Clinical and Molecular Features of Hürthle Cell Carcinoma of the Thyroid

Ana-Maria Chindris, John D. Casler, Victor J. Bernet, Michael Rivera, Colleen Thomas, Jennifer M. Kachergus, Brian M. Necela, Ian D. Hay, Sydney A. Westphal, Clive S. Grant, Geoffrey B. Thompson, Richard T. Schlinkert, E. Aubrey Thompson, and Robert C. Smallridge

Department of Otorhinolaryngology (A.-M.C., J.D.C.) and Division of Endocrinology and Metabolism (V.J.B., R.C.S.), Mayo Clinic, Jacksonville, Florida 32224; Department of Anatomic Pathology (M.R.), Mayo Clinic, Rochester, Minnesota 55905; Departments of Health Sciences Research (C.T.) and Cancer Biology (J.M.K., B.M.N., E.A.T.), Mayo Clinic, Jacksonville, Florida 32224; Division of Endocrinology and Metabolism (I.D.H.), Mayo Clinic, Rochester, Minnesota 55905; Division of Endocrinology and Metabolism (S.A.W.), Mayo Clinic, Scottsdale, Arizona 85259; Department of Surgery (C.S.G., G.B.T.), Mayo Clinic, Rochester, Minnesota 55905; and Department of Surgery (R.T.S.), Mayo Clinic, Scottsdale, Arizona 85259

Context: Hürthle cell cancer (HCC) of the thyroid remains the subject of controversy with respect to natural course, treatment, and follow-up.

Objective: The objective of the study was to evaluate the clinical and molecular features associated with outcome in HCC.

Design: The study was a review of 173 HCC cases treated at Mayo Clinic over 11 years with a median 5.8-year follow-up.

Results: None of the patients with minimally invasive histology had persistent disease, clinical recurrence, or disease-related death. Male gender and TNM stage were independently associated with increased risk of clinical recurrence or death in widely invasive patients. The 5-year cumulative probability of clinical recurrence or death was higher in patients with TNM stage III–IV (females, 74%; males, 91%) compared with patients with TNM stage I–II (females, 0%; males, 17%). Pulmonary metastases were best identified by computed tomography, whereas radioactive iodine scans were positive in only two of 27 cases. Thyroglobulin was detectable in patients with clinical disease, with the notable exception of five patients with distant metastases. The common *TERT* C228T promoter mutation was detected in both widely invasive and minimally invasive tumors. TERT mRNA was below the limit of detection in all samples.

Conclusion: Widely invasive HCC with TNM stage III–IV is aggressive, with low probability of recurrence-free survival. Males have worse outcomes than females. Minimally invasive HCC appears to be considerably less aggressive. Radioactive iodine scan performs poorly in detecting distant disease. Although the *TERT* gene is mutated in HCC, the role of this mutation remains to be demonstrated. **(*J Clin Endocrinol Metab* 100: 55–62, 2015)**

Differentiated thyroid cancer (DTC) has been classified as papillary (85%), follicular (10%), and Hürthle cell (HCC; 3%) (1). Historically, HCC was regarded as a subtype of follicular thyroid cancer (2); therefore, most studies reporting the natural behavior of DTCs have included HCC as part of follicular thyroid cancer, with only

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received March 5, 2014. Accepted September 22, 2014.
First Published Online September 26, 2014

Abbreviations: anti-Tg Ab, anti-Tg antibodies; CI, confidence interval; CT, computed tomography; DTC, differentiated thyroid cancer; EBRT, external beam radiotherapy; HCC, Hürthle cell cancer; HR, hazard ratio; MI, minimally invasive; MRI, magnetic resonance imaging; PD, poorly differentiated; PET, positron emission tomography; RAI, radioactive iodine; Tg, thyroglobulin; US, ultrasound; WI, widely invasive.

a few studies specifically focusing on HCC. HCCs are further defined by the presence and degree of vascular and capsular invasion: the number of foci of capsular invasion, the degree of angioinvasion, the extent of capsular disruption, and invasion of the surrounding thyroid parenchyma. There is disagreement among pathologists regarding the use of these criteria in subclassifying HCCs. Clinically, HCCs are considered as more aggressive, with a more guarded prognosis (1, 3, 4). They are more likely to metastasize into neck soft tissue (5) and distant sites (4) than into cervical lymph nodes, are more iodine resistant, and have a higher mortality (4, 6) than other DTCs, although that concept has been challenged (7–10). A population-level analysis concluded that HCC has a more aggressive behavior, and a separate staging system and practice guidelines should potentially be considered (11). Supporting new evidence indicates that, in fact, HCCs may have a distinct molecular profile compared to other DTCs (12).

