Refining Dynamic Risk Stratification and Prognostic Groups for Differentiated Thyroid Cancer With *TERT* Promoter Mutations

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Context: Currently, no recurrence or mortality risk systems consider molecular testing when predicting thyroid cancer outcomes.

Objective: We developed an integrative prognostic system that incorporates telomerase reverse transcription (*TERT*) promoter mutations into the recently proposed risk reclassification system after initial therapy [dynamic risk stratification (DRS)] to better categorize and predict outcomes.

Design: A total of 357 differentiated thyroid cancer (DTC) patients without initial distant metastasis were enrolled. Among patients with mutated *TERT* and wild-type, recurrence-free survival (RFS) was compared according to DRS grouping. Cox regression was used to calculate adjusted hazard ratios (AHRs) to derive AHR groups. Performance of the AHR grouping system with respect to prediction of structural recurrence and cancer-specific survival (CSS) was assessed against the current DRS system and the tumor/node/metastasis (TNM) classification.

Results: Among 357 patients, there were 90 recurrences and 15 cancer-related deaths during a median of 14 years of follow-up. Patients in higher AHR groups were at higher risk of recurrence (10-year RFS for AHR 1, 2, 3, and 4: 94.9%, 82.7%, 50.2%, and 23.1%; $P < 0.001$) and cancer-related death (10-year CSS: 100.0%. 98.7%, 94.2%, and 76.9%; $P < 0.001$). The proportions of variance explained (PVEs) for the ability of AHR and DRS grouping to predict recurrence were 22.4% and 18.5%. PVEs of AHR and TNM system to predict cancer-related deaths were 11.5% and 7.4%.

Conclusions: The AHR grouping system, a simple two-dimensional prognostic system, is as effective as DRS at predicting structural recurrence and provides clinical implication for long-term CSS in patients with nonmetastatic DTC. (***J Clin Endocrinol Metab*** **102: 1757–1764, 2017)**

Telomere reverse transcription (TERT) activation, one of the hallmarks of cancer, enables unlimited proliferation and is driven by oncogenes (1). Two recently discovered hotspot point mutations (C228T and C250T) in the *TERT* promoter have been found in 71% of melanomas (2, 3) and have also been identified in over 50

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 12 October 2016. Accepted 23 February 2017.
First Published Online 28 February 2017

Abbreviations: AHR, adjusted hazard ratio; AJCC, American Joint Committee on Cancer; CI, confidence interval; CSS, cancer-specific survival; DRS, dynamic risk stratification; DTC, differentiated thyroid cancer; PVE, proportion of variance explained; RFS, recurrence-free survival; TERT, telomerase reverse transcription; Tg, thyroglobulin; TNM, tumor/node/metastasis; TSH, thyroid-stimulating hormone; WT, wild type.

cancer types (4), including thyroid cancer (5). The prognostic power of mutations in the *TERT* promoter highlights their potential use as a clinical biomarker in thyroid cancer (6, 7) and other cancers with low rates of self-renewal, such as cancers of the brain, liver, and melanocytes (8). Furthermore, a new robust molecular classification of glioma subtype has been proposed, based on three common genetic alterations including the *TERT* promoter mutation (9). However, currently, no recurrence or mortality risk systems consider molecular testing results when predicting thyroid cancer outcomes.

In 2015, the American Thyroid Association announced new treatment guidelines for differentiated thyroid cancer (DTC) that highlight the reclassification of cancer recurrence risk after initial treatment. These guidelines have been very useful in applying a composite of information that is available in daily practice at thyroid cancer clinics (10–12). This dynamic risk stratification (DRS) system predicts structural recurrence with higher accuracy than traditional classification based on clinical and pathologic information at baseline (13–15).

Herein, the authors aimed to refine risk prediction for structural recurrence and subsequent thyroid cancer–specific mortality using the *TERT* promoter mutation, in addition to the recently proposed DRS system, in a large cohort of initially nonmetastatic DTC patients with long-term follow-up at a tertiary referral center.

Patients and Methods

Study population and tissue samples

After institutional research ethics board approval, the authors retrospectively analyzed the medical records of DTC patients without distant metastasis at initial diagnosis (M0) who were treated with total thyroidectomy and therapeutic neck dissection from 1994 to 2004. In total, 404 medical records of DTC patients were abstracted for the study. Among them, 47 cases were omitted because of receiving lobectomy alone (n = 6), initial distant metastasis (n = 24), loss to follow-up (n = 6), and failure of *TERT* promoter sequencing (n = 11). The further analyzed cohort consisted of samples from 357 patients. In accordance with international guidelines available at the time, postoperative treatments included thyroid hormone to suppress thyroid-stimulating hormone (TSH) concentration and/or radioactive iodine treatment.

