

# Prognostic Factors in Differentiated Thyroid Cancer Revisited

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**ABSTRACT:** **Background:** More than 90% of all thyroid cancers are differentiated thyroid carcinomas (DTC) with a 10 year survival rate greater than 90%. The commonly used risk stratification systems for DTC include: European Organization for Research and Treatment of Cancer (EORTC), AGES (Age, histologic Grade, Extent of tumor, Size), AMES (Metastasis) and MACIS (Completeness of resection, local Invasion). Other systems are also utilized. Several new factors that may be involved in DTC risk stratification have emerged in recent studies, with other “traditional” factors being challenged.

**Objectives:** To present recent updates in the literature on new potential prognostic factors for DTC.

**Methods:** We conducted a literature review and analysis of publications regarding DTC prognostic factors or risk stratification published in the last 10 years.

**Results:** Several new factors with potential prognostic implications for DTC were noted, including family history, lymph node involvement parameters, positive PET-CT findings, multifocal disease, thyroglobulin level and several molecular markers including *BRAF*. Increasing age is associated with poorer outcome in DTC; however, recent studies suggest that the cutoff point of 45 years may be contested. Furthermore, several studies have shown contradictory results regarding male gender as a negative prognostic factor, thus questioning its prognostic significance.

**Conclusions:** A number of new factors with potential prognostic implications for DTC have emerged and should be addressed. However, their role and possible inclusion in new staging systems has yet to be determined.

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**KEY WORDS:** differentiated thyroid cancer (DTC), prognostic factors, risk stratification, staging systems

fication or staging systems. The purpose of these systems is to select patients with a higher risk of cancer death for more aggressive surgical and adjuvant treatment while those at low risk could be spared aggressive treatment. Some of the commonly used systems are: the European Organization for Research and Treatment of Cancer (EORTC) [5], AGES (Age, histologic Grade, Extent of tumor, Size) [6], AMES (Age, Metastasis, Extent of tumor, Size) [7], MACIS (Metastases, Age, Completeness of resection, Invasion, Size) [8], and the American Joint Committee on Cancer (AJCC) TNM staging system [9]. Each of these systems contains several clinical factors that are considered to be prognostically significant, with a great overlap between these systems. However, these studies included different patient groups. MACIS and AGES scoring systems included only patients with papillary thyroid cancer (PTC), AMES included patients with DTC, while EORTC included all histologic types.

Despite accepted existing risk stratification systems, several limitations exist. These systems address survival rates (all-cause and cancer-specific mortality) and not disease-free survival or recurrence. Because the mortality rate of DTC is low, this poses a restriction in the use of the current risk stratification systems. This has led to the creation of new risk stratification systems estimating the recurrence of thyroid cancer [10-12].

Given the number of staging systems described in the literature, several studies have attempted to compare their predictability in different populations [13-17]. The results of these studies vary, and it still remains unclear which of the currently available staging systems is most accurate for DTC. Recent studies have evaluated new prognostic factors involved in DTC. In addition, some of the “traditional” factors were studied and reevaluated for their prognostic significance. The current work presents the result analysis and recent updates in the literature on new potential risk factors for DTC.

## PATIENTS AND METHODS

A comprehensive literature review of relevant publications was performed by searching the online database of PubMed. Research indexes included the key words thyroid carcinoma/cancer, staging, risk stratification, risk factors or prognostic

Thyroid cancer is now the eighth most common cancer in the United States and its incidence is rising [1,2]. Differentiated thyroid cancer (DTC) represents more than 90% of all thyroid cancers and bears the best prognosis with a 10 year survival rate > 90% [3,4].

