**Review Article**

**Development and challenges of differentiated thyroid cancer**

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**Abstract:** Thyroid cancer is the most common endocrine malignancy. Incidence of thyroid cancer, particularly differentiated thyroid cancer, has substantially increased worldwide. Therefore, appropriate diagnosis and treatment methods for differentiated thyroid cancer are critically important. The current review aimed to explore studies concerning the etiology, epidemiology, diagnosis, and treatment of differentiated thyroid cancer, referring to recent American Thyroid Association and British Thyroid Association guidelines. The current study discusses overdiagnosis and overtreatment of differentiated thyroid carcinomas. Future direction for studies investigating differentiated thyroid cancer, aiming to achieve precise diagnosis and treatment, was also discussed. Accuracy levels of diagnosis and treatment methods of differentiated thyroid cancer have not been high enough. They must be refined by additional studies. Therefore, diagnosis and treatment of differentiated thyroid cancer requires multidisciplinary collaboration, as well as individual management. Careful preoperative evaluations should be performed, selecting reasonable surgical methods and proper adjuvant therapies to achieve accurate diagnoses. These measures will provide optimal treatment for differentiated thyroid cancer patients, helping them to achieve better outcomes.

**Keywords:** Differentiated thyroid cancer, diagnosis, treatment, overdiagnosis, overtreatment

**Introduction**

Incidence of thyroid cancer has increased, worldwide [1-4]. Incidence of thyroid cancer has increased by 211% from 1975 to 2013. Approximately 64,300 new cases were reported in the United States in 2016 [1, 2]. Moreover, according to the latest epidemiological survey, thyroid cancer has become the most common type of cancer in South Korea [3]. Increased incidence rates of thyroid cancer can be attributed to increased incidence of differentiated thyroid cancer (DTC), particularly papillary thyroid cancer (PTC) [1, 4]. In South Korea, rates of thyroid cancer diagnoses increased 15-fold between 1993 and 2011, with PTC accounting for most new cases [3]. DTC derived from follicular cells accounts for more than 90% of all thyroid cancers. There are three types of DTC, including PTC (90%), follicular thyroid cancer (FTC; 7%-8%), and oncocytic thyroid cancer (2%-3%), also known as Hürthle cell thyroid cancer [4, 5]. Therefore, appropriate diagnosis and treatment methods for DTC are critically important.

**Etiology of DTC**

Researchers have focused on investigating the development of thyroid cancer in response to radiation exposure [6]. External radiation exposure, one of the most well-known causes of thyroid cancer, can induce long-term damage to thyroid glands [7]. Thyroid glands of children are especially sensitive to the carcinogenic action of ionizing radiation, with a straight line adequately representing the relationship between dose of radiation and effects [8]. The risk of thyroid cancer increases after a mean dose to the thyroid as low as 0.1 Gy, delivered with a high-dose rate [9]. In children exposed to a dose of 1 Gy, the excess relative risk of thyroid carcinoma is 7.7. In these subjects, most (> 85%) thyroid cancers are attributable to radia-
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According to studies investigating the Chernobyl incident, thyroid cancer is closely related to radioactive materials, including iodine, cesium, plutonium, and stron- tium radioisotopes, particularly iodine [11]. Noticing children exposed to radioactive fallout in the Chernobyl incident have shown an increased incidence of thyroid cancer, with PTC the most common histological type [7, 12]. In addition, diet and environmental factors play important roles in the promotion of DTC incidence. Iodine and selenium intake has also been associated with occurrence of DTC, according to a study reported by Schneider [7]. Chronic iodine deficiencies and iodine excesses have been associated with follicular cell hyperplasia and hypertrophy. These have been attributed to the excessive secretion of thyroid stimulating hormone (TSH). Higher occurrence of DTC has been related to higher serum TSH concentrations [13, 14]. Smoking is an independent risk factor for goitres, but further studies are necessary to determine whether smoking increases incidence of DTC [15]. Genetic factors are also important in occurrence and development of DTC. An increasing number of studies have investigated the genetic aetiology of DTC [16-19]. Familial thyroid cancer has gradually become a recognized cancer in patients with DTC, also known as non-medullary thyroid carcinoma [16]. Several inherited syndromes have been associated with non-medullary thyroid cancer, such as Gardner’s syndrome, Cowden disease, Carney complex, and Werner syndrome [16, 19]. Moreover, genetic rearrangements in RET/PTC and PAX8-PPARG and mutations in RAS, BRAF, the TERT promoter, TP53, PIK3CA, and AKT1 are involved in the tumorigenesis of thyroid carcinoma derived from follicular cells [17, 18]. BRAF mutations account for 47% of PTC cases, while RAS mutations and PAX8-PPARG rearrangement are very common in FTC [17, 18]. However, mechanisms and pathways underlying genetic variations associated with DTC remain unclear. Further studies are necessary to confirm and determine the genetic etiology of DTC.