Patients and Methods

We reviewed medical records of all thyroid cancer patients evaluated at the three Mayo Clinic sites between January 2001 and November 2012 and identified 173 cases of HCC. Clinical information was also obtained from the Mayo Clinic Cancer Registry. The study was approved by the Mayo Clinic Institutional Review Board. Our follow-up analysis started in 2001 when a sensitive thyroglobulin (Tg) assay with a functional sensitivity of 0.1 ng/mL was introduced to the Mayo Clinic Laboratory. Seventy-three patients had their initial treatment at Mayo Clinic, and 100 were treated elsewhere. Of the surgeries performed elsewhere, pathology slides were available and were reviewed by in-house pathologists in 72 cases. Of the remaining 28 cases, all but three had subsequent interventions with pathology specimens evaluated in-house. For the purpose of this clinical study, HCCs were divided into minimally invasive (MI) and widely invasive (WI) groups. HCC-WI tumors were defined as having greater than four foci of angioinvasion with or without capsular invasion or extrathyroidal extension. In addition, those carcinomas showing multiple ($>$ four) foci of capsular invasion with extrathyroidal extension were also designated as HCC-WI. The HCC-MI group was defined as tumors with $\leq$ four foci of capsular invasion without extrathyroidal extension or as tumors with $<$ four foci of vascular invasion. We acknowledge that some authors advocate that only tumors with capsular invasion should be called MI, and those with vascular invasion should be classified separately as "angioinvasive" (13).

Poorly differentiated (PD) HCCs were diagnosed based on mitosis ($\geq$ five per 10 high-power fields) and the presence of necrosis. For consistency in reporting the staging at diagnosis, we used the 2009 American Joint Committee on Cancer criteria, seventh edition (AJCC7) (14). Patients in whom we could not determine a TNM stage were considered "stage X." In cases presenting for evaluation more than 1 year after their initial outside diagnosis, the disease course was recorded from outside documents and the initial consultation note of the Mayo Clinic endocrinologist. We defined recurrent or persistent disease when either a pathology specimen was obtained and interpreted as malignant or radiological documentation of a metastasis was reported as "consistent with" or "highly suggestive of" disease, associated or not with elevation in Tg levels. Images reported as "indeterminate for malignancy" were not counted as abnormal. We considered a patient to have persistent disease if the tumor was reported as incompletely resected or if there was clinical evidence of disease within 4 months after initial treatment (surgery followed or not by adjuvant therapy) according to the AJCC7. In determining a study as false negative, we used as reference a clinically confirmed positive imaging result obtained within no more than 4 months of a negative report. We excluded tests performed after systemic therapy or after a therapeutic intervention targeting that particular metastatic site. All the Tg values are recorded in the absence of anti-Tg antibodies (anti-Tg Ab).

We isolated RNA and DNA from 61 formalin-fixed, paraffin-embedded samples from 13 HCC-MI and 48 HCC-WI cases. We used 3 $\times$ 10-μm formalin-fixed, paraffin-embedded sections from each tumor for simultaneous purification of DNA and RNA using QIAGEN AllPrep kit (catalog no. 80 204). The *TERT* gene promoter region was sequenced as previously described (15). Subsequently, mRNA abundance was measured using the NanoString cancer panel (GXA-CR1 codeset; NanoString Technologies). The results were validated via quantitative RT-PCR. Two-step quantitative reverse transcriptase-mediated real-time PCR was used to measure the abundance of TERT mRNA. Equal aliquots of total RNA from samples were converted to cDNA with the High-Capacity cDNA Archive Kit (Applied Biosystems), and quantitative PCRs were performed in triplicate with 10 ng of cDNA and the TaqMan Universal PCR master mix (Applied Biosystems). Primer/probe sets were bought from Applied Biosystems and are TERT (Hs00972656 and Hs00162669) and POLR2A (Hs0017218). All amplification data were collected with an Applied Biosystems Prism 7900 sequence detector and analyzed with Sequence Detection System software (Applied Biosystems). WRO cells were used as a positive control for TERT mRNA, and cDNA was omitted as a negative control for nonspecific amplification.

Statistical analysis

The 5-year cumulative probability of survival was estimated using the Kaplan-Meier method in the entire cohort and separately according to M stage at initial diagnosis. Among the patients with nonmetastatic HCC-WI disease, Cox proportional hazards regression models were used to explore associations of patient demographics and tumor characteristics with the hazard of recurrence or death after initial diagnosis, where hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. *P* values $\leq$.05 were considered statistically significant. Owing to the relatively small number of patients included in this study, the possibility of a type II error (ie, false-negative association) should be considered when interpreting the findings. Variables significantly associated with the primary endpoint in univariate analysis were included in a multivariable model controlling for age. The Kaplan-Meier method was used to estimate the cumulative probability of recurrence or death after initial diagnosis of nonmetastatic HCC-WI according to factors associated with the endpoint in multivariable analysis. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc) and R Sta-

tistical Software version 2.11.0 (R Foundation for Statistical Computing).

