Published in final edited form as:
Curr Opin Oncol. 2014 January ; 26(1): 1–7. doi:10.1097/CCO.0000000000000022.

New Insights in Risk Stratification of Differentiated Thyroid Cancer

Maria Papaleontiou, M.D. [Clinical Lecturer] and
Division of Metabolism, Endocrinology and Diabetes, Department of Medicine, Domino's Farms, 24 Frank Lloyd Wright Drive, PO Box 451, University of Michigan Health System, Ann Arbor, MI 48105, USA., Phone: (734) 647-5871; Fax: (734) 647-2145; mpapaleo@med.umich.edu

Megan R. Haymart, M.D. [Assistant Professor of Medicine]
Division of Metabolism, Endocrinology and Diabetes, and Hematology/Oncology, Department of Medicine, North Campus Research Complex, Building 16 Rm. 408E, University of Michigan Health System, Ann Arbor, MI 48109, USA., Phone: (734) 615-6745; Fax: (734) 936-8944; meganhay@umich.edu

Abstract

Purpose of review—Numerous staging and scoring systems exist for differentiated thyroid cancer (DTC), but all harbor limitations. This has prompted investigation for new factors with prognostic implications for DTC.

Recent findings—Several new factors that may be involved in DTC risk stratification have emerged, such as thyroid stimulating hormone and molecular markers. In addition, others are controversial and being challenged, such as age, gender and lymph node involvement.

Summary—The purpose of this review is to present recent updates in the literature on new potential risk stratification predictors for DTC.

Keywords

Differentiated thyroid cancer; survival; risk stratification

INTRODUCTION

Thyroid cancer is now the eighth most common cancer in the United States and its incidence is rising (1–4). Data from the Surveillance, Epidemiology, and End Results Program (SEER) predict that an estimated 60,220 men and women will be diagnosed with thyroid cancer and 1,850 men and women will die of thyroid cancer in 2013 (5). Differentiated thyroid cancer (DTC) represents more than 90% of all thyroid cancers and carries the best prognosis with a 10-year survival rate greater than 90% (6).

Address all correspondence and requests for reprints to: Megan R. Haymart, M.D., Assistant Professor of Medicine, Division of Metabolism, Endocrinology and Diabetes, and Hematology/Oncology, Department of Medicine, North Campus Research Complex, Building 16 Rm. 408E, University of Michigan Health System, Ann Arbor, MI 48109, USA., Phone: (734) 615-6745; Fax: (734) 936-8944; meganhay@umich.edu.

CONFLICTS OF INTEREST
The authors have no conflicts of interest to disclose.

Several risk stratification systems for thyroid cancer have been proposed based on the likelihood of disease-specific death after initial diagnosis. The American Joint Committee on Cancer (AJCC) TNM staging system is the most commonly used system and is based on an age cutoff of 45 years of age. Several scoring systems have also been developed including the Metastases, Age, Completeness of resection, Invasion, and Size (MACIS) score and Age, Metastases, Extent of disease, and Size (AMES), whose predictive values are limited to papillary thyroid cancer (7–15). All staging and scoring systems have the characteristic that with advancing stage, all-cause and cancer-specific mortality rises (7–17).

Despite accepted existing risk stratification systems, several limitations exist. These systems address survival rates and not recurrence, and as the number of deaths from thyroid cancer is small, this poses a restriction in the use of the current risk stratification systems. Moreover, a small risk of death or recurrence still exists in patients with differentiated thyroid cancer (DTC) classified as low risk, thus necessitating long-term follow-up. This has led to the creation of new risk stratification systems estimating recurrence of thyroid cancer (18–21). However, in terms of survival, new predictive factors for continuous risk assessment are also needed and are currently being investigated.

The purpose of this review is to present recent updates in the literature on new potential risk stratification predictors for DTC. For the purpose of this paper, we will focus on survival, not recurrence.

NEW POTENTIAL FACTORS INVOLVED IN DTC RISK STRATIFICATION

Several potential factors that may be involved in DTC risk stratification have recently been investigated and are described below, including age, gender, lymph node involvement, thyroid stimulating hormone (TSH) and molecular markers (Table 1).

Age

DTC is the only human malignancy to include age as part of the staging system, despite the fact that advanced age is known to be associated with worse survival in many types of cancer (22,23). Traditionally, the age cutoff of 45 years has been and continues to be used in current DTC staging guidelines (24). However, new research has recently emerged evaluating the impact of age on DTC survival.

A retrospective analysis based on the Surveillance Epidemiology and End Results (SEER) database examined patients diagnosed with either papillary or follicular thyroid cancer between 1988 and 2003 (n=29,225), and conducted Kaplan-Maier survival analyses to estimate disease-specific survival based on patient age range. The study showed that patients 45 years and older had significantly worse survival than younger patients ($p<0.0001$). More specifically, there was a significant decrease in disease-specific survival first seen in patients aged 35 years and older and survival continued to steadily decrease with each additional decade of age ($p<0.001$). The study concluded that increasing age is associated with poorer survival in DTC and this relationship represents a continuum (25).