Diagnosis of DTC

Imaging examinations

According to most recent American Thyroid Association (ATA) and British Thyroid Association (BTA) guidelines, imaging examinations play an important role in the management of DTC [4, 20]. Ultrasonography (US) procedures are an economic and non-invasive method of inspection. They are routinely used to evaluate thyroid nodules [19]. US can distinguish benign nodules from malignant nodules. It can evaluate the size, number, boundary, and vascularity of the nodules [21, 22]. In 2009, Park et al. [23] proposed the thyroid imaging reporting and data system (TI-RADS) for stratifying thyroid nodules according to the probability of malignancy based on the 12 features of thyroid nodules that are observable on US. Currently, TI-RADS is widely used to assess thyroid nodules in clinical practice [4]. Recently, new ultrasonic technology has been developed and applied, including high-resolution ultrasound (HRUS), ultrasound elastography (USE), and contrast-enhanced ultrasound (CEUS) [24, 25]. The use of USE can improve imaging evaluations of thyroid lesions, potentially avoiding unnecessary fine-needle aspiration (FNA) cytology or surgery for benign nodules [25]. Real-time elastography (RTE) and shear wave elastography (SWE) are two primary forms of USE. RTE is superior to SWE in distinguishing malignant nodules from benign thyroid nodules [26]. CEUS may be a valuable supplemental tool in the diagnosis of malignant thyroid nodules. The overall mean sensitivity and specificity of CEUS has been shown to be 90% and 86%, respectively [27]. However, the overall diagnostic value of HRUS is superior to that of RTE and CEUS [28]. In addition, compared to the use of HRUS alone, the combined use of RTE, CEUS, and HRUS can improve both diagnostic sensitivity and specificity [28]. Shin JH [22] also discussed ultrasonic characteristics of the PTC variant. These are helpful in predicting the biological behavior of PTC and improving the diagnostic value of ultrasounds. However, because US is highly dependent on both the equipment and the operator, US should be combined with other imaging techniques to distinguish malignant nodes from normal nodes.

The use of computed tomographic (CT) scanner technology increases the detection of small thyroid nodules. It has unique advantages in the evaluation of invasion in external organs, such as the trachea, esophagus, and chest [7, 29]. Cervical lymph node metastasis is common in patients with DTC. CT was shown to be superior to US in detecting metastatic nodal involvement, preoperatively [30]. However, there are no well-established criteria for the use of CT in distinguishing malignant nodules from benign thyroid nodules, particularly for nodules with diameters less than 1 cm [29].
Positron emission tomography (PET) is not routinely used in examining thyroid nodules. PET is widely used for diagnosis and surveillance of many types of tumors [31]. Occasionally, thyroid nodules are detected, incidentally, when using PET to detect other tumors [7]. These incidentally-discovered thyroid nodules deserve specific attention. Up to 50% of these nodules may contain thyroid cancer [12]. In intermediate-to-high risk patients with DTC, Kim et al. [31] reported that sensitivity levels, specificity levels, positive predictive values, negative predictive values, and diagnostic accuracy rates of PET scans for detection of persistent or recurrent thyroid carcinoma were 50%, 98.4%, 83.3%, 92.3%, and 91.5%, respectively [31].

FNA

FNA is the gold standard preoperative procedure for assessment of benign and malignant thyroid nodules [4]. Current ATA guidelines indicate that ultrasound-guided FNA (US-FNA) is the most effective method for assessment of thyroid nodules preoperatively, indicating that preoperative FNA can avoid excessive treatment of benign nodules [4]. In addition, BTA guidelines have recommended that all patients with suspected thyroid cancer should undergo US-FNA [16]. According to a retrospective study, sensitivity and specificity levels, positive predictive values, negative predictive values, and diagnostic accuracy levels of US-FNA were 50%, 98.4%, 83.3%, 92.3%, and 91.5%, respectively [32]. Zhao et al. [33] found that US-FNA is accurate and efficient in triaging patients that require post-thyroidectomy follow-ups for recurrent thyroid carcinoma. However, it is currently estimated that cytologically indeterminate results are diagnosed in up to 25% to 30% of thyroid biopsies, particularly follicular adenomas, follicular thyroid carcinomas, and follicular variant papillary thyroid carcinomas [4, 5, 34]. Therefore, molecular diagnostic testing can be used as an important supplementary diagnostic tool, reducing unnecessary surgeries and two-stage operations, reducing complications and medical expenses, and individually managing patients with DTC [34, 35].