Results

A total of 173 cases with a diagnosis of HCC were evaluated: 118, 32, and 23 at Mayo Clinic Rochester, Florida, and Arizona, respectively. The cohort of patients with HCC was 54% female and ranged in age from 18 to 85 years at the time of diagnosis (median, 62 y). Metastatic disease was detected in 11% of patients at the initial diagnosis. Median size of the primary tumor was 3.5 cm (range, 0.4–18.5 cm), with 73% classified as WI, 25% as MI, and 2% as PD. The 126 WI tumors included two that exhibited extensive angioinvasion in the absence of capsular invasion. Among the 44 MI tumors, 20 had capsular invasion only, seven had vascular invasion only, and seven had both vascular and capsular invasion. Vascular invasion status was not reported for 10 MI patients. Table 1 summarizes patient demographics and tumor characteristics for WI, MI, and PD tumors.

Initial diagnosis and therapy

Initial diagnosis was made at the time of the thyroid surgery in 163 cases, by biopsy at a distant site in nine (bone in six cases; lung, mediastinum, and adrenal gland in one case each), and in one inoperable case by neck incisional biopsy. Thyroid surgery was performed in 171 of 173 patients. One case was deemed inoperable due to extensive local disease, and the second had advanced concomitant lung adenocarcinoma. Seventy patients had total thyroidectomy, 63 had lobectomy (followed in 54 cases by completion thyroidectomy), and 33 patients had subtotal (n = 5) or near-total (n = 28) thyroidectomy. Five patients had prior lobectomy at locations other than the Mayo Clinic (reportedly for benign disease) and presented later with advanced HCC. Nodal surgery was done in 73 cases, and 16 patients had lymph node involvement. After initial surgery, ablative radioactive iodine (RAI) treatment was administered in 148 patients. The initial dose was known in 129 cases (median, 100 mCi; range, 27.3 to 230.0 mCi). Three cases with moderately advanced disease had external beam radiotherapy (EBRT) instead of RAI.

Imaging and follow-up

A variety of imaging methods were employed in follow-up, including radiography (x-ray), recombinant TSH-stimulated or hypothyroid RAI scans, computed tomography (CT), positron emission tomography (PET) with or

Table 1. Clinical and Tumor Characteristics of 173 Patients With HCC

Characteristic	All HCC	HCC-MI	HCC-WI	HCC-PD
n	173	44	126	3
Male gender, n (%)	80 (46.2)	19 (43.2)	60 (47.6)	1 (33.3)
Age at diagnosis, median (range), y	62 (18–85)	61 (18–85)	63 (19–84)	68 (57–74)
Tumors				
n	153	43	107	3
Median size (range), cm	3.5 (0.4–18.5)	2.7 (1.0–7.5)	4.0 (0.4–18.5)	3.0 (1.9–6.0)
Size >4 cm, n (%)	56 (36.6)	7 (16.3)	48 (44.9)	1 (33.3)
T stage, n (%)				
T1a	5 (2.9)	3 (6.8)	2 (1.6)	0 (0.0)
T1b	21 (12.1)	10 (22.7)	11 (8.7)	0 (0.0)
T2	56 (32.4)	22 (50.0)	33 (26.2)	1 (33.3)
T3	59 (34.1)	9 (20.5)	50 (39.7)	0 (0.0)
T4a	17 (9.8)	0 (0.0)	15 (11.9)	2 (66.7)
T4b	1 (0.6)	0 (0.0)	1 (0.8)	0 (0.0)
Tx	14 (8.1)	0 (0.0)	14 (11.1)	0 (0.0)
N stage, n (%)				
N0	57 (32.9)	13 (29.5)	43 (34.1)	1 (33.3)
N1a	7 (4.0)	0 (0.0)	6 (4.8)	1 (33.3)
N1b	9 (5.2)	0 (0.0)	9 (7.1)	0 (0.0)
Nx	100 (57.8)	31 (70.5)	68 (54.0)	1 (33.3)
M status, n (%)				
M0	154 (89.0)	44 (100.0)	109 (86.5)	1 (33.3)
M1	19 (11.0)	0 (0.0)	17 (13.5)	2 (66.7)
TNM stage, n (%)				
I	20 (11.6)	8 (18.2)	12 (9.5)	0 (0.0)
II	16 (9.2)	5 (11.4)	11 (8.7)	0 (0.0)
III	20 (11.6)	3 (6.8)	17 (13.5)	0 (0.0)
IVA	10 (5.8)	0 (0.0)	10 (7.9)	0 (0.0)
IVB	0 (0.0)	0 (0.0)	16 (12.7)	2 (66.7)
IVC	18 (10.4)	28 (63.6)	60 (47.6)	1 (33.3)
No TNM stage assigned (X)	89 (51.4)	8 (18.2)	12 (9.5)	0 (0.0)