Also using the SEER database, Bischoff LA et al. obtained data for histology-confirmed papillary thyroid cancer and stratified them in 5-year categories by age at diagnosis from 20–64 years old, with patients 65 years of age and older categorized together (n=53,581). Overall 5-year survival remained above 90% for all age groups under 65 years, while patients 65 years old and over had a progressively less favorable prognosis with each advancing age group (26).

In another study, Amphlett et al (27) identified thyroid cancer cases registered in the Welsh Cancer Intelligence and Surveillance Unit from 1985 through 2010 (n=1747) and performed survival analyses. Survival was determined for five-year diagnosis periods for all-cause mortality and thyroid cancer-specific mortality. Factors that significantly reduced survival included age over 65 years ($p<0.001$, >65 years vs. 15–64 years), as well as male sex.

Survival data were also collected in a prospective database study conducted on 2011 DTC patients at a single German hospital from 1980–2011. Survival data for the general German population were obtained and matched to the DTC population studied for age and sex. The authors demonstrated that patients who were at least 45 years old at diagnosis and had extensive perithyroidal invasion (AJCC/TNM stages IVa and IVb), lateral cervical lymph node metastases (Stage IVa) or distant metastases (stage IVc) showed a clearly reduced life expectancy. In patients who were over 60 years of age at diagnosis, the loss of life expectancy was greater than for those aged 45–59 years in all groups. The life expectancy was not reduced in patients with TNM stages I, II or III (16).

New data are emerging on the prognostic significance of age in DTC that suggest an older age than 45 may be a more accurate age cutoff for prognosis. Use of an older age cutoff would lead to downstaging many patients with DTC and may lead to potentially avoiding unnecessary ancillary therapies in patients with favorable prognosis. Further studies are required to determine whether an older age cutoff versus a staging system using age as a continuum is needed.

Gender

Despite a higher incidence of DTC, overall survival was reported to be better in women in several cohorts both by univariate and multivariate analyses (28–31). It is hypothesized that worse outcomes in men may potentially be accounted for by a more aggressive behavior of DTC in these patients. Other studies have shown no effect of gender on overall survival (32,33).

A recent study by Jonklaas et al. (34) aimed to determine whether there were gender differences in the overall and disease-specific mortality of patients with papillary thyroid cancer in the National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG) Registry (n=3,572). The study concluded that a gender advantage in survival for women with papillary thyroid cancer reflected a generalized gender advantage seen in the United States population. They also showed that once the diagnosis of papillary thyroid cancer was made, disease-specific survival of women was similar to men after adjusting for presenting disease stage and age. In addition, although with adjustments for stage women as a group had a similar disease-specific survival to men, women with stage I and II disease had better

outcomes than men when comparing individuals diagnosed before age 55 years old. The impact of the age cutoff of 55 years is interesting as this corresponds to the age at which most women in the United States have attained menopause (35,36).

Yang L et al. (37) studied patients registered in the SEER database with thyroid cancer (n=29,225) and found that male patients showed higher cumulative incidence of death compared with their female counterparts ($p<0.001$). Nilubol N et al. (38) also used the SEER database and performed multivariate analyses between male sex, disease-specific survival and features of tumor aggressiveness in thyroid cancer of follicular cell origin (n=61,523). They found that sex was not an independent prognostic factor for disease-specific survival.

Another recent study investigated the correlation between gender and the thyroid cancer mortality in a cohort of 435 patients who underwent thyroid surgery for stage II–IV papillary thyroid cancer (39). They demonstrated that 20.6% of females as compared to 40.8% of males exhibited postoperative disease progression. Multiple regression analysis showed that male gender was an independent risk factor for thyroid cancer recurrence and mortality.

The influence of gender on DTC survival is controversial, as gender-related ascertainment bias may exist. It is possible that men reach medical attention at an older age with more advanced disease or women present earlier and are screened more thoroughly. Also, as women have lower all-cause mortality rates and live longer than men (40), mortality should be adjusted to gender-specific overall survival rates. Moreover, literature that has examined the impact of estrogen on thyroid cancer is inconsistent and numerous studies have reported conflicting relationships between estrogen status and incidence and aggressiveness of DTC (41–47). Recently published guidelines concerning high-risk cases of papillary and follicular thyroid carcinomas do not consider gender as a risk factor (24) and further research is needed to determine whether there is a correlation.

Lymph Node Involvement

DTC staging systems consider metastatic lymph nodes, when included, as a binary entity, i.e. presence versus absence. The extent of initial surgery and the role of lymph node dissection for papillary thyroid cancer remain controversial. The debate stems from the uncertain prognostic significance of metastatic cervical lymph nodes in papillary thyroid cancer, as with thorough inspection up to 90% of patients will have micrometastatic disease (48,49). The association between clinically positive lymph node metastases and recurrence is well recognized (50), but their significance on survival remains debatable.