Molecular marker examinations

Molecular diagnostic testing can be classified broadly into two categories, including “rule-out” malignancy and “rule-in” malignancy approaches [34, 36]. Gene expression classifier (GEC) is a “rule-out” test widely used for DTC. It combines an assay signature of 167 genes with commercial cytologic examinations [36, 37]. Negative predictive values of GEC for atypia of undetermined significance or follicular lesions of undetermined significance (AUS-FLUS), follicular neoplasms or suspicious for a follicular neoplasm (FN-SFN), and suspicious-for-malignancy cytologies were shown to be 95%, 94% and 85%, respectively [34, 37]. Negative predictive values indicate the number of negative tests that are true negatives. Therefore, preoperative GEC may reduce costs, risks, and patient burden associated with surgery [36]. In contrast to GEC, the seven-gene panel is a “rule-in” test for DTC [38]. Positive predictive values of the seven-gene panel in 967 samples for AUS-FLUS and FN-SFN were 88% and 87%, respectively [39]. The seven-gene panel includes BRAF, NRAS, HRAS, and KRAS mutations and gene fusions of RET and PTC1, RET and PTC3, and PAX8 and PPARG [34, 40]. The most common genetic alteration observed in thyroid cancer is the BRAF V600E mutation, occurring in approximately 40-45% of all PTC cases [35, 41, 42]. In addition, according to a systematic review and meta-analysis, overall sensitivity and specificity rates of using BRAF V600E for diagnosis of thyroid malignancy were 40% and 100%, respectively [43]. Molecular markers are recommended by the latest guidelines. However, their sensitivity and cost-effectiveness must be further improved. More prospective studies are needed to determine their clinical value [4, 5, 35]. In conclusion, the molecular method plays a supporting role in the diagnosis of differentiated benign nodules and malignant thyroid nodules. The combined use of imaging and FNA cytologic findings is necessary for clinicians to accurately manage thyroid nodules.

Treatment and prognosis of DTC

Age, sex, nodule size, lymph node metastasis, resection extent, distant metastasis, and adjuvant therapy are related to prognosis of DTC [1, 4, 20]. Most DTCs are early primary diseases and patients have a very good prognosis [25]. According to the Surveillance, Epidemiology, and End Results-9 (SEER-9) cancer registry program, between 1994-2013, incidence-based mortality was 0.32 per 100,000 person-years.
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for DTC in the United States [1]. However, patients with invasive DTC, extrathyroidal extension, or distant metastasis had a poor prognosis and high mortality rates [44]. Invasive DTC is relatively frequent, occurring in approximately 13% to 15% of DTC patients [45]. A study showed that the sites of invasion included muscles (53%), trachea (37%), laryngeal nerves (47%), esophagus (21%), larynx (12%), and other sites (30%) [46]. Overall survival rates of invasive DTC were 79% at 5 years, 63% at 10 years, and 54% at 15 years [46]. Moreover, another study showed that five-year survival and recurrence rates for invasive DTC were 78% and 52%, respectively [47]. In a large-sample study, the overall 5-year survival for patients with extrathyroidal invasion, regardless of treatment, was 78%. This is considerably lower than the overall 93% 5-year survival for all patients with well-differentiated disease [47]. Therefore, treatment for patients with DTC requires a multidisciplinary approach by the surgeons, endocrinologists, imagologists, radiologists, and pathologists, guiding adequate assessment, appropriate surgery, radiation therapy, and other adjuvant therapies for invasive DTC [7, 44, 48].