Table 2. Imaging Tests Utilized in Follow-Up and Their False-Negative Detection Rate at Three Most Frequent Metastatic Sites

	Clinically Confirmed Metastases With a False-Negative Test		
Test Type	**Lung**	**Mediastinum**	**Osseous**
CT	1/49 (2)	0/11 (0)	1/16 (6)
PET	4/24 (17)	0/12 (0)	0/13 (0)
MRI	—	0/1 (0)	0/14 (0)
Radiography	5/19 (26)	4/5 (80)	2/5 (40)
Octreoscan	—	—	0/3 (0)
Bone scan	—	—	1/8 (13)
RAI scan	25/27 (93)[a]	4/7 (57)	2/6 (33)

Data are expressed as fraction (percent). In determining a study as false negative, we used as reference a clinically confirmed positive imaging result obtained within no more than 4 months of a negative result. The tests performed after chemotherapy or a therapeutic intervention targeting that particular metastatic site were excluded. Dashes signify that no cases were reported.

[a] Eight of 27 RAI scans were post-therapy scans; one diagnostic and one post-therapy scan identified disease.

without CT for attenuation correction, magnetic resonance imaging (MRI), bone scan, and octreoscan. In determining a study to be false negative, we used as reference a clinically confirmed positive imaging result obtained within no more than 4 months of a negative result. Tests performed after chemotherapy or a therapeutic intervention targeting that particular metastatic site were excluded. CT, PET/CT, and MRI have low false-negative rates in detecting mediastinal and osseous lesions (Table 2). The data suggest that pulmonary metastases were best identified by CT (false-negative rate = 2%). RAI scans (either TSH-stimulated or hypothyroid) exhibited a very high false-negative detection rate; in most cases (31 of 40), the tumors did not take up iodine, irrespective of the site.

Tg levels in follow-up

Sensitive Tg assays have been available for over a decade, and in patients who do not have anti-Tg Ab, an increase in Tg levels after thyroidectomy is suggestive of recurrence. Of 82 patients with recurrent/persistent disease in this study, suppressed Tg measurements ranged between <0.1 and 234 000 ng/mL, and stimulated Tg measurements ranged between <0.1 and 132 000 ng/mL. However, in five patients with metastatic disease, suppressed and/or stimulated Tg levels remained undetectable throughout their follow-up, despite the presence of histologically confirmed metastatic disease. None of these patients expressed anti-Tg Ab; neither could any of the clinical characteristics of these patients, described in Table 3, account in any obvious way for the failure of these tumors to secrete Tg.

Outcome

The published data on outcome among HCC patients are, in some cases, contradictory (3, 4, 7). We therefore felt that it would be useful to summarize the outcome from a large number of HCC patients treated at a single institution. Median follow-up time in the present study, defined as the time from the initial diagnosis to last contact or death, was 69.8 months (range, 0.1 to 400.0 mo). In two cases, patient follow-up was less than 4 weeks because patients were not followed at the Mayo Clinic. The 5-year cumulative probability of survival was 85% (95% CI, 79–91%) among the entire cohort of 173 HCC patients, but only 24% among patients with M1 stage at presentation (95% CI, 0–50%), and 91% among patients who presented with M0 stage disease (95% CI, 86–96%). The cumulative probability of death after initial diagnosis is presented in Figure 1A, separated according to M stage.

In evaluating risk factors for clinical recurrence or death, patients were excluded from the analysis if they had metastatic disease at initial diagnosis (n = 19), persistent disease that did not respond to initial treatment (n = 11), or fewer than 3 months of follow-up at our institution (n = 9). Of the 134 patients remaining (94 HCC-WI, 39 HCC-MI, and 1 HCC-PD), 59 patients had a clinical recurrence

Table 3. Clinical Characteristics of Five Patients With Distant Disease and Undetectable Tg

Gender/ Age, y	TNM Stage at Initial Diagnosis	Histology at Initial Diagnosis	Distant Disease Location	Initial Method of Detection	Treatment of Distant Disease	Status at Last Follow-Up	Months From Initial Diagnosis to Last Follow-Up	Months From Distant Disease Diagnosis to Last Follow-Up	Type of Tg Measurement With Distant Disease
M/80	T3N0M0	HCC-WI	8th left rib, L1 vertebra	CXR, MRI	Rib resection and reconstruction	DOD	40	20	Tg supp, Tg stim
M/58	T3N0M0	HCC-WI	Liver	Chest CT, confirmed on MRI and biopsy	Pazopanib × 11 mo (escape) followed by metastasis resection	Alive with disease	43	31	Tg supp, Tg stim
M/67	T3N0M0	HCC-WI	Lung, ilium	Chest CT, MRI	EBRT (bone)	DOD	97	38	Tg supp
F/57	T4N0M1	HCC-PD	Lung, L2 vertebra	Chest CT	Pazopanib	Alive with disease	25	25	Tg supp
M/55	TxN0M0	HCC-WI	Lung, T6 vertebra, skin	Post-therapy scan	EBRT (bone), pazopanib	DOD	161	84	Tg supp, Tg stim

M, male; F, female; CXR, chest x-ray; DOD, death of disease; Tg supp, suppressed Tg; Tg stim, stimulated Tg.