Genomic DNA was extracted using a Qiagen DNA formalin-fixed, paraffin-embedded tissue kit (Qiagen, Hilden, Germany) according to manufacturer instructions for all available tissue blocks. Promoter mutations in the *TERT* gene were ascertained by seminested polymerase chain reaction and sequencing as previously described (2, 7, 16). Clinical information including disease description, treatment, and outcomes were obtained from our institutional thyroid cancer database, which is maintained regularly, with each patient followed-up at least once yearly. All patients were initially staged according to the American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification system (seventh edition) that incorporates both anatomic (primary site, reginal lymph nodes, and distant metastatic sites) and nonanatomic (age at diagnosis) prognostic factors (17).

Follow-up and outcomes

Follow-up was maintained by a database coordinator through review of clinical charts. Patient survival status and cause of death were ascertained by linkage to national death certificate data from the Korea National Statistical Office to further enhance data quality. Thyroid cancer-specific survival (CSS) was determined from time of initial surgery to last follow-up or time of death from thyroid cancer (patient death from other causes were censored at time of death). Structural recurrence, as opposed to biochemical recurrence, was defined as recurrent or persistent disease determined pathologically or cytologically to be malignant tissue and/or highly suspicious metastatic lesions on imaging studies (11, 15). Recurrence-free survival was defined as the time from initial surgery to development of the first evidence of structural recurrence.

Dynamic risk stratification

As recommended by the 2015 American Thyroid Association guidelines (10, 11), the authors evaluated clinical data obtained during follow-up and divided patients into four categories according to response to therapy at 1 year (6 to 18 months) after initial radioactive iodine treatment: (1) *excellent* response was defined as imaging negative for disease recurrence with serum thyroglobulin (Tg) <0.2 ng/mL basal or <1 ng/mL TSH stimulated; (2) *indeterminate* response was defined as nonspecific findings on imaging studies, serum Tg 0.2 to 1 ng/mL basal or 1 to 10 ng/mL TSH stimulated, or Tg antibodies stable or decreasing; (3) *biochemical incomplete* response was defined as imaging negative for disease recurrence with serum Tg >1 ng/mL basal or >10 ng/mL TSH stimulated or increasing Tg antibody titer; and (4) *structural incomplete* response was defined as structural (neck ultrasound, computed tomography) or functional (whole-body scan or ^{18}F-fluorodeoxyglucose positron emission tomography) evidence of disease in imaging studies with any Tg concentration.

For subsets of patients who did not undergo radioactive iodine treatment, the response was categorized according to the recently validated response definitions with modified Tg thresholds 1 year after initial surgery (18).

Statistical analysis

The authors stratified patients with DTC by *TERT* promoter mutational status and categories of DRS. To derive alternative prognostic groupings, Cox regression was used to calculate unadjusted and adjusted hazard ratios (AHRs; adjusted with age at diagnosis, sex, histologic type, multifocality, tumor size, extrathyroidal invasion, lymph node metastasis, and radioactive iodine treatment) for risk of structural recurrence with *TERT* status and DRS combinations considering minimal hazard difference, the order of DRS categories, and the sample size balance between the prognostic groups (19). The derived

groups were termed AHR groups. Recurrence-free survival was calculated by the Kaplan–Meier method using log-rank tests for comparisons.

To estimate how well a risk stratification system explained the outcome of interest, we computed the proportions of variance explained (PVEs) in Cox regression models (11, 20, 21). PVE (%) ranges from 0 to 100; larger numbers suggest better predictability. PVE was determined using the mathematical formula: $PVE = 1 - \exp(-G^2/n)$, where G^2 is the maximum likelihood ratio that is determined on analysis of χ^2 test associated with the null hypothesis; n is the total number of valid cases in the study (22). In addition, we estimated the discriminating ability of the different models using the C-statistics for a model containing DRS or the AHR groups as the sole independent variable. The null value for the C-statistic was 0.5, with a maximum of 1.0 (with higher values being better) (23). The model diagnostic included both graphical and statistical checks of the proportional hazards assumption based on the log-minus-log plot and χ^2 tests (24).

The proposed AHR grouping was evaluated via the internal validation based on 1000 datasets generated by the stratified bootstrapping technique. To avoid severe rare event problems in the bootstrap datasets, we broke the original dataset into subdatasets according to recurrence (yes/no) and AHR group combinations, drew a random sample with replacement respectively from each subdataset, and formed a bootstrap dataset by combing the random samples from subdatasets (25). To check reproducibility, explanatory power, and predictability of AHR grouping, Cox regressions for structural recurrence and thyroid cancer–related death were conducted with each of 1000 bootstrap datasets, and the distributions of HR estimates, PVE values, and C-statistics were investigated.

