory for thyroid cancer patients.

Tg is a large (660 kDa) glycoprotein that is produced only from thyroid follicular cells, and serves as a precursor of thyroid hormone biosynthesis. Tg is contained in thyroid follicles, but some Tg is released from the follicle probably in accordance with thyroid hormone release, and therefore some Tg is always found in the serum and Tg levels have a rough correlation with the functioning thyroid mass. When bilateral total thyroidectomy is done, especially if it is followed by radioiodine remnant ablation leaving no remaining normal thyroid tissues, Tg should be undetectable. Any detectable Tg level may suggest the presence of abnormal thyroid follicular cells, which in turn may mean recurrent/persistent DTC cells. In this regard, measurement of Tg level is the best guidance for surveillance of DTC patients for monitoring the recurrence or persistence of cancer in patients who have undergone thyroid surgery and radioiodine remnant ablation, because the only source of Tg is thyroid tissue, which may be normal or neoplastic [47,48]. Stimulated Tg (sTg) is a serum Tg measured after endogenous TSH simulation by thyroid hormone withdrawal or after exogenous rhTSH administration. Several studies have reported that serum sTg level obtained after thyroid hormone withdrawal during the first year of follow-up has a high degree of sensitivity and specificity to detect recurrent/persistent thyroid cancer [47,49]. Since Tg production by normal or abnormal (neoplastic) follicular cells is partly dependent upon thyrotropin stimulation, interpretation of the Tg level should be cautious, considering the simultaneously measured thyrotropin level [50,51].

Most of the currently used assays have functional sensitivity between 0.5 and 1.0 ng/mL (first-generation assays). First generation assays cannot differentiate the small remnant amount of thyroid tissue after surgery or small amounts of persistent or recurrent thyroid cancer tissues, and stimulation by endogenous or exogenous thyrotropin was necessary. Recently, more sensitive assays with functional sensitivity around 0.1 ng/mL have been developed (ultrasensitive Tg assays) [52]. Using these sensitive Tg assay methods, the need for thyrotropin stimulation may be reduced, at least in low-risk groups, since it has very high negative predictive value [53-55]. In low-risk patients, ultrasensitive Tg assay under thyroxine administration may replace thyrotropin-stimulated Tg measurement. However, due to insufficient positive predictive value of this ultrasensitive Tg assay method, the stimulated Tg level may be determined in intermediate- and high-risk patients [54].

For DTC, the impact of therapy is rather high, and with extensive surgery and high-dose radioactive iodine therapy, many patients have an excellent prognosis, even despite an advanced tumor stage at diagnosis. In this regard, dynamic risk stratification (DRS) at certain intervals after initial treatment may predict final outcomes, especially recurrence, more accurately [56]. Tuttle et al. [56] suggested that patients may be restratified according to stimulated Tg level at 1 year after the initial treatment, and they are in accordance with the response to the initial treatment. They divided patients into excellent, acceptable, biochemically incomplete and structurally incomplete response groups. In the first three groups, no evidence of disease was found with imaging studies, but their stimulated Tg levels were below 1 ng/mL, between 1 and 10 ng/mL, and over 10 ng/mL, respectively. If the suppressed Tg level is above 1 ng/mL or the stimulated Tg level rises, the pa-

tient belongs to the biochemical incomplete response group. If a suspicious disease is found by any imaging study, the patient belongs to the structural incomplete response. This DRS strategy more accurately predicts disease free survival, since the impact of treatment is included in the classification system. We modified this system and included the titers of Tg antibody [57]. In the low- and intermediate-risk groups, all recurrence was found within 8 years after surgery with modern techniques, rendering very long term meticulous follow-up rather simple [58].

ALTERNATIVE THERAPY FOR RADIOACTIVE IODINE REFRACTORY DTC

Radioiodine treatment is a very effective treatment for metastasis cancer from DTC. However, only two thirds of patients with metastases show substantial radioactive iodine uptake, and only 42% of them are cured [59]. Thus various alternative therapies have been tried in radioioidine refractory DTC. These can be divided into two major categories: redifferentiation therapy and targeted therapy. There have been many clinical trials with regard to these therapies.

Retinoic acid (RA) binds to nuclear receptors designated as RA receptors or retinoid X receptors, and these bound complexes induce expression of specific retinoid-target genes by functioning on the RA-responsive element that is located in the promoter sites. In thyroid cancers, RA induces redifferentiation of cancer cells and expression of the NIS gene. As a result, radioiodine uptake of tumors and serum Tg level are expected to increase with RA treatment [60,61]. However, the results are currently somewhat limited. Recently, there is another approach using selumetinib, an MEK inhibitor, as a redifferentiating agent of radioiodine refractory metastatic disease. The first pilot study showed very promising results, and such a treatment modality will probably be clinically available within several years [62].

DTC is usually associated with genetic alterations in signaling pathways, which are responsible for cell growth and transformation. Of these genetic mutations, *RET/PTC* and *BRAF* mutations have been studied as therapeutic targets in advanced PTCs. The genetic abnormalities that involve *RET* proto-oncogene via rearrangements leading to the formation of chimeric protein kinases results in constitutive activation tyrosine kinase pathways in thyroid epithelial cells. DTCs frequently show abnormal activation of Ras-Raf pathways by the mutation of Ras and *BRAF* proteins. Point mutations leading to *BRAF* signaling independent of binding to Ras have been reported in 35% to 70% of PTCs. In addition, vascular endothelial growth factor (VEGF) and other angiogenesis factors secreted by tumors act on VEGF receptors and platelet-derived growth factor receptors, which are vascular endothelial cell receptor tyrosine kinases, and angiogenesis is promoted as a result. All of these findings are plausible for clinical trials of kinase inhibitors, which inhibit such growth signals in tumor cells and angiogenesis signals in vascular endothelial cells.

There have been around 10 reported phase two studies of antiangiogenic agents in DTC using axitinib [63], motesanib [64], pazopanib [65], sunitinib [66], vandetanib [67], and sorafenib [68-72]. Recently, the first phase 3 study for radioactive-refractory locally advanced or metastatic DTC using sorafenib were published. Sorafenib is the first approved agent for the treatment of progressive iodine refractory advanced thyroid cancer in Korea and may be very helpful for those patients [73].

CONCLUSIONS

Thyroid cancer is increasing all over the world and the exact cause of this increase is still debated. The development of powerful molecular biology techniques has enabled a specific diagnosis of thyroid cancer in cytologically indeterminate cases. The initial treatment of well-differentiated thyroid cancer is surgery followed by RRA and further studies are needed to determine the optimal dosage of radioactive iodine for DTC patients with intermediate to high risk. DRS have begun to restratified the risk in accordance with the response to the initial treatment. For the iodine refractory metastatic disease, redifferentiation therapy and targeted therapy are two promising alternative treatments. Sorafenib is the first approved agent for the treatment of progressive iodine refractory advanced thyroid cancer in Korea and may be very helpful for radioactive-refractory locally advanced or metastatic DTC.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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