Surgery

Surgery is the main treatment for DTC. However, the range of primary surgeries and prophylactic central lymph node dissections remains controversial [46, 47]. The two main surgical approaches used are total thyroidectomy (or near total thyroidectomy) and thyroid lobectomy. Retrospective studies performed by Bilimoria et al. indicated that risks of death and relapse associated with thyroidectomy are lower than those associated with lobectomy for treatment of PTC with tumors greater than 1 cm in diameter [48]. 2009 ATA guidelines and many other guidelines recommend that total thyroidectomy for DTC is indicated for tumors greater than 1 cm in diameter [49, 50]. These guidelines have also recommended routine prophylactic central lymph node dissection [48]. However, 2015 ATA guidelines were revised and recommend that patients with DTC with a diameter greater than 4 cm and N1 or M1 clinical stages should undergo total thyroidectomy procedures, while patients that have DTC with a diameter between 1 cm and 4 cm should undergo lobectomy procedures [4]. Prophylactic central lymph node dissection should be considered for patients that have an advanced primary tumor (T3N0 or T4N0) or clinical lateral neck disease (cN1b) [4]. European guidelines recommend total thyroidectomy procedures for patients with DTC > 4 cm or high-risk patients with all tumor sizes. They recommend a lobectomy for low-risk patients with DTC < 1 cm. However, a consensus has not been reached regarding the management of DTC between 1 cm and 4 cm. Furthermore, international guidelines recommend therapeutic lymph node dissection for patients with clinically positive nodal (N1) disease in the central or lateral neck compartment. However, no guidelines actively recommend routine prophylactic lateral neck dissection [4, 20, 51]. The extent of the operative dissection and whether the prophylactic central lymph node dissection should be routinely performed remain controversial. Thus, further studies are necessary to provide prospective evidence.

Radioactive iodine (RAI)

The most current ATA guidelines describe the effects of adjuvant therapy using RAI after total thyroidectomy or near total thyroidectomy procedures for DTC. These methods include melting the remaining thyroid tissue, cleaning potential microscopic carcinoma foci after surgery, and removal of foci that are local or metastatic. These measures reduce the risk of relapse and increase survival rates [4, 52]. ATA guidelines strongly recommend RAI treatment for high-risk DTC patients and advise RAI treatment for medium-risk patients. However, RAI is not recommended for medium-risk patients that show invasion from the thyroid without a highly invasive tissue subtype and small metastatic carcinoma foci observed under a microscope [4]. RAI is also not advised for low-risk patients [4]. Zhang et al. [53] retrospectively evaluated the effects of RAI in intermediate-risk DTC patients in a study involving 8,601 patients. The RAI group benefited more in terms of overall survival times than the groups that did not receive RAI therapy. No obvious differences were observed in cancer-specific survival [53]. Yang et al. [54] performed a retrospective analysis involving 11,832 patients with stage IV DTC. The patients were categorized as the RAI group, external beam radiotherapy group (EBRT), and group without adju-
vant radiation. The RAI group had higher five-year and ten-year survival rates than the other two groups [54]. Although Cohen et al. [48] suggested that RAI therapy reduced the risk of relapse in DTC patients, RAI increased the risks of salivary gland dysfunction, dental caries, gustatory change, nasolacrimal tear duct dysfunction, leukaemia, and salivary gland carcinoma. All currently available knowledge was obtained from retrospective studies. Therefore, more prospective studies regarding the use of postoperative RAI are necessary to confirm the findings of these retrospective studies.

**Other adjuvant therapies**

Other adjuvant therapies include TSH suppression therapy, EBRT, and molecular targeting treatment. TSH suppression can be used in postoperative DTC patients to reduce the endogenous stimulation of residual DTC cells. This reduces relapse rates and increases survival rates [55]. A meta-analysis conducted by McGriff et al. [56] indicated that TSH suppression therapy reduces risks of disease progression, relapse, and death. However, Sugitani et al. [57] showed that using TSH suppression therapy in low-risk DTC patients was not beneficial. TSH suppression therapy in DTC patients has been shown to affect cardiovascular and skeletal systems, leading to ill consequences [55]. Recent ATA and BTA guidelines do not recommend TSH suppression therapy for postoperative patients that are defined as low-risk, providing a detailed description regarding the dose and standard of TSH suppression therapy [4, 20]. Recent ATA and BTA guidelines recommend that EBRT should be used in the three following situations: 1) Locally advanced disease accompanied by dilation of the parathyroid during surgery; 2) Residual disease; and 3) Relapse of carcinoma in a patient that is not able to endure a second surgery [4, 20]. However, using EBRT in DTC patients is both rare and controversial. Mangoni et al. [58] analyzed many clinical research results and proposed that EBRT should be used only in high-risk DTC patients with oesophageal or tracheal invasion or other local metastasis. Recently, targeted therapy has been developed and molecular-targeted agents have also been considered for advanced DTC patients resistant to radioiodine (RAI-R) [4, 59]. Targeted agents can inhibit tyrosine kinase receptors (TK-R), which are responsible for tumor growth and angiogenesis [59]. Sorafenib and lenvatinib have been authorized by the Food and Drug Administration (FDA) and the European Medical Agency (EMA) to be used as a treatment for advanced RAI-R. However, statistical support has been limited regarding the extension of overall survival times [59]. Development and clinical application of these two agents, along with other molecular-targeted agents, require further study.