Finally, the authors calculated thyroid CSS for each AHR group. The performance of the AHR grouping was assessed against the seventh edition AJCC TNM system for predicting thyroid CSS. Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC) and R 3.3.2 (The R Foundation, Vienna, Austria; http://www.R-project.org/) software. All tests were two-sided with $P < 0.05$ considered statistically significant.

Results

Table 1 shows the characteristics of the 357 patients with DTC at baseline. The vast majority of tumors were unifocal (72.3%) and papillary thyroid cancer (85.7%). In 42.3% of patients, age at diagnosis was over 45 years; in 63.3% of patients, AJCC TNM classification was stage I or II. *TERT* promoter mutations were detected in 8.4% of patients: 7.6% were *TERT* C228T and 0.8% were C250T mutations. According to the DRS system, patients were classified into four prognostic groups according to the response to initial therapy: excellent (35.0%), indeterminate (46.8%), biochemical incomplete (8.7%), and structural incomplete (9.5%).

There were 90 structural recurrences (25.2%) over a median follow-up of 14 years (range, 1 to 21 years). A reduction in 10-year recurrence-free survival (RFS) in higher DRS groups was evident [92.7%, 81.3%, 43.9%, and 41.2% for *excellent*, *indeterminate*, *biochemical incomplete*, and *structural incomplete* responses, respectively; $P < 0.001$; Fig. 1(b)]. When patients were stratified according *TERT* promoter mutational status, the HRs for structural recurrence increased with increasing DRS severity both in mutant and wild-type (WT) *TERT* (*P* for trend <.001 and 0.026; Table 2).

AHR modeling produced the following four prognostic groups (Tables 3 and 4): AHR 1 (patients with excellent response and WT *TERT*), AHR 2 (patients with indeterminate response and WT *TERT*), AHR 3 (patients with biochemical/structural incomplete response and WT *TERT* or with excellent/indeterminate response and mutant *TERT*), AHR 4 (patients with biochemical/structural incomplete response and mutant *TERT*),

Table 1. Characteristics of the Study Population at Baseline

Characteristics	N (%)
Number	357
Sex	
Female	301 (84.3)
Male	56 (15.7)
Age at diagnosis, y	
Median (range)	43 (16–81)
Tumor size, cm	
Median (range)	2.7 (0.4–12.0)
TERT promoter mutations	
WT	327 (91.6)
C228T	27 (7.6)
C250T	3 (0.8)
Histologic type	
PTC	306 (85.7)
FTC	51 (14.3)
Multifocality	
Absent	258 (72.3)
Present	99 (27.7)
Lymph node metastasis	
Absent	178 (49.9)
Present	178 (49.9)
Missing data	1 (0.3)
Extrathyroidal invasion	
Absent	100 (28.0)
Present	218 (61.1)
Missing data	39 (10.9)
AJCC TNM stage	
I	209 (58.5)
II	17 (4.8)
III	100 (28.0)
IVA	31 (8.7)
Radioactive iodine treatment	
Yes	337 (94.4)
No	20 (5.6)
Follow-up duration, y	
Median (range)	14.0 (1.1–21.4)

Abbreviations: FTC, follicular thyroid cancer; PTC, papillary thyroid cancer.

