

## Differentiated Thyroid Cancer and Radioiodine Therapy After New TNM Staging System

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**Received:** November 25, 2019; **Published:** December 31, 2019

### Abstract

Differentiated thyroid cancer (DTC) has one of the most frequent diagnosed, especially among women and young adults. The DTC is represented by papillary (90%) and follicular forms (10%) with their multiple variants. The outcomes are generally very good, the recurrence rates are low and survival rates are excellent. Several staging system have been generated to inform DTC management. One of the most widely used is the tumor-nodes-metastasis (TNM) classification elaborated by the American Joint Committee on Cancer (AJCC), which allow to predict the risk of cancer-related death. Recently the 8<sup>th</sup> edition of the AJCC staging system was published. The main changes with respect to 7<sup>th</sup> edition are an increase in the age threshold for defining high risk of DC-related death (55 vs 44 years old) and a decrease in the unfavorable prognostic significance for some findings (i.e. microscopic extra-thyroidal extension). Consequently, also the management of DTC after surgery changed, reducing the treatment with radioactive iodine (RAI) adjuvant therapy only for patients with high risks. Some scientists in the world, endocrinologist and nuclear medicine, became to evidence strong differences of opinion about the guidelines recommendations continuing to use RAI adjuvant therapy. To reduce these discrepancies a joint statement was find between the more important four Society in the world to restore trust and confidence and a sense of collegiality between scientists and patients affected. However, there are still authors in the literature who continue to treat patients (except micro carcinoma) still with RIT. About 10 - 15% of patients need an additional dose of RIT to complete the ablation of thyroid residues, while in a small percentage of patients an activity may be present in the pulmonary region (diffuse or nummular type) while still more rare is the manifestation of secondary lesions in the bones or in other organs.

**Keywords:** Differentiated Thyroid Cancer (DTC); Tumor-Nodes-Metastasis (TNM); Radioactive Iodine (RAI)

### Introduction

Differentiated thyroid cancer (DTC) has one of the most frequent diagnosed, especially among women and young adults affecting one of 25,000 people in Europe and increasing in the world in the last years. The DTC is represented by papillary (90%) and follicular forms (10%) with their multiple variants. The outcomes are generally very good, the recurrence rates are low and survival rates are excellent. Several staging system have been generated to inform DTC management. One of the most widely used is the tumor-nodes-metastasis (TNM) classification elaborated by the American Joint Committee on Cancer (AJCC), which allow to predict the risk of cancer-related death. Recently the 8<sup>th</sup> edition of the AJCC staging system was published. The main changes with respect to 7<sup>th</sup> edition are an increase in the age threshold for defining high risk of DC-related death (55 vs 44 years old) and a decrease in the unfavorable prognostic significance for some findings (i.e. microscopic extra-thyroidal extension). Consequently, also the management of DTC after surgery changed, reducing the

treatment with radioactive iodine (RAI) adjuvant therapy only for patients with high risks. Some scientists in the world, endocrinologist and nuclear medicine, became to evidence strong differences of opinion about the guidelines recommendations continuing to use RAI adjuvant therapy. To reduce these discrepancies a joint statement was find between the more important four Society in the world to restore trust and confidence and a sense of collegiality between scientists and patients affected.

### Discussion

After the American Thyroid Association (ATA) management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer [1] the basic goals of initial therapy for patients with DTC are to improve overall and disease-specific survival, reduce the risk of persistent/recurrent disease and associated morbidity, and permit accurate disease staging and risk stratification, while minimizing treatment-related morbidity and unnecessary therapy. The specific goals of initial therapy are to 1. Remove the primary tumor, disease that has extended beyond the thyroid capsule, and clinically significant lymph node metastases. Completeness of surgical resection is an important determinant of outcome, while residual metastatic lymph nodes represent the most common site of disease persistence/recurrence [2,3]. 2. Minimize the risk of disease recurrence and metastatic spread. Adequate surgery is the most important treatment variable influencing prognosis, while RAI treatment, TSH suppression, and other treatments each play adjunctive roles in at least some patients [4-6]. 3. Facilitate postoperative treatment with RAI, where appropriate. For patients undergoing RAI remnant ablation, or RAI treatment of presumed (adjuvant therapy) or known (therapy) residual or metastatic disease, removal of all normal thyroid tissue is an important element of initial surgery [7]. 4. Permit accurate staging and risk stratification of the disease. Because disease staging and risk stratification should be used to guide initial prognostication, disease management, and follow-up strategies, accurate postoperative risk assessment is a crucial element in the management of patients with DTC [8,9]. 5. Permit accurate long-term surveillance for disease recurrence. 6. Minimize treatment-related morbidity. The extent of surgery and the experience of the surgeon both play important roles in determining the risk of surgical complications.