**Future studies and challenges**

Thyroid cancer has been found to be closely related to other diseases. It has been associated with prostate cancer, kidney cancer, lymphoma, leukaemia, and breast cancer, with breast cancer accounting for 36% of all secondary malignancies originating from DTC [60]. In addition, a nationwide population-based study in Korea showed that patients with vitiligo had an increased risk of thyroid cancer [61]. Therefore, further studies are necessary to investigate the correlation between thyroid cancer and other diseases, as well as the mechanisms of action, to identify common genes and molecular markers and determine whether treatment of one disease affects other diseases.

Moreover, overdiagnosis and overtreatment of thyroid carcinomas have attracted considerable attention [3, 62, 63]. It has been reported that thyroid cancer has the highest overdiagnosis rate of all cancers in adolescents and young adults (if not of all ages), attributed to the growing availability and increasing sensitivity of imaging methods [62, 64, 65]. However, most patients with DTC receive treatment, including total thyroidectomy procedures in the majority of adolescents and young adults (AYAs) [65]. The absolute increase in thyroid cancer in women was almost 4 times greater than that of men [66]. Because of the number of thyroid cancer cases in women, there is increased potential of cosmetic disfiguration from a thyroidectomy-induced neck scar, menstrual irregularities that may occur with radioiodine (RAI) therapy, the unnecessary burden of daily thyroid hormone replacement, and anxiety and related psychosomatic symptoms [65]. Despite the dramatic increase in incidence, mortality rates from thyroid cancer remain stable [3, 66]. Therefore, the problems of overdiagnosis and overtreatment must be clearly understood and
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taken seriously. Fortunately, many groups are addressing this issue. In the US, a subgroup of PTC has been reclassified as non-invasive follicular thyroid neoplasm with papillary-like nuclear features. It is considered benign enough to warrant observation instead of intervention [65]. In South Korea, a study group has been organized, called the Physician Coalition for Prevention of Overdiagnosis of Thyroid Cancer [62]. It is expected that an increasing number of doctors will pay closer attention to this problem, working together to find effective solutions.

Notably, the following challenges in DTC remain to be studied: (1) Etiology of DTC and approaches to achieve early detection and reduced morbidity; (2) Use of molecular markers and approaches to improve the sensitivity and specificity of diagnosis and reduce costs [35, 36]; (3) Application criteria and balance points for the active monitoring and immediate surgical intervention [67, 68]; (4) Methods to improve DTC surgery, including the extent of operative dissection of tumors with diameters between 1 cm and 4 cm [68] and the safety and efficacy of prophylactic central lymph node dissection; (5) Use of RAI and approaches to reduce risks and increase benefits; (6) Rational use and dosage of TSH suppression therapy [57]; (7) Risks and benefits of EBRT [54]; and (8) Combined use of tyrosine kinase inhibitors and other adjuvant therapies, such as EBRT, as well as the exploration of new targeted drugs [59].

Conclusion

In conclusion, methods for diagnosis and treatment of DTC have been continuously developed. New technologies have been developed and applied in clinical practice. However, accuracy levels of diagnosis and treatment methods of DTC are not high enough and must be refined by additional studies. Although USG and FNAC are quite accurate in diagnosing malignancies, additional investigations are needed to further improve sensitivity rates. Certain asymptomatic PTCs have not been diagnosed, some subtypes of DTC have not been clearly diagnosed, and some invasive DTCs have not been treated in time [34, 50]. Moreover, overdiagnosis and overtreatment have been reported in thyroid cancer patients [1, 3]. Resolving these diagnostic problems requires a joint effort. Diagnosis and treatment of DTC necessitates not only individual management but also multidisciplinary collaboration across several departments, including surgery, ultrasound, endocrine, imaging, and pathology. Careful preoperative evaluations should be performed, selecting reasonable surgical methods and proper adjuvant therapies. The aim should be to improve accurate diagnoses and provide optimal treatment for DTC patients, helping them to achieve better outcomes.

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References

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[31] Kim MH, Jh O, Ko SH, Bae JS, Lim DJ, Kim SH, Baek KH, Lee JM, Kang MI and Cha BY. Role of
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