The impact of lymph node involvement on survival on patients with papillary and follicular thyroid cancer was investigated in a study of 33,088 patients identified in the SEER registry between 1988 and 2003 (51). Patients were stratified by age (<45 versus ≥45 years) and pathology (papillary/follicular). It was established that in patients with papillary thyroid cancer <45 years, lymph node disease did not influence survival ($p=0.535$), whereas in patients ≥45 years, lymph node involvement was associated with 46% increased risk of death ($p<0.001$). In patients with follicular carcinoma lymph node involvement conferred increased risk of death in both age groups ($p\leq0.002$).

By utilizing the SEER database Schneider DF et al. analyzed adult patients who underwent thyroidectomy with lymph node dissection (n=10,955) and a lymph node ratio (metastatic lymph nodes to total lymph nodes) was calculated. Patients with less than three lymph nodes collected were excluded. After comparing Kaplan-Meier survival estimates and overall disease-specific mortality rates, they found that patients with a lymph node ratio ≥ 0.42 experienced a 77% higher disease-specific mortality rate compared to those with metastatic lymph nodes as a whole (52).

Beal SH et al. also used the SEER database to identify all patients with primary non-metastatic DTC who underwent thyroidectomy with at least one lymph node removed between 1988 and 2004. Kaplan-Meier survival curves for lymph node yield (number of lymph nodes harvested) and metastatic lymph node ratio were compared. In multivariable analysis, increasing lymph node yield was associated with poorer survival in all patients (p=0.001) and node-negative patients (p=0.03), but not for node-positive patients (p=0.27). Metastatic lymph node ratio did not influence survival in node-positive patients (p=0.84) (53).

More recently, another study determined that the lymph node ratio is an important independent prognostic factor in papillary thyroid cancer and can be used in conjunction with existing staging systems (54). A retrospective analysis was conducted of 198 patients with papillary thyroid cancer undergoing total thyroidectomy with neck dissection at a single institution between 1987 and 2011. The lymph node ratio was associated with a decrease in disease-free survival (p=0.005). Patients with a lymph node ratio of 0.30 or higher had a 3.4 times higher risk of persistent or recurrent disease compared with patients with a lymph node ratio of 0 (p=0.031).

There is an ongoing controversy regarding the association of lymph node involvement in DTC and survival, and whether prophylactic central lymph node dissection should be performed in these patients. Randomized prospective controlled trials are currently lacking and more research is needed to determine the prognostic role of prophylactic central lymph node dissection in the management of DTC.

Thyroid Stimulating Hormone (TSH)

Serum TSH concentration is directly associated with the risk of cancer in a thyroid nodule (55–57), and TSH suppression has been shown to improve prognosis of high-risk DTC patients (58–60). In a retrospective cohort study of 1198 patients who underwent thyroid surgery at a single hospital for DTC, risk of malignancy correlated with higher TSH level on both univariate and multivariate analyses (p=0.007) (57). More specifically, the likelihood of malignancy was 16% when serum TSH was less than 0.06 mIU/L versus 52% when 5 mIU/L or greater (p=0.001). In another retrospective cohort study by the same investigators, mean TSH was shown to be significantly higher in thyroid cancer patients regardless of age. (61).

Serum TSH has also been associated not only with thyroid cancer incidence but also with advanced tumor stage (56,57,62). A recent systematic review by Fiore et al. (56) examined studies focusing on the relationship between TSH and DTC. It was concluded that in

patients with nodular thyroid disease, the risk of thyroid malignancy increases with serum TSH, and even within normal ranges, higher TSH values are associated with a higher frequency and more advanced stage of thyroid cancer. Haymart et al also showed that higher serum TSH level is associated with extrathyroidal extension of disease (61) in a retrospective cohort study of 1361 patients who underwent thyroid surgery between 1994 and 2007 at a single institution. On multivariate analysis of high-risk features associated with poor prognosis, there was a significant association between higher TSH and extrathyroidal extension (p=0.002). Another study also evaluated the association of preoperative serum TSH levels with the advance of DTC and its high-risk clinicopathological features in Korean patients. Using multiple logistic regression, they found that preoperative TSH level was a predictive factor for the presence of extrathyroidal extension (p=0.008) and lateral lymph node metastases (p=0.025) (62).

In order to assess the prognostic significance of serum TSH and thyroglobulin antibody status at the time of patients' thyroid cancer diagnosis, McLeod et al. analyzed prospective data from The National Thyroid Cancer Treatment Cooperative Study (NTCTCS), a large non-randomized thyroid cancer registry. Geometric mean serum TSH levels were higher in patients with higher stage disease (stage III/IV=1.48 versus 1.02 mIU/L for stages I/II; p=0.006) and this relationship persisted in those aged ≥45 years after adjusting for sex (p=0.01). Disease recurrence and all-cause mortality occurred in 37 and 38 TSH cohort patients respectively, which limited the power for survival analysis in this study. Perioperative thyroglobulin antibody titer was not an independent predictor of DTC prognosis (63). Of note, a positive serum thyroglobulin antibody test was deemed an independent predictor for thyroid malignancy in a thyroid nodule, regardless of the presence of autoimmune thyroiditis, in another study (64).