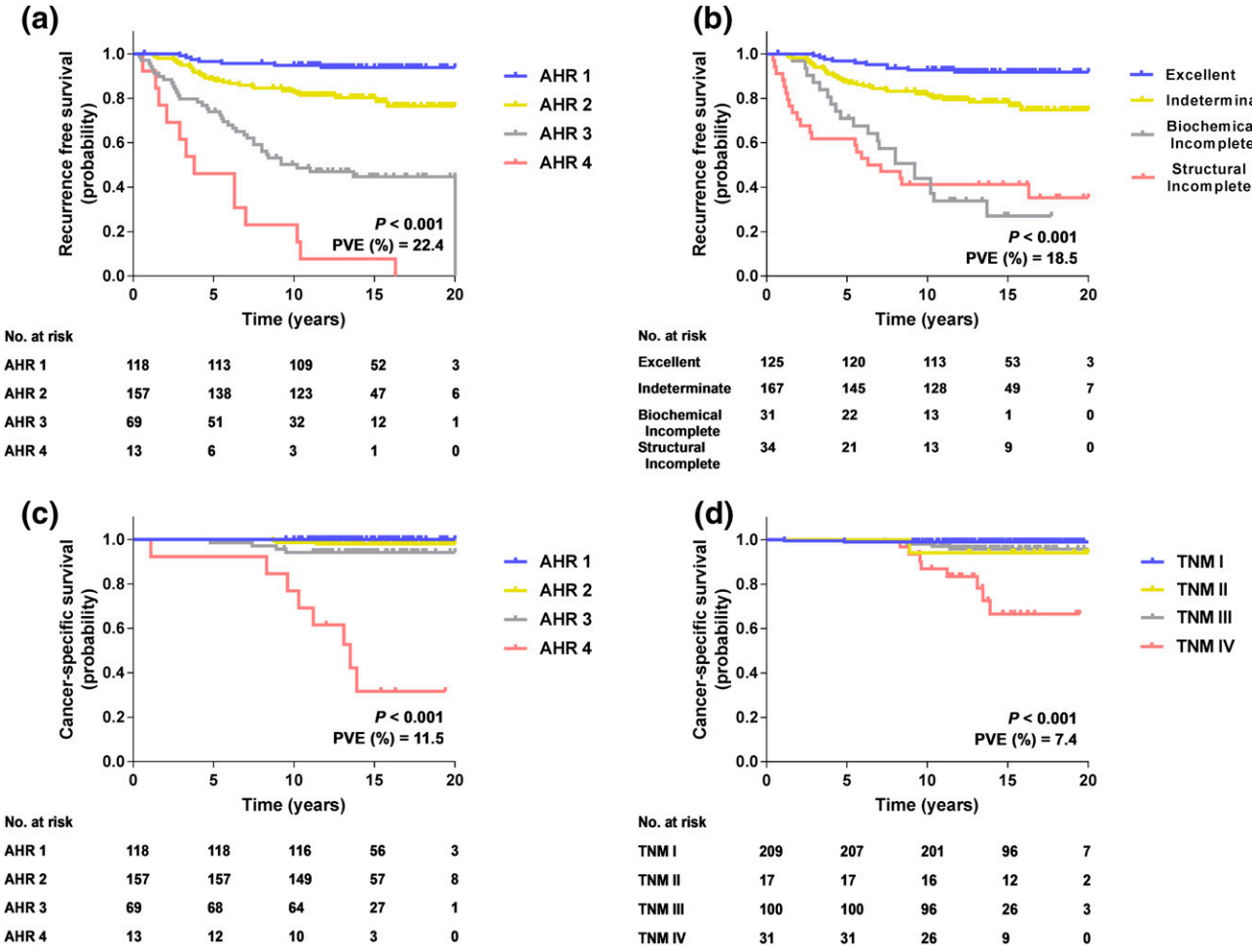

Figure 1. RFS according to (a) the prognostic groups based on AHR from Cox regression and (b) the dynamic risk stratification. Thyroid CSS according to (c) the AHR and (d) the seventh AJCC TNM stage.

with corresponding 10-year RFS rates of 94.9%, 82.7%, 50.2%, and 23.1%, respectively ($P < 0.001$).

Table 4 shows AHR grouping as a predictor of structural recurrence after adjusting for coexisting conditions. The Kaplan–Meier analysis of RFS [Fig. 1(a)] showed that each increase in AHR severity was associated with increased structural recurrence ($P < 0.001$). The calculated hazard ratios were placed within the interquartile ranges of hazard ratio distribution produced from 1000 bootstrap datasets (Supplemental Fig. 1) and

Table 2. Hazard Ratios of Categories of Dynamic Risk Stratification for Structural Recurrence by *TERT* Promoter Mutational Status

	TERT$_{WT}$ (n = 327)						*TERT*$_{mutated}$ (n = 30)					
	Structural Recurrence		Unadjusted		Adjusted[a]		Structural Recurrence		Unadjusted		Adjusted[a]	
Response to Therapy	Events/ Total (%)	10-y RFS, %	HR (95% CI)	*P*	HR (95% CI)	*P*	Events/ Total (%)	10-y RFS, %	HR (95% CI)	*P*	HR (95% CI)	*P*
Excellent	7/118 (5.9)	94.9	1.00 (referent)		1.00 (referent)		3/7 (42.9)	57.1	8.65 (2.23–33.53)	0.002	9.53 (2.32–39.18)	0.002
Indeterminate	32/157 (20.4)	82.7	3.73 (1.64–8.45)	0.002	3.85 (1.69–8.76)	0.001	6/10 (60.0)	60.0	12.26 (4.06–37.03)	<0.001	13.29 (4.27–41.36)	<0.001
Biochemical incomplete	13/23 (56.5)	50.6	12.94 (5.15–32.51)	<0.001	11.03 (4.34–28.02)	<0.001	8/8 (100.0)	25.0	33.70 (12.11–93.77)	<0.001	30.13 (9.89–91.74)	<0.001
Structural incomplete	16/29 (55.2)	44.8	14.65 (6.02–35.64)	<0.001	13.41 (5.41–33.25)	<0.001	5/5 (100.0)	20.0	42.94 (13.57–135.85)	<0.001	38.03 (10.90–132.67)	<0.001

[a] A Cox model adjusting for age at diagnosis, sex, histologic type, multifocality, tumor size, extrathyroidal invasion, lymph node metastasis, and radioactive iodine treatment.