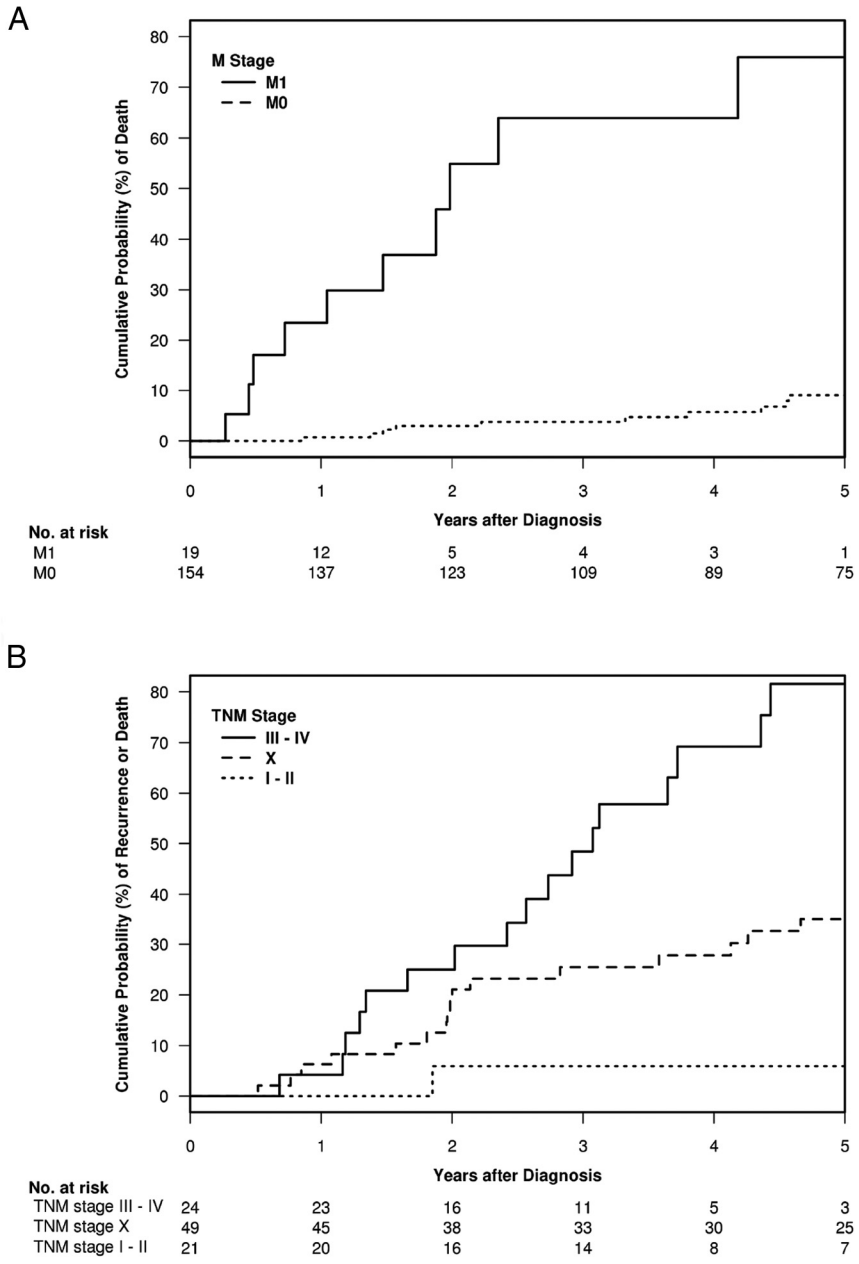

Figure 1. Kaplan-Meier estimates of the outcome of HCC patients. A, Estimate of the cumulative probability of death among HCC patients with metastasis (M1 stage) and without metastasis (M0 stage). B, Estimate of the cumulative probability of recurrence or death among patients with nonmetastatic (M0) HCC-WI separated according to tumor stage (TNM). Estimates were given separately for TNM stage I–II, TNM stage III–IV, and unstaged (TNM stage X).

or death. Among the 39 patients with HCC-MI, there were no clinical recurrences and no HCC-related deaths. Owing to the absence of clinical recurrence and HCC-related death among HCC-MI patients in our study, we limited our analysis of potential risk factors to the 94 patients with HCC-WI.