A number of past studies have identified various clinicopathologic predictors for DTC and devised risk-group strati-

**Table 1.** Prognostic value of the “classic” factors included in the most commonly used staging systems

	TNM		TNM				TNM			
	MACIS		MACIS				MACIS			
	AMES		AMES				AMES			
	AGES						AGES			
	EORTC			Extrathyroid extension	Tumor size	Distant metastasis	Complete resection	LN involvement	No. of LN	Clinical stage
	Gender	Age	Histologic grade							
Total studies evaluating (total patients)	37 (136,892)	45 (326,988)	23 (66,724)	27 (114,496)	38 (216,774)	29 (208,794)	12 (66,994)	38 (212,023)	7 (5120)	22 (163,538)
Showed prognostic significance	14	34	15	21	34	28	10	34	5	21
Did not show prognostic significance	23	11	8	5	4	1	2	4	2	1
Percentage of articles that showed prognostic significance	37.84%	75.56%	65.22%	80.77%	89.47%	96.55%	83.33%	89.47%	71.43%	95.45%

LN = lymph nodes; MACIS = Metastases, Age, Completeness of resection, Invasion, Size; AMES = Age, Metastasis, Extent of tumor, Size; AGES = Age, histologic Grade, Extent of tumor, Size; EORTC = European Organization for Research and Treatment of Cancer

**Table 2.** Prognostic value of different factors not included in the most commonly used staging systems

	Vascular invasion	Capsular invasion	Multifocal disease	Total thyroidectomy	Bilateral tumor	Location of LN	Postoperative radiation	Lymph node ratio	Postoperative TG level	Positive PET-CT findings
Total studies evaluating (total patients)	8 (4346)	11 (4840)	10 (1548)	4 (1115)	3 (3636)	6 (1429)	3 (97,287)	6 (4429)	13 (6991)	6 (538)
Showed prognostic significance	4	5	4	1	2	3	3	5	13	5
Did not show prognostic significance	4	6	6	3	1	3	0	1	0	1
Percentage of studies that showed prognostic significance	50%	45%	40%	25%	66%	50%	100%	83%	100%	83%

factors. Only English-language publications were included, almost all from 2005–2015. Studies that included papillary microcarcinoma or specific age groups were excluded.

After exclusions, the recent 100 relevant publications were included. The results of these studies were analyzed quantitatively. Prognostic significance was defined when the study results showed that a factor affected overall survival, disease-free survival or disease-specific survival with statistical significance ( $P$  value < 0.05).

**RESULTS**

The results of the study are summarized in Tables 1-4. Table 1 shows the results of the prognostic value of the “classic” factors included in the most commonly used staging systems. The factors included in each system are highlighted in different colors in the top rows. The total number of studies that evaluated each factor is noted along with the total number of patients included in these studies. Among studies that evaluated each factor, the number and percentage of studies that found prognostic value with statistically significant results ( $P$  < 0.05) are noted.

Gender and histologic grade were found to have prognostic value in only a small percentage of studies. In contrast to past studies that found male gender to be a negative survival

**Table 3.** Factors shown to have prognostic significance in a small number of studies

	Tumor location inside the gland	Family history	Body mass index	Smoking
Total studies evaluating (total patients)	1 (246)	1 (1262)	1 (2057)	1 (89)
Showed prognostic significance	1	1	1	1
Did not show prognostic significance	0	0	0	0
Percentage of studies that showed prognostic significance	100%	100%	100%	100%

prognostic factor, most of the studies in our review failed to show the prognostic value of gender. Age and number of lymph nodes (LN) were found to have prognostic value in approximately three-quarters of the studies reviewed. Tumor size, distant metastasis, LN involvement and clinical stage were all found to have prognostic value in  $\geq 90\%$  of studies.

Tables 2 and 3 show the results of the prognostic value of several different factors that are not included in the most commonly used staging systems. Vascular invasion, capsular invasion and multifocal disease were shown to have prognostic significance in less than half of the studies reviewed. In contrast, postoperative radiation, lymph node (LN) ratio, postoperative thyroglobulin (TG) levels and positive positron emission tomography-computed tomography (PET-CT) findings were