Postoperative staging for thyroid cancer, as for other cancer types, is used (i) to provide prognostic information, which is of value when considering disease surveillance and therapeutic strategies, and (ii) to enable risk-stratified description of patients for communication among health care professionals, tracking by cancer registries, and research purposes. Accurate initial staging requires a detailed understanding of all pertinent risk stratification data, whether they were obtained as part of preoperative testing, during the operation(s), or as part of postoperative follow-up. It is also important to emphasize that in many cases the written pathology report the surgical specimen does not convey critical risk factors such as preoperative vocal cord paralysis, extent of gross extra thyroidal invasion, completeness of resection, or remaining gross residual disease. Over the years, multiple staging systems have been developed to predict the risk of mortality in patients with DTC [10,11]. Each of the systems uses some combination of age at diagnosis, size of the primary tumor, specific tumor histology, and extra thyroidal spread of the tumor (direct extension of the tumor outside the thyroid gland, loco-regional metastases, and/or distant metastases) to stratify patients into one of several categories with differing risks of death from thyroid cancer. A quantitative approach based on histology, age, lymph node metastases, tumor size, and extra thyroidal extension utilizing TNM staging has recently been proposed and validated [12,13] as in table 1 from AJCC 7<sup>th</sup> Edition/TNM Classification System for Differentiated Thyroid Carcinoma.

Because the AJCC/TNM risk of mortality staging system does not adequately predict the risk of recurrence in DTC [14,15], the 2009 version of the ATA thyroid cancer guidelines proposed a three-tiered clinico-pathologic risk stratification system that classified patients as having low, intermediate, or high risk of recurrence [16]. Low risk patients were defined as having intrathyroidal DTC with no evidence of extra thyroidal extension, vascular invasion, or metastases. Intermediate-risk patients demonstrated either microscopic extra thyroidal extension, cervical lymph node metastases, RAI-avid disease in the neck outside the thyroid bed, vascular invasion, or aggressive tumor histology. High risk patients had gross extra thyroidal extension, incomplete tumor resection, distant metastases, or inappropriate postoperative serum Tg values.

T0 No evidence of primary tumor
T1a Tumor < 1 cm, without extra thyroidal extension
T1b Tumor > 1 cm but < 2 cm in greatest dimension, without extra thyroidal extension
T2 Tumor > 2 cm but < 4 cm in greatest dimension, without extra thyroidal extension.
T3 Tumor > 4 cm in greatest dimension limited to the thyroid or Any size tumor with minimal extra thyroidal extension (e.g. extension into sternothyroid muscle or peri--thyroidal soft tissues).
T4a Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.
T4b Tumor of any size invading pre-vertebral fascia or encasing carotid artery or mediastinal vessels
N0 No metastatic nodes
N1a Metastases to level VI (pre-tracheal, para-tracheal, and pre-laryngeal/Delphian lymph nodes).
N1b Metastases to unilateral, bilateral, or contra lateral cervical (levels I, II III, IV, or V) or retro pharyngeal or superior mediastinal lymph nodes (level VII)
M0 No distant metastases
M1 Distant metastases

**Table 1**

Recently a new AJCC 8<sup>th</sup> Edition/TNM Classification System has been published [17] in which the age risk of disease-specific mortality was raised from 45 years to 55 years. This change increases the proportion of relatively young patients whose mortality risk can be defined solely on the basis of the absence or presence of distant metastases (stage I and II, respectively). The originally patients classified as stage 3 or 4 were re-classified as stage 2, raising the proportion of patients with stage 1 - 2 DTC from 64% or 94%. Using this method the adjuvant radioactive iodine therapy (RIT) has suggested only in patients with stage 3 and 4.