Associations of patient demographics and tumor characteristics with clinical recurrence or death among patients with HCC-WI are presented in Table 4. In univariate analysis, only male gender ($P = .023$) and TNM stage ($P = .001$) were associated with clinical recurrence or death. In the final multivariable model (controlling for age at diagnosis), male gender (HR, 1.85; $P = .029$) and TNM stage III–IV (HR [vs TNM stage I], 14.36; $P < .001$) remained significantly associated with clinical recurrence or death among patients with HCC-WI. Figure 1B displays the cumulative probability of clinical recurrence or death according to TNM stage among patients with HCC-WI. The 5-year cumulative probability of recurrence or death among patients with TNM stage I–II was 0% among females (95% CI, 0–60%) and 17% among males (95% CI, 0–47%), as shown in Supplemental Table 1. Among patients with TNM stage III–IV, the 5-year cumulative probability of recurrence or death was 74% among females (95% CI, 44–100%) and 91% among males (95% CI, 73–100%).

TERT promoter mutations

Mutations to the TERT promoter (so-called C228T and C250T) have been previously reported in HCC. Landa et al (16) analyzed a small cohort of HCC patients and observed that such mutations were limited to HCC-WI tumors. A possible link between TERT promoter mutations and progression in DTC has been suggested (17). We extracted DNA and assayed for TERT promoter sequence variation in 48 HCC-WI and 13 HCC-MI samples, as described in *Patients and Methods*. Among these, eight tumors harbored C228T mutations, and there were six cases of HCC-WI and two cases of HCC-MI (one with both capsular and vascular invasion and one with vascular invasion only). We did not identify any sample with the C250T mutation. An additional exon 1 deletion mutation was detected in one sample (as described in Supplemental Figure 1). The number of samples available for analysis precludes any definitive conclusion about the distribution of TERT promoter mutations in HCC-WI vs HCC-MI tumors, but the data are inconsistent with the conclusion that such mutations are limited to more aggressive tumors. A recent report described the presence of

Table 4. Associations With Clinical Recurrence or Death Among 94 Patients With HCC-WI

	Associations With Clinical Recurrence or Death			
	Single Variable Analysis		Multivariable Model	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Gender		.023		.029
Female	1.00 (reference)		1.00 (reference)	
Male	1.90 (1.09–3.29)		1.85 (1.07–3.21)	
Age at diagnosis (10 y)	1.05 (0.84–1.32)	.66		
Size of primary lesion (1 cm)[a]	1.12 (0.96–1.31)	.15		
T stage		.49		
T1–T2	1.00 (reference)			
T3–T4	1.32 (0.70–2.50			
Tx	1.61 (0.71–3.64)			
N stage		.30		
N0	1.00 (reference)			
N1	1.64 (0.61–4.44)			
Nx	0.79 (0.43–1.44)			
TNM stage		.001		<.001
I	1.00 (reference)		1.00 (reference)	
II	1.34 (0.08–21.49)		1.37 (0.08–23.10)	
III–IV	12.27 (1.64–91.99)		14.36 (1.77–116.78)	
X	4.53 (0.61–33.47)		4.94 (0.63–38.43)	

Cox proportional hazard regression was use to estimate the hazard of developing clinical recurrence or death after initial treatment of non-metastatic HCC-WI in patients who responded to initial treatment and had at least 3 months of follow-up. The multivariable model included variables with *P* values <.05 in single variable analysis while controlling for age at diagnosis.

[a] Size of the primary lesion was not available for 11 patients.

TERT promoter mutations in follicular adenomas and showed that such mutations are associated with increased TERT mRNA expression (18). However, as shown in Supplemental Table 2, we were unable to detect TERT mRNA in our HCC samples using either NanoString technology or quantitative real-time PCR under conditions that were capable of detecting TERT mRNA in a positive control sample (WRO cells). Because of the negative nature of the data and the difficulty of proving a negative result, it is difficult to reach any definitive conclusions about the potential functional significance of TERT promoter mutations in HCC.

Discussion

Our study reports the Mayo Clinic's experience with HCC over the past decade. Our patient characteristics were similar to those reported by other referral centers (3, 19). The 5-year overall survival rate in our cohort was 85%. Several other studies reported 5-year survival ranging from 74 to 91.3% (10, 11, 20, 21). Our data emphasize that precise histological characterization is an important factor in prognostic evaluation. Despite including minimally angioinvasive tumors as HCC-MI, we did not find any cases of metastatic disease in any of the 44 patients with HCC-MI. The literature reports that HCC-MI is associated with a less aggressive profile (19, 22, 23). In conclusion, our results, in association with several other studies of smaller numbers of patients indicate that there is very little risk of recurrence with HCC-MI. Although our median follow-up time of 5.8 years is shorter than the one reported in other studies (22), it exceeds the time to first recurrence reported in one study as being less than 3.5 years (24).