Molecular Markers

Substantial developments have occurred in understanding the molecular mechanisms of thyroid cancer in the past 5–10 years (65). Several molecular markers have been studied for their diagnostic and prognostic significance on the basis of which more effective management strategies for DTC are being developed.

Numerous studies have shown that BRAF mutation is a prognostic genetic marker that has improved risk stratification and has tailored management of patients with thyroid cancer, including those with conventionally low risk disease. BRAF mutation is highly prevalent in recurrent papillary thyroid cancer, ranging from 78%–95% (66–69). As the disease-specific survival among patients with papillary thyroid cancer is excellent, BRAF mutational status may be most relevant to recurrence risk. The addition of BRAF mutational status to established risk algorithms has been shown to improve the discrimination of risk recurrence in patients undergoing total thyroidectomy for papillary thyroid cancer. The 5-year cumulative papillary thyroid cancer recurrence incidence in a 356 patient cohort was 20% among patients $BRAF^{V600E}$ versus 8% of patients with BRAF wild type. $BRAF^{V600E}$ was significantly associated with time to recurrence when added to the AMES, MACIS, AJCC/TNM and ATA recurrence-risk category (70).

Many large well-designed studies demonstrated a close association of BRAF mutation with major clinicopathological risk factors, such as extrathyroidal extension, lymph node metastasis and advanced TNM stage III/VI of papillary thyroid cancer, which are associated with increased rates of recurrence and mortality (71). In a retrospective review of 977 papillary thyroid microcarcinoma cases that underwent surgical resection between 2001 and 2010 at a single institution, univariate analysis showed that $BRAF^{V600E}$ mutation was significantly associated with advanced disease stage. Multiple logistic regression analyses showed a significant association between $BRAF^{V600E}$ and extrathyroidal extension and lymph node metastases (72).

In another retrospective study of 1849 patients with papillary thyroid cancer who underwent initial treatment at 13 centers in 7 countries between 1978 and 2011, the presence of $BRAF^{V600E}$ mutation was significantly associated with increased cancer-related mortality. Overall mortality was 5.3% in $BRAF^{V600E}$ positive versus 1.1% in mutation-negative patients ($p<0.001$) (73).

On the contrary, Zoghlami A et al. conducted a retrospective study in which BRAF mutation status did not significantly correlate with various clinicopathological factors studied including advanced age, extrathyroidal extension, multifocal tumor, cervical lymph node metastasis, tumor size and advance stage. The same study showed no significant difference in tumor recurrence rate between the two subgroups of mutant BRAF and wild-type BRAF patients (74).

In contrast to BRAF mutation, RAS mutations and RET/PTC rearrangements, which are also common genetic alterations in papillary thyroid cancer, are much less commonly associated with aggressive pathogenesis (75). The significance of RAS mutations was examined in a large number of follicular thyroid adenomas and carcinomas at a single institution in Japan (76). It was found that 30% of adenomas versus 57% of carcinomas harbored RAS mutations, which was predominantly found in the NRAS codon 61 ($p<0.01$) and the rate of gene mutations was significantly higher in the carcinomas than the adenomas ($p<0.01$). The NRAS codon 61 mutation in follicular carcinomas was positively associated with distant metastases ($p<0.05$) and RAS mutations were associated with poor overall patient survival ($p<0.05$). RAS mutations were also studied by Gupta N et al. (77) by looking at 68 aspirates from 66 patients undergoing fine-needle aspiration. All RAS-positive papillary thyroid cancers (n=46) were found to be of low-grade follicular variant histology.

Mutational analysis was performed on 62 papillary thyroid cancers in regions surrounding Chernobyl, Ukraine, to assess the associations between mutation types and thyroid cancer risk (78). RET/PTC rearrangements were most common (35%), followed by BRAF (15%), and RAS (8%) point mutations. Two tumors were identified that carried PAX8/PPARγ. There was an association found between chromosomal rearrangements, but not point mutations, and I-131 exposure, pointing to a possible role of iodine deficiency in generation of RET/PTC rearrangements in these patients (78). A study investigating follicular Hurthle cell tumors found that RET/PTC rearrangements existed in 38% of follicular Hurthle cell carcinomas and PAX8/PPARγ rearrangement was present in 27% (79).

CONCLUSION

A number of staging and scoring systems exist for DTC but these harbor limitations. This has elicited further investigation for new factors with potential prognostic implications for DTC, including TSH and molecular markers, and led to challenging of current controversial prognostic markers, such as age, gender and lymph node involvement. Further research is needed to delineate the role of these markers in DTC prognosis and whether their inclusion in staging is warranted.