Because of these concerns more International Society (European Association of Nuclear Medicine and the Society of Nuclear medicine and Molecular Imaging) declined to endorse the new guidelines and decided to continue to use RIT. To address some of the differences in opinion and controversies associated with RIT in DTC, the American Thyroid Association (ATA), the European Thyroid Association (ETA), the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine, each one participate to the Martinique meeting [18]. In this meeting every scientist of each society, find an interdisciplinary cooperation to define the goals of RIT on management of DTC. The results of this meeting lead to a new principals: 1) advancing and understanding of optimal thyroid cancer management and requires a committeemen by clinicians, researchers, patients, and organizations to engage in proactive, purposeful, and inclusive interdisciplinary cooperation. 2) the goal of RIT should be characterized as remnant ablation, adjuvant treatment of know disease using standardized definitions. 3) Assessment of postoperative disease status is required to optimize proper selective for RIT (remnant ablation, adjuvant treatment, or treatment of know diseases). 4) Postoperative disease status should be standardized and integrated into routine clinical care. 5) Optimal patient selection for RIT adjuvant treatment requires consideration and evaluation of multiple factors beyond postoperative status and risk stratification. 6) Te optimal administered TIT activity for adjuvant treatment cannot be definitely determined from published literature, Until data are available, selection of the administered activity for adjuvant treatment should be based on multidisciplinary team management recommendation. 7) Characteristics used to classify patients as RIT refractory should be used to risk stratify patients with regard to the likelihood that a tumor will respond to RIT and not necessary as definitive criteria to mandate whether RIT should be recommended. 8) RIT refractory criteria will continue to evolve as (i) additional studies addresses important limitations and technical issue confounding the current literature, (ii) techniques for radioactive iodine imaging are optimized and standardized, and (iii) re-differentiation therapies enhance the effectiveness of RIT. 9) Major gaps in knowledge

and evidence regarding optimal use of RIT should be addressed with properly designed studies. In conclusion, by fostering an open, productive, evidenced-based discussion, the Martinique meeting restored trust, confidence, and sense of collegiality between individuals and organization that are committed to optimal management for patient with DTC.

### Conclusion

Differentiated thyroid cancer (DTC) has become one of the most frequently diagnosed malignancies, especially among women and young adults. The outcomes are generally very good: disease recurrence rates are low, and survival rates are excellent. Evidence-based management is crucial to avoid overtreatment of these low-risk tumors, which can reduce quality of life and yet identify accurately those requiring more aggressive therapy. Recently the 8<sup>th</sup> edition of the AJCC staging system for thyroid cancer (AJCC-8) was recently published with important changes on TNM, reducing substantially the level of risk for patients affected and consequently the use of RIT.

However, there are still authors in the literature who continue to treat patients (except micro carcinoma) still with RIT. This therapy can be performed both in conditions of hypothyroidism (after withdrawal therapy) or more recently without therapy withdrawal, but in euthyroid status after stimulation with recombinant human TSH (Thyrogen). This last method allows avoiding the symptoms related to the hypothyroidism such as asthenia, difficulty in concentration, weight gain for tissue imbibition's and water retention, constipation, etc. Moreover, the high serum TSH condition is necessary for the stimulation of thyroid cells both for the production of thyroglobulin, and for the ability to iodine concentration. The percentages of ablation and therefore of remission of the disease vary between 90 and 98% depending on the series published in the literature. RIT is followed by total body post-therapy scintigraphy that allows the visualization of radioactive iodine concentration sites, making it possible to "map" the distribution of thyroid cells in the whole body.

About 10 - 15% of patients need an additional dose of RIT to complete the ablation of thyroid residues, while in a small percentage of patients an activity may be present in the pulmonary region (diffuse or nummular type) while still more rare is the manifestation of secondary lesions in the bones or in other organs.

### Declaration of Interest

The authors declare there is not conflicting of interest that could be perceived as prejudicing of this article.

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**Volume 5 Issue 1 Januray 2020**

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