We found male gender and TNM stage III–IV as independent risk factors for poor outcome (recurrence or death) consistent with data in the literature (3, 11, 19–21). In our study, most disease-related deaths occurred among older males with M1 stage at diagnosis. Despite the fact that incidence of disease is higher among the females (10, 11), cumulative probability of recurrence or death within 5 years was 91% for males with stage III–IV disease compared with 74% for females with same stage disease. M1 status was, however, by far the most important predictor for poor outcome.

Recommended follow-up for DTC consists of serum Tg, I^{123}, or I^{131} uptake and scan and neck ultrasound (US). Additional imaging modalities such as ^{18}F-fluorodeoxyglucose-PET are also recommended in high-risk patients (1, 25, 26) for initial staging and follow-up; however, its impact on cure, survival, and progression-free survival is not yet well defined. We found that RAI scans performed poorly in detecting distant disease, as also reported by others (21, 27, 28). Follow-up with Tg, neck US, and chest CT (as in our practice) or with PET/CT as suggested by others are reasonable alternatives (29, 30).

A rise in Tg level after thyroidectomy is suggestive of recurrence. However, patients can present with widely metastatic HCC and undetectable Tg (stimulated or suppressed) and negative neck US. We report here five such cases among 126 HCC-WI patients. This is acknowledged in the American Thyroid Association guidelines (1), where it is specified that "an aggressive or poorly differentiated tumor may be present despite low basal or stimulated Tg." Therefore, clinical judgment needs to be used in choosing follow-up methods for HCC patients, especially in high-risk cases.

One study reported detection of TERT promoter mutations in four of 17 HCC-WI and none of the eight HCC-MI tumors (31). We observed a similar frequency of TERT promoter mutations; however, such mutations were not restricted to HCC-WI among our patients. Furthermore, our inability to detect TERT mRNA in any HCC tumor suggests that any conclusions about the role of TERT mutations, TERT expression, and HCC progression will require additional consideration.

Summary

To our knowledge, this study represents the largest clinical analysis of patients with HCC performed in a single institution. HCC-MI appears to have a benign behavior and may benefit from a less aggressive therapeutic approach, whereas patients with distant disease at diagnosis have a poor prognosis. Because RAI scans have a very low sensitivity to detect distant disease, alternative imaging methods should be routinely used in follow-up, at least in high-risk patients. We agree with the suggestion that HCC may benefit from an individualized staging system and management guidelines (11). Additionally, due to the rarity of this disease, a national HCC tissue repository would allow studies to elucidate the molecular mechanisms responsible for HCC clinical behavior.

Acknowledgments

The authors thank Nancy Diehl for the development and maintenance of the Mayo Clinic Thyroid Cancer Registry and Kathleen Norton for manuscript preparation.

Address all correspondence and requests for reprints to: Ana-Maria Chindris, MD, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224. E-mail: chindris.anamaria@mayo.edu.

Financial support comes from generous gifts from James Russell and Martha Crawford as well as Alfred D. and Audrey M. Petersen, and from the Center for Individualized Medicine and the Mayo Clinic Foundation.

Disclosure Summary: The authors have no conflicts of interests to disclose.