Acknowledgments

The authors report that they do not have any relevant financial relationships with any commercial interests. Dr. Papaleontiou is supported by the NIH Institutional National Research Service Award (5T32DK007245-37) and Dr. Haymart is funded by grant 1K07CA154595-01 from the National Institutes of Health.

REFERENCES

1. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. Cancer. 2009; 115:3801–3807. [PubMed: 19598221]
2. Enewold L, Zhu K, Ron E, et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980–2005. Cancer Epidemiol Biomarkers Prev. 2009; 18:784–791. [PubMed: 19240234]
3. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist. 2007; 12:20–37. [PubMed: 17227898]
4. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013 Jan; 63(1):11–30. [PubMed: 23335087]
5. Howlader, N.; Noone, AM.; Krapcho, M., et al., editors. SEER Cancer Statistics Review, 1975–2010. Bethesda, MD: National Cancer Institute; 2013. http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER website
6. Sherman SI. Thyroid carcinoma. Lancet. 2003; 361:501–511. [PubMed: 12583960]
7. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, et al. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery. 1993; 114:1050–1057. [PubMed: 8256208]
8. Hay ID, Grant CS, Taylor WF, McConahey WM. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery. 1987; 102:1088–1095. [PubMed: 3686348]
9. Pasieka JL, Zedenius J, Auer G, et al. Addition of nuclear DNA content to the AMES risk-group classification for papillary thyroid cancer. Surgery. 1992; 112:1154–1159. [PubMed: 1455318]
10. Byar DP, Green SB, Dor P, et al. A prognostic index for thyroid carcinoma. A study of the E.O.R.T.C. Thyroid Cancer Cooperative Group. Eur J Cancer. 1979; 15:1033–1041. [PubMed: 510341]
11. Sobin, LH.; Wittekind, C. TNM classification of malignant tumours. 5th ed.. Berlin, Heidelberg, New York, Tokyo: Springer; 1997.
12. Sobin, LH.; Wittekind, C. TNM classification of malignant tumours. 6th ed.. New York: Wiley-Liss; 2002.
13. Sobin, LH.; Gospodarowicz, MK.; Wittekind, C. TNM classification of malignant tumours. 7th ed.. New York: Wiley-Blackwell; 2009.
14. Brierley JD, Panzarella T, Tsang RW, et al. A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example. Cancer. 1997; 79:2414–2423. [PubMed: 9191532]

15. Dean DS, Hay ID. Prognostic indicators in differentiated thyroid carcinoma. Cancer Control. 2000; 7(3):229–239. [PubMed: 10832109]

16. Verburg FA, Mader U, Tanase K, et al. Life expectancy is reduced in differentiated thyroid cancer patients ≥45 years old with extensive local tumor invasion, lateral lymph node, or distant metastases at diagnosis and normal in all other DTC patients. J Clin Endocrinol Metab. 2013; 98:172–180. [PubMed: 23150687]

17. Verburg FA, Mader U, Kruitwagen CL, et al. A comparison of prognostic classification systems for differentiated thyroid carcinoma. Clin Endocrinol (Oxf). 2010; 72:830–838. [PubMed: 19863574]

18. Tuttle RM, Tala H, Shah J, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid. 2010; 20:1341–1349. [PubMed: 21034228]

19. Pitoia F, Bueno F, Urcluoli C, et al. Outcome of patients with differentiated thyroid cancer risk stratified according to the American Thyroid Association and Latin-American Thyroid Society risk of recurrence classification systems. Thyroid. 2013 Jul 25. (Epub ahead of print).

20. Nixon IJ, Ganly I, Patel SG, et al. The results of selective use of radioactive iodine on survival and on recurrence in the management of papillary thyroid cancer, based on Memorial Sloan-Kettering Cancer Center risk group stratification. Thyroid. 2013 Jun; 23(6):683–694. [PubMed: 23742290]

21. Tuttle RM, Leboeuf R. Follow up approaches in thyroid cancer: A risk adapted paradigm. Endocrinol Metab Clin N Am. 2008; 37:419–435.

22. Wang J, Wang FW. Impact of age on clinical presentation, treatment, and cancer-specific survival of patients with small-cell carcinoma of the prostate. Clin Interv Aging. 2013; 8:871–877. [PubMed: 23885169]

23. Eaker S, Dickman PW, Bergkvist L, et al. Differences in management of older women influence breast cancer survival: results from a population-based database in Sweden. PLoS Med. 2006 Mar. 3(3):s25.

24. Cooper, Ds; Doherty, GM.; Haugen, BR., et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009; 19(11):1–48. [PubMed: 19119978]

25. Oyer SL, Smith VA, Lentsch EJ. Reevaluating the prognostic significance of age in differentiated thyroid cancer. Otoralyngol Head Neck Surg. 2012 Aug; 147(2):221–226.

26. Bischoff LA, Curry J, Ahmed J, et al. Staging of papillary thyroid cancer: Why age 45? Thyroid. 2012; 22(1):A-74. This study highlights that patients 65 years and older with DTC have a progressively less favorable prognosis than younger ones. This may have implications in re-investigating the cutoff of 45 years included in current staging guidelines.