Table 3. Definitions of the AHR Groups That Incorporate *TERT* Promoter Mutations Into the Dynamic Risk Stratification System

Alternative Grouping	Definitions
AHR 1	Patients with excellent response and WT *TERT*
AHR 2	Patients with indeterminate response and WT *TERT*
AHR 3	Patients with biochemical/structural incomplete response and WT *TERT* or with excellent/indeterminate response and mutant *TERT*
AHR 4	Patients with biochemical/structural incomplete response and mutant *TERT*

were also contained in the 95% bootstrap confidence intervals (CIs). The PVEs indicating the ability of AHR and DRS grouping to explain the risk of recurrence were 22.4% (95% CI, 20.2 to 24.6) and 18.5% (95% CI, 14.4 to 22.7), respectively [Fig. 1(a) and 1(b)]. The C-statistics indicating risk predictability were 0.75 (95% CI, 0.74 to 0.76) for AHR and 0.73 (95% CI, 0.70 to 0.76) for DRS alone. Of note, patterns of initial recurrence showed that distant recurrence, as opposed to locoregional recurrences, seemed to be more common in patients with higher AHR groups than those with lower AHR groups (17.6% in AHRs 3 and 4 vs 5.1% in AHRs 1 and 2, $P = 0.07$) when the analysis was performed separately using only the recurrent cases.

There were 17 deaths (4.8%) during follow-up, and the majority of patients (88.2%) died of thyroid cancer. The survivors ranked the lower AHR groups (79.5% were AHRs 1 and 2) than those who died of thyroid cancer (80.0% were AHR 3s and 4, $P < 0.001$). Table 5 and Fig. 1(c) show that AHR group was also a predictor of death from thyroid cancer after correction for coexisting conditions. Whereas there was no thyroid cancer–related death among the AHR 1 group, the highest AHR group (AHR 4) was associated with a mortality rate of 23.1% at 10 years. These same data are shown in Fig. 1(d) in relation to the AJCC TNM stage. The PVEs for the risk of thyroid cancer–specific death were 11.5% (95% CI, 11.0 to 12.1) for the AHR grouping and 7.4% (95% CI, 2.7 to 12.1) for the AJCC TNM system [Fig. 1(c) and 1(d)]. The C-statistic values were 0.86 (95% CI, 0.85 to 0.87) for AHR and 0.80 (95% CI, 0.69 to 0.91) for AJCC TNM system.

Discussion

A considerable body of evidence supports the hypothesis that cancers with *TERT* mutated DTC and WT DTC show different clinical behaviors and may require different treatment choices (26, 27). However, there is currently a lack of consensus about how best to incorporate specific molecular markers into prognostication of thyroid cancer in the context of other clinicopathologic risk factors. Refined prognostic groups of nonmetastatic DTC assume routine assessment of *TERT* promoter mutational status, because the plausibility or practicality of considering all nonmetastatic DTC genotypic variants of the same disease with identical DRS classification is questionable. The overall poor prognosis of patients with *TERT* mutated thyroid cancer even after successful initial treatment represents a legacy effect of the mutations and suggests that molecular subtyping based on *TERT* status will be useful in improving management of individual patients.

To our knowledge, this is the first work to demonstrate an improvement in risk stratification for oncologic outcomes by using *TERT* status in conjunction with the 2015 American Thyroid Association DRS system, which is a widely applicable risk stratification paradigm for structural recurrence. Our overarching hypothesis that the risk prediction based on standard clinicopathologic risk factors can be augmented by molecular findings is further supported by the important observation by Dr. Xing *et al.* that reported significant interactions between $BRAF^{V600E}$ mutation and several established risk factors, such that the risk of mortality was higher in patients with the mutation compared with those with WT in the setting of lymph node metastasis, distant metastasis, AJCC TNM stage IV, and age ≥45 years at diagnosis (28).

Table 4. Hazard Ratios of Alternative Prognostic Grouping for Structural Recurrence Based on AHR From Cox Regression

	Structural Recurrence		Unadjusted		Adjusted[a]	
Alternative Grouping	Events/Total (%)	10-y RFS, %	HR (95% CI)	*P*	HR (95% CI)	*P*
AHR 1	7/118 (5.9)	94.9	1.00 (referent)		1.00 (referent)	
AHR 2	32/157 (20.4)	82.7	3.73 (1.65–8.46)	0.002	3.84 (1.69–8.75)	0.001
AHR 3	38/69 (55.1)	50.2	12.98 (5.78–29.12)	<0.001	12.13 (5.38–27.38)	<0.001
AHR 4	13/13 (100.0)	23.1	36.82 (14.59–92.94)	<0.001	33.73 (12.38–91.92)	<0.001

[a] A Cox model adjusting for age at diagnosis, sex, histologic type, multifocality, tumor size, extrathyroidal invasion, lymph node metastasis, and radioactive iodine treatment.