References

1. **American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, 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;19:1167–1214.
2. **DeLellis R, Lloyd R, Heitz P, Eng C.** Pathology & Genetics of Tumours of Endocrine Organs. IARC WHO Classification of Tumors. Geneva, Switzerland: World Health Organization; 2004.
3. **Mills SC, Haq M, Smellie WJ, Harmer C.** Hürthle cell carcinoma of the thyroid: retrospective review of 62 patients treated at the Royal Marsden Hospital between 1946 and 2003. *Eur J Surg Oncol*. 2009; 35:230–234.
4. **Shaha AR, Shah JP, Loree TR.** Patterns of nodal and distant metastasis based on histologic varieties in differentiated carcinoma of the thyroid. *Am J Surg*. 1996;172:692–694.
5. **Bishop JA, Wu G, Tufano RP, Westra WH.** Histological patterns of locoregional recurrence in Hürthle cell carcinoma of the thyroid gland. *Thyroid*. 2012;22:690–694.
6. **Kushchayeva Y, Duh QY, Kebebew E, D'Avanzo A, Clark OH.** Comparison of clinical characteristics at diagnosis and during follow-up in 118 patients with Hürthle cell or follicular thyroid cancer. *Am J Surg*. 2008;195:457–462.
7. **Khafif A, Khafif RA, Attie JN.** Hürthle cell carcinoma: a malignancy of low-grade potential. *Head Neck*. 1999;21:506–511.
8. **Bhattacharyya N.** Survival and prognosis in Hürthle cell carcinoma of the thyroid gland. *Arch Otolaryngol Head Neck Surg*. 2003;129: 207–210.
9. **Haigh PI, Urbach DR.** The treatment and prognosis of Hürthle cell follicular thyroid carcinoma compared with its non-Hürthle cell counterpart. *Surgery*. 2005;138:1152–1157; discussion 1157–1158.
10. **Nagar S, Aschebrook-Kilfoy B, Kaplan EL, Angelos P, Grogan RH.** Hurthle cell carcinoma: an update on survival over the last 35 years. *Surgery*. 2013;154:1263–1271; discussion 1271.
11. **Goffredo P, Roman SA, Sosa JA.** Hürthle cell carcinoma: a population-level analysis of 3311 patients. *Cancer*. 2013;119:504–511.
12. **Ganly I, Ricarte Filho J, Eng S, et al.** Genomic dissection of Hürthle cell carcinoma reveals a unique class of thyroid malignancy. *J Clin Endocrinol Metab*. 2013;98:E962–E972.
13. **Livolsi V, Asa SL.** *Endocrine Pathology*. Philadelphia, PA: Churchill Livingstone; 2002.
14. **Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A.** AJCC Cancer Staging Manual, 7th ed. New York, NY: Springer; 2010.
15. **Horn S, Figl A, Rachakonda PS, et al.** TERT promoter mutations in familial and sporadic melanoma. *Science*. 2013;339:959–961.
16. **Landa I, Ganly I, Chan TA, et al.** Frequent somatic TERT promoter mutations in thyroid cancer: higher prevalence in advanced forms of the disease. *J Clin Endocrinol Metab*. 2013;98:E1562–E1566.
17. **Melo M, da Rocha AG, Vinagre J, et al.** TERT promoter mutations are a major indicator of poor outcome in differentiated thyroid carcinomas. *J Clin Endocrinol Metab*. 2014;99:E754–E765.
18. **Wang N, Liu T, Sofiadis A, et al.** TERT promoter mutation as an early genetic event activating telomerase in follicular thyroid adenoma (FTA) and atypical FTA. *Cancer* 2014;120:2965–2979.
19. **Stojadinovic A, Hoos A, Ghossein RA, et al.** Hürthle cell carcinoma: a 60-year experience. *Ann Surg Oncol*. 2002;9:197–203.
20. **Kushchayeva Y, Duh QY, Kebebew E, Clark OH.** Prognostic indications for Hürthle cell cancer. *World J Surg*. 2004;28:1266–1270.
21. **Lopez-Penabad L, Chiu AC, Hoff AO, et al.** Prognostic factors in patients with Hürthle cell neoplasms of the thyroid. *Cancer*. 2003; 97:1186–1194.
22. **Stojadinovic A, Ghossein RA, Hoos A, et al.** Hürthle cell carcinoma: a critical histopathologic appraisal. *J Clin Oncol*. 2001;19:2616–2625.
23. **Ghossein RA, Hiltzik DH, Carlson DL, et al.** Prognostic factors of recurrence in encapsulated Hürthle cell carcinoma of the thyroid

gland: a clinicopathologic study of 50 cases. *Cancer*. 2006;106:1669–1676.
24. **Goldstein NS, Czako P, Neill JS.** Metastatic minimally invasive (encapsulated) follicular and Hürthle cell thyroid carcinoma: a study of 34 patients. *Mod Pathol*. 2000;13:123–130.
25. **Lind P, Kohlfürst S.** Respective roles of thyroglobulin, radioiodine imaging, and positron emission tomography in the assessment of thyroid cancer. *Semin Nucl Med*. 2006;36:194–205.
26. **Abraham T, Schöder H.** Thyroid cancer–indications and opportunities for positron emission tomography/computed tomography imaging. *Semin Nucl Med*. 2011;41:121–138.
27. **Har-El G, Hadar T, Segal K, Levy R, Sidi J.** Hürthle cell carcinoma of the thyroid gland. A tumor of moderate malignancy. *Cancer*. 1986;57:1613–1617.
28. **Leboulleux S, El Bez I, Borget I, et al.** Postradioiodine treatment whole-body scan in the era of 18-fluorodeoxyglucose positron emission tomography for differentiated thyroid carcinoma with elevated serum thyroglobulin levels. *Thyroid*. 2012;22:832–838.
29. **Lang BH.** The role of 18F-fluorodeoxyglucose positron emission tomography in the prognostication, diagnosis, and management of thyroid carcinoma. *J Thyroid Res*. 2012;2012:198313.
30. **Pryma DA, Schöder H, Gönen M, Robbins RJ, Larson SM, Yeung HW.** Diagnostic accuracy and prognostic value of 18F-FDG PET in Hürthle cell thyroid cancer patients. *J Nucl Med*. 2006;47:1260–1266.
31. **Landa I, Ganly I, Chan TA, Mitsutake N, Matsuse M, Ibrahimpasic T, Ghossein RA, Fagin JA.** Frequent somatic TERT promoter mutations in thyroid cancer: higher prevalence in advanced forms of the disease. *J Clin Endocrinol Metab*. 2013;98:E1562–E1566.