27. Amphlett B, Lawson Z, Abdulrahman GO Jr, et al. Recent Trends in the Incidence, Geographical Distribution, and Survival From Thyroid Cancer in Wales, 1985–2010. Thyroid. 2013 Jun 14. (Epub ahead of print).

28. Akslen LA, Haldorsen T, Thoresen SO, Glattre E. Survival and causes of death in thyroid cancer: a population-based study of 2479 cases from Norway. Cancer Res. 1991; 51:1234–1241. [PubMed: 1997164]

29. Cunningham MP, Duda RB, Recant W, et al. Survival discriminants for differentiated thyroid cancer. Am J Surg. 1990; 160:344–347. [PubMed: 2221232]

30. Micheli A, Ciampichini R, Oberaigner W, et al. The advantage of women in cancer survival: an analysis of EUROCARE-4data. Eur J Cancer. 2009; 45:1017–1027. [PubMed: 19109009]

31. Tubiana M, Schlumberger M, Rougier P, et al. Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. Cancer. 1985; 55:794–804. [PubMed: 3967174]

32. Carcangiu ML, Zampi G, Pupi A, et al. Papillary carcinoma of the thyroid. A clinicopathologic study of 241cases treated at the University of Florence, Italy. Cancer. 1985; 55:805–828. [PubMed: 3967175]

33. Elisei R, Molinaro E, Agate L, et al. Are the clinical and pathological features of differentiated thyroid carcinoma really changed over the last 35 years? Study on 4187 patients from a single

Italian institution to answer this question. J Clin Endocrinol Metab. 2010; 95:1516–1527. [PubMed: 20156922]

34. Jonklaas J, Nogueras-Gonzalez G, Mursell M, et al. The impact of age and gender on papillary thyroid cancer survival. J Clin Endocrinol Metab. 2012; 97:E878–E888. [PubMed: 22496497] This is one of the largest studies showing a gender advantage in survival for women with papillary thyroid cancer. The fact that women with stage I and II disease had better outcomes than men when diagnosed before age 55 years, may imply there are hormonal influences on survival.
35. Weinstein M, Gorrindo T, Riley A, et al. Timing of menopause and patterns of menstrual bleeding. Am J Epidemiol. 2003; 158:782–791. [PubMed: 14561668]
36. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. Maturitas. 1992; 14:103–115. [PubMed: 1565019]
37. Yang L, Shen W, Sakamoto N. Population-based study evaluating and predicting the probability of death resulting from thyroid cancer and other causes among patients with thyroid cancer. J Clin Oncol. 2013 Feb 1; 31(4):468–474. [PubMed: 23270002]
38. Nilubol N, Zhang L, Kebebew E. Multivariate analysis of the relationship between male sex, disease-specific survival, and features of tumor aggressiveness in thyroid cancer of follicular cell origin. Thyroid. 2013 Jun; 23(6):695–702. [PubMed: 23194434]
39. Hsieh SH, Chen S-T, Hsueh C, et al. Gender-specific variation in the prognosis of papillary thyroid cancer TNM stages II to IV. Int J Endocrinol. 2012; 2012:379097. [PubMed: 23304140] This study showed that male gender was an independent risk factor for thyroid cancer recurrence and mortality. This has implications on gender as a potential prognostic marker.
40. 2003 United States life tables. 2003. www.cdc.gov/nchs/data/statab/lewk3pdf.
41. Mack WJ, Preston-Martin S, Bernstein L, et al. Reproductive and hormonal risk factors for thyroid cancer in Los Angeles County females. Cancer Epidemiol Biomarkers Prev. 1999; 8:991–999. [PubMed: 10566554]
42. Negri E, Dal Maso L, Ron E, et al. A pooled analysis of case-control studies of thyroid cancer. II. Menstrual and reproductive factors. Cancer Causes Control. 1999; 10:143–155. [PubMed: 10231163]
43. Sakoda LC, Horn-Ross PL. Reproductive and menstrual history and papillary thyroid cancer risk: the San Francisco Bay Area thyroid cancer study. Cancer Epidemiol Biomarkers Prev. 2002; 11:51–57. [PubMed: 11815401]
44. Rossing MA, Voigt LF, Wicklund KG, Daling JR. Reproductive factors and risk of papillary thyroid cancer in women. Am J Epidemiol. 2000; 151:765–772. [PubMed: 10965973]
45. Rajoria S, Suriano R, Shanmugam A, et al. Metastatic phenotype is regulated by estrogen in thyroid cells. Thyroid. 2010; 20:33–41. [PubMed: 20067378]
46. Parlea L, Fahim L, Munoz D, et al. Follicular carcinoma of the thyroid with aggressive metastatic behavior in a pregnant woman: report of a case and review of the literature. Hormones (Athens). 2006; 5:295–302. [PubMed: 17178705]
47. Leboeuf R, Emerick LE, Martorella AJ, Tuttle RM. Impact of pregnancy on serum thyroglobulin and detection of recurrent disease shortly after delivery in thyroid cancer survivors. Thyroid. 2007; 17:543–547. [PubMed: 17614775]
48. Qubain SW, Nakano S, Baba M, et al. Distribution of lymph node micrometastasis in pN0 well-differentiated thyroid carcinoma. Surgery. 2002; 131:249–256. [PubMed: 11894028]
49. Arturi F, Russo D, Giuffrida D, et al. Early diagnosis by genetic analysis of differentiated thyroid cancer metastases in small lymph nodes. J Clin Endocrinol. 1997; 82:1638–1641.
50. Wada N, Suganuma N, Nakayama H, et al. Microscopic regional lymph node status in papillary thyroid carcinoma with and without lymphadenopathy and its relation to outcomes. Langenbecks Arch Surg. 2007; 392:417–422. [PubMed: 17562092]
51. Zaydfudim V, Feurer ID, Griffin MR, Phay JE. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. Surgery. 2008 Dec; 144(6):1070–1077. [PubMed: 19041020]
52. Schneider DF, Chen H, Sippel RS. Impact of lymph node ratio on survival in papillary thyroid cancer. Ann Surg Oncol. 2013 Jun; 20(6):1906–1911. [PubMed: 23263904] This study revisited using a specific lymph node ratio in a large patient sample to predict disease-specific mortality.