Table 5. Hazard Ratios of Alternative Prognostic Grouping for Thyroid Cancer-Related Death Based on AHR From Cox Regression

	Cancer-Related Death		Unadjusted		Adjusted[a]	
Alternative Grouping	**Events/Total (%)**	**10-y CSS, %**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
AHR 1	0/118 (0)	100.0	NA		NA	
AHR 2	3/157 (1.9)	98.7	1.00 (referent)		1.00 (referent)	
AHR 3	4/69 (5.8)	94.2	2.95 (0.66–13.19)	0.157	2.84 (0.52–15.59)	0.230
AHR 4	8/13 (61.5)	76.9	38.14 (10.11–143.95)	<0.001	7.67 (1.29–45.63)	0.025

[a] A Cox model adjusting for age at diagnosis, sex, histologic type, multifocality, tumor size, extrathyroidal invasion, lymph node metastasis, and radioactive iodine treatment.

For predicting disease mortality, AJCC TNM staging is recommended for all patients with DTC. However, the system imperfectly predicts thyroid cancer–specific deaths in individual patients because it does not take into account important clinicopathologic features such as tumor histology, molecular profile, or effectiveness of initial therapy (11). Although the refined AHR groups were proposed to optimize prediction of structural recurrence after initial therapy, a surrogate outcome (29), it also satisfies the prognostic needs of the nonmetastatic DTC population by serving as a tool to determine survival prediction. The authors believe that the AHR grouping is useful because it includes one domain that quantifies the early treatment response (DRS) and another domain that is an independent predictor of thyroid cancer–specific death (*TERT* mutations) (7).

It has been noted in a previous study that there was residual risk of recurrence (14% during a median of 7 years of follow-up) among initially high-risk patients who showed *excellent* response and therefore may require more intense follow-up (15). As *TERT* mutations are often associated with aggressive histologic features, the previous results corroborate our finding that *TERT* mutated cases should be regarded as AHR 3, even though they achieved short-term remission. However, the mortality risk among patients in this category was quite low compared with the morality risk of patients in the AHR 4 group, who showed persistent biochemical or structural evidence of disease after initial therapy. Therefore, from the standpoint of thyroid cancer–related death, it is important for patients with *TERT* mutated DTC to achieve at least an *indeterminate* response after 1 year of initial therapy (Supplemental Table 1).

For AHR 4 patients, it is questionable whether additional adjuvant radioiodine ablation can reduce later loco-regional and distant recurrence. The *TERT* mutations are closely related with stemness of the cancer cells (30) and dedifferentiated histology (7), which indicate poor response to radioiodine ablation therapy. A recent Chinese study in patients with metastatic DTC reported that those with *TERT* mutated tumors showed less radioiodine uptake, as demonstrated by lower mean tumor/background ratios in posttherapeutic scan images, than those with WT *TERT* tumors (31). Thus, the authors suggest that AHR 4 be prespecified as a radioactive iodine refractory DTC (32) and be considered first for redifferentiation therapy (12, 33), such as mitogen-activated protein kinase kinase inhibitor (selumetinib) (34) or selective BRAF inhibitor (dabrafenib) (35) enhanced radioactive iodine uptake, rather than unconditional repeat administration of radioisotope.

There are several limitations to this study. First, this was a retrospective study and was thus prone to selection bias. Second, the proposed AHR groupings were derived from the data set of a single institution that might not be generalizable to the population at large. Therefore, external validation is encouraged using independent comprehensive data sets that comprise the full spectrum from early to advanced disease, which are often unavailable in prospective data sets. Third, many of the CIs were very wide in the multivariate analyses which indicated poor power or precision, because of the small sample size of these subgroups. Lastly, we did not address the classification in metastatic (M1) disease given the high likelihood of persistent structural disease in this population.

In summary, the AHR grouping, a simple two-dimensional prognostic system, is as effective as DRS at predicting structural recurrence and provides clinical implication for long-term CSS in patients with nonmetastatic DTC. The present data also demonstrate that the DRS template can be used to incorporate molecular markers into the classification while also permitting follow-up information to be updated. Novel therapeutic options are needed to target patients in the AHR 4 group.

Acknowledgments

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This research was supported by a grant (CB-2011-03-02) from the Korean Foundation for Cancer Research (J.H.C).

Disclosure Summary: The authors have nothing to disclose.