**Table 4.** Prognostic value of different molecular markers possibly involved in thyroid cancer

	BRAF	PAX8-PPAR $\gamma$	P53	KI67	Estrogen and androgen receptors	Galectin 3	EGFR	Krüppel-like factor 17	Serum TG antibody levels	P27	MIRNA-222 and micro RNA-146b	IL-4, IL-10, CRP	UKPa	S-phase fraction	DNA ploidy	Human securin pituitary tumor-transforming gene (hPTTG)
Total studies evaluating (total patients)	16 (5950)	2 (5959)	3 (342)	3 (405)	1 (91)	1 (168)	1 (168)	1 (50)	1 (225)	1 (43)	1 (104)	1 (120)	2 (291)	1 (344)	1 (344)	1 (95)
Showed prognostic significance	8	2	3	3	1	0	1	1	1	1	1	1	1	1	1	1
Did not show prognostic significance	8	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0
Percentage of studies that showed prognostic significance	50%	100%	100%	100%	100%	0%	100%	100%	100%	100%	100%	100%	50%	100%	100%	100%

TG = thyroglobulin, CRP = C-reactive protein, EGFR = estimated glomerular filtration rate

found to have prognostic significance in a high percentage of studies. The factors included in Table 3 were all shown to have prognostic value, albeit in a small number of studies. Family history relates to a first-degree family member with thyroid cancer.

Table 4 shows the results for various molecular markers with possible involvement in thyroid cancer. BRAF was evaluated in 16 studies but was found to be prognostically significant in only 8 (50%) of them. Most of these factors were shown to have prognostic significance, albeit in a small number of studies.

#### AGE

As mentioned, this factor correlated with prognosis in approximately 75% of the studies reviewed. Existing staging systems state the age cutoff point for adverse prognosis at 45 (TNM, DAMES) or 40 years (MACIS, AGES). In our review 18% of studies that showed prognostic significance of age found different cutoff points. Three studies found this factor to be associated with prognosis as a continuous range without a significant cutoff point. Two studies defined 55 years as the appropriate cutoff point; one study stated a cutoff point of under 20 or over 60 years.

#### BRAF

Some of the studies that did not show prognostic significance (overall survival, disease-free survival or disease-specific survival with statistical significance) demonstrated an association with some of the other clinicopathological risk factors.

## DISCUSSION

Predictive staging systems are essential for accurate prognostic information, treatment algorithms and exchange of accurate research information between medical centers. Although the prognosis of DTC is generally good, up to 10% of patients would eventually die of the disease and an even greater proportion would face the morbidity of recurrences [3,4,10,11]. As a

result, a number of studies have identified various clinicopathologic predictors for PTC and devised risk-group stratification or staging systems to select those at high risk of cancer death for more aggressive surgical and adjuvant treatment while those at low risk would be spared aggressive treatment [5-8]. Yet, none of these systems is universally accepted. Additionally, none of these classifications has shown clear superiority, and application of these systems to a single population has shown incompatible findings compared with the original studies [18,19].

Because of the low mortality rate of DTC, the fact that most of these staging systems addressed overall survival and mortality as their prognostic outcome limits their applicability. Another limitation is the variability of patient selection between these studies. The EORTC system was developed based on a cohort of 507 patients with all histologic types of thyroid cancer (including medullary and anaplastic carcinoma). AMES was developed based on a cohort of 814 patients with DTC, AGES and MACIS based on 1779 patients with papillary thyroid cancer alone. This questions the applicability of these systems to all DTC patients.

Despite the variability between these systems, most factors were included in more than one of them and were therefore considered “widely accepted” prognostic factors. This includes age, gender, tumor size and extension, LN involvement and distant metastasis.

#### GENDER

Despite a higher incidence of DTC, overall survival was found both by univariate and multivariate analyses in several cohorts to be better in women [20,21]. It is hypothesized that worse outcomes in men may potentially be accounted for by a more aggressive behavior of DTC in these patients. In our review most of the studies did not find male gender to be an adverse prognostic factor, with only 37% of studies supporting a correlation between male gender and adverse outcome. One should consider gender-related ascertainment

bias as a possible explanation for past findings. Perhaps men seek medical attention at an older age with a more advanced disease. Also because women have lower all-cause mortality rates and live longer than men, gender-specific overall survival rates should be used instead of mortality. The impact of estrogen on thyroid cancer is debatable and numerous studies have reported conflicting results regarding hormone levels and progressive disease [22].

