Time Course and Predictors of Structural Disease Progression in Pulmonary Metastases Arising from Follicular Cell–Derived Thyroid Cancer

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Background: With the advent of molecular targeted therapy for the management of radioactive iodine (RAI) refractory, progressive metastatic thyroid cancer, it becomes important to define the time course and risk factors for structural disease progression in follicular cell–derived thyroid cancer (FCDTC) patients. This will help in defining the optimal time to start these therapies and better define their impact on structural disease progression.

Objectives: This retrospective review of 199 consecutive patients with FCDTC presenting with lung metastasis examined the progression-free survival (PFS) in thyroid cancer patients with lung metastasis treated with surgery and RAI, and who had not received molecular targeted therapy or chemotherapy.

Results: The median overall survival (OS) was 10.45 years, while the median PFS was 3.65 years. A strong correlation was found between OS and PFS. PFS is shorter in patients with RAI refractory disease, poorly differentiated/Hürthle cell histologies, male sex, fluorodeoxyglucose-avid metastatic foci, older age (>45 years), and pulmonary metastases >1 cm. At final follow-up (a median of 6.9 years from lung metastasis diagnosis), 68% of the patients had progressed and 46% had died.

Conclusions: With the exception of younger patients with low disease burden, most patients presenting with lung metastasis from FCDTC (RAI avid and RAI refractory) using standard-of-care approaches will have disease progression on long-term follow-up. Additional studies are needed to identify novel therapies that would improve the PFS of such patients.

Introduction

FOR MANY YEARS, RADIOACTIVE IODINE (RAI) therapy has been the mainstay of therapy for metastatic thyroid cancer of follicular cell origin. In the setting of distant metastases, a survival benefit has been demonstrated in patients with RAI-avid disease, particularly in younger patients (<40 years of age at distant metastasis diagnosis), those with subcentimeter pulmonary metastases, and those with non-fluorodeoxyglucose-positron emission tomography (FDG-PET)-avid metastatic lesions (1–3). Despite being an effective therapy, RAI is usually not curative in patients with distant metastases, with more than half of patients demonstrating structural disease progression by the end of the follow-up period, despite repeated RAI treatment (4).

Over the last few years, the availability of oral agents that specifically target known oncogenic pathways in RAI refractory thyroid cancer has led to a renewed interest in systemic therapies for metastatic thyroid cancer. On the basis of two randomized prospective clinical trials demonstrating

significant improvement in progression-free survival (PFS), the Food and Drug Administration approved both sorafenib and lenvatinib in the treatment of locally recurrent or metastatic, progressive, RAI refractory metastatic thyroid cancer (5,6). Furthermore, the 2015 American Thyroid Association guidelines for the management of thyroid nodules and differentiated thyroid cancer recommend considering the use of molecular targeted therapies in RAI refractory follicular cell–derived thyroid cancer (FCDTC) patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease that is not otherwise amenable to suitable control via other approaches (7).

While multiple studies have examined risk factors associated with overall survival (OS) and disease-specific survival in FCDTC (8), no study has adequately described the time course or risk factors for structural disease progression in metastatic FCDTC in patients being cared for in routine clinical practice outside of the highly selected placebo control groups enrolled in randomized clinical trials. In order for clinicians to be able to evaluate the potential impact of these

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novel systemic therapies on structural disease progression, it is critical to have a better understanding of the natural history of distant metastases from FCDTC following standard therapies (thyroidectomy, RAI, and thyrotropin [TSH] suppression).

Therefore, the goal of this retrospective study was to describe the time course and risk factors for structural disease progression in a cohort of FCDTC patients with pulmonary metastases (RAI avid or RAI refractory) being followed at a major cancer center prior to the widespread availability of molecularly targeted therapies. It was predicted that younger patients with well-differentiated tumor histologies, small metastatic tumor burden, and RAI-avid FDG-PET-negative tumors would be less likely to progress over time. Here, the PFS (as opposed to OS) outcome was examined in patients with lung metastasis from FCDTC treated only with RAI and TSH suppressive therapy.