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;**144**(5):646–674.
2. Huang FW, Hodis E, Xu MJ, Kryukov GV, Chin L, Garraway LA. Highly recurrent TERT promoter mutations in human melanoma. *Science*. 2013;**339**(6122):957–959.
3. Horn S, Figl A, Rachakonda PS, Fischer C, Sucker A, Gast A, Kadel S, Moll I, Nagore E, Hemminki K, Schadendorf D, Kumar R. TERT promoter mutations in familial and sporadic melanoma. *Science*. 2013;**339**(6122):959–961.
4. Bell RJ, Rube HT, Xavier-Magalhães A, Costa BM, Mancini A, Song JS, Costello JF. Understanding TERT promoter mutations: a common path to immortality. *Mol Cancer Res*. 2016;**14**(4):315–323.
5. Liu X, Bishop J, Shan Y, Pai S, Liu D, Murugan AK, Sun H, El-Naggar AK, Xing M. Highly prevalent TERT promoter mutations in aggressive thyroid cancers. *Endocr Relat Cancer*. 2013;**20**(4):603–610.
6. Melo M, da Rocha AG, Vinagre J, Batista R, Peixoto J, Tavares C, Celestino R, Almeida A, Salgado C, Eloy C, Castro P, Prazeres H, Lima J, Amaro T, Lobo C, Martins MJ, Moura M, Cavaco B, Leite V, Cameselle-Teijeiro JM, Carrilho F, Carvalheiro M, Máximo V, Sobrinho-Simões M, Soares P. TERT promoter mutations are a major indicator of poor outcome in differentiated thyroid carcinomas. *J Clin Endocrinol Metab*. 2014;**99**(5):E754–E765.
7. Kim TH, Kim YE, Ahn S, Kim JY, Ki CS, Oh YL, Kim K, Yun JW, Park WY, Choe JH, Kim JH, Kim JS, Kim SW, Chung JH. TERT promoter mutations and long-term survival in patients with thyroid cancer. *Endocr Relat Cancer*. 2016;**23**(10):813–823.
8. Killela PJ, Reitman ZJ, Jiao Y, Bettegowda C, Agrawal N, Diaz LA Jr, Friedman AH, Friedman H, Gallia GL, Giovanella BC, Grollman AP, He TC, He Y, Hruban RH, Jallo GI, Mandahl N, Meeker AK, Mertens F, Netto GJ, Rasheed BA, Riggins GJ, Rosenquist TA, Schiffman M, Shih IeM, Theodorescu D, Torbenson MS, Velculescu VE, Wang TL, Wentzensen N, Wood LD, Zhang M, McLendon RE, Bigner DD, Kinzler KW, Vogelstein B, Papadopoulos N, Yan H. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. *Proc Natl Acad Sci USA*. 2013;**110**(15):6021–6026.
9. Eckel-Passow JE, Lachance DH, Molinaro AM, Walsh KM, Decker PA, Sicotte H, Pekmezci M, Rice T, Kosel ML, Smirnov IV, Sarkar G, Caron AA, Kollmeyer TM, Praska CE, Chada AR, Halder C, Hansen HM, McCoy LS, Bracci PM, Marshall R, Zheng S, Reis GF, Pico AR, O'Neill BP, Buckner JC, Giannini C, Huse JT, Perry A, Tihan T, Berger MS, Chang SM, Prados MD, Wiemels J, Wiencke JK, Wrensch MR, Jenkins RB. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. *N Engl J Med*. 2015;**372**(26):2499–2508.
10. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. *Lancet*. 2016;**388**(10061):2783–2795.
11. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;**26**(1):1–133.
12. Kim TY, Kim WG, Kim WB, Shong YK. Current status and future perspectives in differentiated thyroid cancer. *Endocrinol Metab (Seoul)*. 2014;**29**(3):217–225.
13. National Comprehensive Cancer Network. Thyroid carcinoma (Version 1.2016). http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed 6 August 2016.
14. Jeon MJ, Kim WG, Park WR, Han JM, Kim TY, Song DE, Chung KW, Ryu JS, Hong SJ, Shong YK, Kim WB. Modified dynamic risk stratification for predicting recurrence using the response to initial therapy in patients with differentiated thyroid carcinoma. *Eur J Endocrinol*. 2013;**170**(1):23–30.
15. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, Brokhin M, Omry G, Fagin JA, Shaha A. 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**(12):1341–1349.
16. Sohn SY, Park WY, Shin HT, Bae JS, Ki CS, Oh YL, Kim SW, Chung JH. Highly concordant key genetic alterations in primary tumors and matched distant metastases in differentiated thyroid cancer. *Thyroid*. 2016;**26**(5):672–682.
17. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. *AJCC cancer staging manual*, 7th ed. New York, NY: Springer; 2010.
18. Momesso DP, Vaisman F, Yang SP, Bulzico DA, Corbo R, Vaisman M, Tuttle RM. Dynamic risk stratification in patients with differentiated thyroid cancer treated without radioactive iodine. *J Clin Endocrinol Metab*. 2016;**101**(7):2692–2700.
19. Huang SH, Xu W, Waldron J, Siu L, Shen X, Tong L, Ringash J, Bayley A, Kim J, Hope A, Cho J, Giuliani M, Hansen A, Irish J, Gilbert R, Gullane P, Perez-Ordonez B, Weinreb I, Liu FF, O'Sullivan B. Refining American Joint Committee on Cancer/Union for International Cancer Control TNM stage and prognostic groups for human papillomavirus-related oropharyngeal carcinomas. *J Clin Oncol*. 2015;**33**(8):836–845.
20. Kim M, Kim YN, Kim WG, Park S, Kwon H, Jeon MJ, Ahn HS, Jung SH, Kim SW, Kim WB, Chung JH, Shong YK, Kim TH, Kim TY. Optimal cut-off age in the TNM Staging system of differentiated thyroid cancer: is 55 years better than 45 years? *Clin Endocrinol (Oxf)*. 2017;**86**(3):438–443.
21. Lang BH, Lo CY, Chan WF, Lam KY, Wan KY. Staging systems for papillary thyroid carcinoma: a review and comparison. *Ann Surg*. 2007;**245**(3):366–378.
22. Schemper M, Stare J. Explained variation in survival analysis. *Stat Med*. 1996;**15**(19):1999–2012.
23. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;**350**(10):1005–1012.
24. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;**15**(4):361–387.
25. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, Vickers AJ, Ransohoff DF, Collins GS. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med*. 2015;**162**(1):W1–73.
26. Liu R, Xing M. TERT promoter mutations in thyroid cancer. *Endocr Relat Cancer*. 2016;**23**(3):R143–R155.
27. Yin DT, Yu K, Lu RQ, Li X, Xu J, Lei M, Li H, Wang Y, Liu Z. Clinicopathological significance of TERT promoter mutation in papillary thyroid carcinomas: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)*. 2016;**85**(2):299–305.
28. Xing M, Alzahrani AS, Carson KA, Viola D, Elisei R, Bendlova B, Yip L, Mian C, Vianello F, Tuttle RM, Robenshtok E, Fagin JA, Puxeddu E, Fugazzola L, Czarniecka A, Jarzab B, O'Neill CJ, Sywak MS, Lam AK, Riesco-Eizaguirre G, Santisteban P, Nakayama H, Tufano RP, Pai SI, Zeiger MA, Westra WH, Clark DP, Clifton-Bligh R, Sidransky D, Ladenson PW, Sykorova V. Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. *JAMA*. 2013;**309**(14):1493–1501.
29. Vaisman F, Tala H, Grewal R, Tuttle RM. In differentiated thyroid cancer, an incomplete structural response to therapy is associated