53. Beal SH, Chen SL, Schneider PD, Martinez SR. An evaluation of lymph node yield and lymph node ratio in well-differentiated thyroid carcinoma. Am Surg. 2010 Jan; 76(1):28–32. [PubMed: 20135936]
54. Vas Nunes JH, Clark JR, Gao K, et al. Prognostic implications of lymph node yield and lymph node ratio in papillary thyroid carcinoma. Thyroid. 2013 Jul; 23(7):811–816. [PubMed: 23373961] This study validated that the lymph node ratio is an important independent prognostic factor in papillary thyroid cancer, and may be potentially used in DTC staging.
55. McLeod DS, Watters KF, Carpenter AD, et al. Thyrotropin and thyroid cancer diagnosis: a systematic review and dose-response meta-analysis. J Clin Endocrinol Metab. 97:2682–2692. [PubMed: 22622023]
56. Fiore E, Vitti P. Serum TSH and risk of papillary thyroid cancer in nodular thyroid disease. J Clin Endocrinol Metab. 2012; 97:1134–1145. [PubMed: 22278420]
57. Haymart MR, Repplinger DJ, Leverson GE, et al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. J Clin Endocrinol Metab. 2008; 93:809–814. [PubMed: 18160464]
58. Pujol P, Daures JP, Nsakala N, et al. Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. J Clin Endocrinol Metab. 1996; 81:4318–4323. [PubMed: 8954034]
59. Jonklaas J, Sarlis NJ, Litofsky D, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid. 2006; 16:1229–1242. [PubMed: 17199433]
60. Hovens GC, Stokkel MP, Kievit J, et al. Associations of serum thyrotropin concentrations with recurrence and death in differentiated thyroid cancer. J Clin Endocrinol Metab. 2007; 92:2610–2615. [PubMed: 17426094]
61. Haymart MR, Glinberg SL, Liu J, et al. Higher serum TSH in thyroid cancer patients occurs independent of age and correlates with extrathyroidal extension. Clin Endocrinol (Oxf). 2009; 71:434–439. [PubMed: 19067720]
62. Kim SS, Lee BJ, Lee JC, et al. Preoperative serum thyroid stimulating hormone levels in well-differentiated thyroid carcinoma is a predictive factor for lateral lymph node metastasis as well as extrathyroidal extension in Korean patients: a single-center experience. Endocrine. 2011 Jun; 39(3):259–265. [PubMed: 21161440]
63. McLeod DSA, Cooper DS, Ladenson PW, et al. Prognosis of differentiated thyroid cancer in relation to serum TSH and thyroglobulin antibody status at time of diagnosis. Thyroid. 2013 Jun 3. (Epub ahead of print).
64. Kim ES, Lim DJ, Baek KH, et al. Thyroglobulin antibody is associated with increased cancer risk in thyroid nodules. Thyroid. 2010 Aug; 20(8):885–891. [PubMed: 20465529]
65. Xing M, Haugen BR, Schlumberger M. Progress in molecular-based management of differentiated thyroid cancer. The Lancet. 2013 Mar; 381(9871):1058–1069.
66. Ricarte-Filho JC, Ryder M, Chitale DA, et al. Mutational profile of advanced primary and metastatic radioactive iodine-refractory thyroid cancers reveals distinct pathogenetic roles for BRAF, PIK3CA, and AKT1. Cancer Res. 2009; 69:4885–4893. [PubMed: 19487299]
67. Tufano RP, Bishop J, Wu G. Reoperative central compartment dissection for patients with recurrent/persistent papillary thyroid cancer: efficacy, safety, and the association of the BRAF mutation. Laryngoscope. 2012; 122:1634–1640. [PubMed: 22549559]
68. Barollo S, Pennelli G, Vianello F, et al. BRAF in primary and recurrent papillary thyroid cancers: the relationship with (131)I and 2-[(18)F]fluoro-2-deoxy-D-glucose uptake ability. Eur J Endocrinol. 2010; 163:659–663. [PubMed: 20647301]
69. Henderson YC, Shellenberger TD, Williams MD, et al. High rate of BRAF and RET/PTC dual mutations associated with recurrent papillary thyroid carcinoma. Clin Cancer Res. 2009; 15:485–491. [PubMed: 19147753]
70. Prescott JD, Sadow PM, Hodin RA, et al. BRAF V600E status adds incremental value to current risk classification systems in predicting papillary thyroid carcinoma recurrence. Surgery. 2012 Dec; 152(6):984–990. [PubMed: 23158172]
71. Xing M. Prognostic utility of BRAF mutation in papillary thyroid cancer. Mol Cell Endocrinol. 2010 May 28; 32(1):86–93. [PubMed: 19883729]