#### AGE

Although advanced age is known to be associated with increased mortality in many types of cancer, DTC is the only human malignancy to include age as part of the staging system [9]. Traditionally, the age cutoff of 45 years has been and continues to be used in current DTC staging guidelines. As shown in our review most studies found age to be a prognostic factor, but 25% of studies failed to show a correlation between age and prognosis. Perhaps the reason is the use of an inaccurate cutoff point. Some studies found that the association between increasing age and worse outcome should be evaluated more accurately as a continuum. These studies stated that different cutoff points were evaluated and no single point was found as an accurate cutoff point. Other studies suggest an age older than 45 as a more accurate cutoff for prognosis. The clinical implication of the latter finding would be down-staging of many patients with DTC, thus potentially avoiding unnecessary therapies in patients with favorable prognosis.

#### TUMOR STAGING

The results of histologic grade and number of lymph nodes as prognostic factors were inconclusive, with about one-third of studies failing to show prognostic value. This may be due to the heterogeneity of patients in the original staging systems and in the newer studies reviewed.

DTC staging systems consider metastatic lymph nodes, when included, as a binary entity (presence versus absence). Clinically positive lymph nodes are associated with recurrence [9-11], but the effect on survival is controversial. Therefore, the extent of initial surgery and the role of central lymph node dissection for papillary thyroid cancer remain debatable. Perhaps LN ratio, a more recently evaluated factor shown to have prognostic value in over 80% of the studies reviewed is a more accurate analysis of LN involvement. According to our study, tumor size, distant metastasis, LN involvement and clinical stage were all found to have prognostic value.

#### OTHER CLINICAL FACTORS

Recently, other clinical factors not included in the commonly used staging systems have emerged. Among those reviewed, the factors found to have definite prognostic value are postoperative radiation, LN ratio, postoperative thyroglobulin levels, and positive PET-CT findings. In contrast, the results of

vascular invasion, capsular invasion and multifocal disease are less definitive and, therefore, the role of these factors is questionable. Body mass index, smoking, tumor location inside the gland, and family history of thyroid carcinoma were shown to have prognostic value in a single study. Clearly, further studies are needed for evaluation of their prognostic significance.

#### MOLECULAR MARKERS

Technologic advancement has led to better understanding of the molecular mechanisms of thyroid cancer and the discovery of many molecular markers involved in these mechanisms. Several molecular markers have been studied for their diagnostic and prognostic significance in DTC and new molecular markers are still emerging.

BRAF V600E mutation has been found in primary PTCs with a prevalence of approximately 45% [23]. Many authors have demonstrated that the presence of the BRAF mutation in PTC is an independent risk factor for recurrence and that a test for the BRAF mutation prior to any treatment intervention may be useful to optimize surgical treatment [24,25].

In our study BRAF was found to be prognostically significant (including DSS and DFS) in only half the studies. However, some of the studies that failed to show prognostic value with statistically significant results demonstrated an association with some of the other clinicopathological risk factors (distant metastasis, extrathyroidal invasion, advanced pathological stage, and LN metastasis).

Ki67, P53, PAX8-PPAR $\gamma$  and other molecular markers are showing promising results; however, further studies are needed.

#### CONCLUSIONS

A number of staging and scoring systems exist for DTC but these harbor limitations. When evaluating the "traditional" factors, tumor size, distant metastasis, LN involvement and clinical stage were all found to have definite prognostic value, but the results of histologic grade and number of lymph nodes are less conclusive. Gender should be reconsidered as a prognostic factor. Regarding patient age, a different cutoff point than 45 years may be more accurate for prognosis.

A number of new factors with potential prognostic implications for DTC have emerged. These include clinical factors (postoperative radiation, LN ratio, postoperative TG levels and positive PET-CT findings) and molecular markers (BRAF, Ki67, P53, PAX8-PPAR $\gamma$ ). The role of these factors and possible inclusion in new staging systems are yet to be determined.

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## “One of the oldest human needs is having someone to wonder where you are when you don't come home at night”

Margaret Mead (1901-1978), American cultural anthropologist and often controversial academic who popularized the insights of anthropology in modern American and Western culture. Her reports detailing the attitudes towards sex in South Pacific and Southeast Asian traditional cultures influenced the 1960s sexual revolution. She was a proponent of broadening sexual mores within a context of traditional Western religious life