with significantly worse clinical outcomes than only an incomplete thyroglobulin response. *Thyroid*. 2011;**21**(12):1317–1322.
30. Liu Z, Li Q, Li K, Chen L, Li W, Hou M, Liu T, Yang J, Lindvall C, Björkholm M, Jia J, Xu D. Telomerase reverse transcriptase promotes epithelial-mesenchymal transition and stem cell-like traits in cancer cells. *Oncogene*. 2013;**32**(36):4203–4213.
31. Yang X, Li J, Li X, Liang Z, Gao W, Liang J, Cheng S, Lin Y. TERT promoter mutation predicts radioiodine-refractory in distant metastatic differentiated thyroid cancer. *J Nucl Med*. 2017;**58**(2):258–265.
32. Schlumberger M, Brose M, Elisei R, Leboulleux S, Luster M, Pitoia F, Pacini F. Definition and management of radioactive iodine-refractory differentiated thyroid cancer. *Lancet Diabetes Endocrinol*. 2014;**2**(5):356–358.
33. Spitzweg C, Bible KC, Hofbauer LC, Morris JC. Advanced radioiodine-refractory differentiated thyroid cancer: the sodium iodide symporter and other emerging therapeutic targets. *Lancet Diabetes Endocrinol*. 2014;**2**(10):830–842.
34. Ho AL, Grewal RK, Leboeuf R, Sherman EJ, Pfister DG, Deandreis D, Pentlow KS, Zanzonico PB, Haque S, Gavane S, Ghossein RA, Ricarte-Filho JC, Domínguez JM, Shen R, Tuttle RM, Larson SM, Fagin JA. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *N Engl J Med*. 2013;**368**(7):623–632.
35. Rothenberg SM, McFadden DG, Palmer EL, Daniels GH, Wirth LJ. Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib. *Clin Cancer Res*. 2015;**21**(5):1028–1035.