72. Zheng X, Wei S, Han Y, et al. Papillary microcarcinoma of the thyroid: clinical characteristics and BRAF(V600E) mutational status of 977 cases. Ann Surg Oncol. 2013 Jul; 20(7):2266–2273. [PubMed: 23370668]

73. Xing M, Alzahrani AS, Carson KA, et al. Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. JAMA. 2013 Apr 10; 309(14):1493–1501. [PubMed: 23571588] This is the only international multi-center study that showed the presence of $BRAF^{V600E}$ mutation was significantly associated with increased cancer-related mortality.

74. Zoghlami A, Roussel F, Sabourin JC, et al. BRAF mutation in papillary thyroid carcinoma: Predictive value for long-term prognosis and radioiodine sensitivity. Eur Ann Otorhinolaryngol Head Neck Dis. 2013 Jul 8. (Epub ahead of print).

75. Rusinek D, Szpak-Ulczok S, Jarzab B. Gene expression profile of human thyroid cancer in relation to its mutational status. J Mol Endocrinol. 2011 Nov 2; 47(3):R91–R103. [PubMed: 21798995]

76. Fukahori M, Yoshida A, Hayashi H, et al. The associations between RAS mutations and clinical characteristics in follicular thyroid tumors: new insights from a single center and a large patient cohort. Thyroid. 2012 Jul; 22(7):683–689. [PubMed: 22650231]

77. Gupta N, Dasyan AK, Carty SE, et al. RAS mutations in thyroid FNA specimens are highly predictive of predominantly low-risk follicular pattern cancers. J Clin Endocrinol Metab. 2013 May; 98(5):E914–E922. [PubMed: 23539734]

78. Leeman-Neill RJ, Brenner AV, Little MP, et al. RET/PTC and PAX8/PPARγ chromosomal rearrangements in post-Chernobyl thyroid cancer and their association with iodine-131 radiation dose and other characteristics. Cancer. 2013 May 15; 119(10):1792–1799. [PubMed: 23436219]

79. De Vries MM, Celestino R, Castro P, et al. RET/PTC rearrangement is prevalent in follicular Hurthle cell carcinomas. Histopathology. 2012 Nov.(6195):833–843. [PubMed: 22803838]

KEY POINTS

- Many staging and scoring systems for differentiated thyroid cancer currently exist but limitations have prompted investigation for new prognostic markers in risk stratification.
- The current age cutoff of 45 years in existing DTC staging guidelines is being challenged, and new data are emerging that an older age cutoff or evaluating age as a continuum may be more appropriate prognostically.
- The influence of gender on DTC survival is controversial and further studies are needed to determine its significance.
- Further research is needed to delineate the effect of lymph node involvement on DTC survival and the role of prophylactic central lymph node dissection in these patients.
- New potential risk stratifiers for DTC are emerging, including TSH and molecular markers, such as BRAF, RAS, RET/PTC and PAX8/PPARγ.

Table 1

Summary of New Potential Prognostic Markers in DTC Risk Stratification.

Prognostic Variable	Previous/Current Assumptions	Current Challenges	Research Direction
Age	<45 years versus ≥45 years	Continuum versus an older cutoff age	Need to re-evaluate age in DTC staging
Gender	No difference between male and female	Difference in subgroups, i.e. age>55	Re-evaluate impact of gender on DTC prognosis; what is the etiology of the differences?
Lymph Node Involvement	Prognostic role if age ≥45 years	Unclear whether it is a prognostic factor	Does lymph node resection improve outcome in DTC patients?
TSH	Not a prognostic factor	Higher TSH is associated with more advanced disease	Is TSH important at the population level / should it be included in the staging system?
Molecular Markers	Not studied	BRAF, RAS, RET/PTC, PAX8/PPARγ are associated with worse prognosis	Can these molecular markers be used to determine extent of surgery and/or need for radioactive iodine treatment?