Materials and Methods

Patients

After obtaining Institutional Review Board approval, all FCDTC patients with pulmonary metastases (either at diagnosis or identified at any time during follow-up) that underwent remnant ablation, adjuvant therapy, therapy of distant metastasis, or diagnostic whole-body scanning (DxWBS) following total thyroidectomy between 1993 and 2012 were retrospectively reviewed.

Presence of lung metastasis from thyroid cancer was established based on serial cross-sectional imaging, FDG-PET scanning, and/or presence of RAI uptake in the lungs on DxWBS or on post-therapy (RxWBS) scanning after RAI therapy. The reports of the DxWBS and RxWBS were reviewed for all patients. The actual images were available in nearly all patients (88%) and were reviewed. All patients had cross-sectional imaging at the time of lung metastasis diagnosis. Lung metastases were classified as micrometastasis if all pulmonary lesions measured <1 cm in the longest diameter, or macrometastasis if any single lesion measured >1 cm.

Patients with uptake on RxWBS were classified as having RAI-avid tumors. Patients without visible uptake on RxWBS or with uptake in <10% of multiple pulmonary lesions were defined as having RAI refractory tumors.

Patients were excluded from the analysis for the following reasons: (i) patients did not receive thyroid surgery due to unresectable disease; (ii) patients with bone-only metastasis or other sites of distant metastasis without lung involvement; (iii) patients with anaplastic thyroid cancer; (iv) patients who were started directly on chemotherapy or molecular targeted therapy at time of metastasis diagnosis without intervening RAI therapy; (v) those with concomitant second primary cancer in which the status of the other cancer was either active or unknown; (vi) inadequate follow-up data; and (vii) chronic TSH elevation. From 273 potential patients, 199 patients were ultimately included in the analysis.

Histopathologic analysis

Tumors were classified according to the last World Health Organization criteria, with the exception of tall cell variant (TCV-PTC) and poorly differentiated thyroid cancer (PDTC) (9). Tumors were classified as TCV-PTC if they contained

≥50% tall cells. The latter cell type was defined as having a height at least twice its width with an oncocyctic cytoplasm (10). PDTC were defined by proliferative grading features: ≥5 mitoses/10 high-power fields and/or tumor necrosis regardless of architectural pattern (11). This definition differs from the most recent Turin proposal that requires the presence of a solid/trabecular/insular growth pattern in addition to proliferative grading (12). In a recent study, both classifications were found to be comparable in predicting intermediate prognosis of thyroid cancer (13).

Repeat radioiodine therapies

The decision to treat with RAI, the choice of the preparation method (recombinant human TSH [rhTSH] vs. thyroid hormone withdrawal [THW]), and the choice of RAI-administered activity were all performed at the discretion of the treating physician. All patients were asked to adhere to a low-iodine diet 5–7 days prior to the planned RAI treatment.

Patient follow-up

Patients were examined at 3–12-month intervals. The timing of repeat cross-sectional imaging, RAI scanning, and/or repeat RAI therapy was performed at the discretion of the treating physician. The frequency of imaging tests and follow-up visits were based on the clinical course of the disease.

Clinical endpoint

Clinically significant structural disease progression was defined as either (i) at least a 30% increase in the longest diameter of a pulmonary metastasis measuring >1 cm at baseline or by ≥5 mm for lung metastasis measuring <1 cm at baseline; or (ii) identification of new lesions in the lungs and/or other distant sites (bones, liver, kidney, brain, adrenals). A rise in thyroglobulin and/or antithyroglobulin antibody titers alone without evidence of structural progression was not considered as disease progression.

Statistical methods

Continuous data are presented as means and standard deviations or medians and ranges, as appropriate for each variable. Categorical comparisons were performed with the chi-square test, and continuous variables were compared using Student's *t*-test or one-way analysis of variance, as appropriate.

The primary endpoint was PFS from the time of identification of the lung metastasis. OS and PFS from the time of diagnosis of the lung metastases were examined using Kaplan–Meier survival curve analyses. The effects of prognostic variables on PFS was evaluated using log-rank testing.

To establish predictors for rapid structural disease progression, the patients were divided into three groups based on the rate of their disease progression: (i) rapid progressors: those who progressed in less than a year after lung metastasis diagnosis; (ii) slow progressors: those who progressed within one to five years after lung metastasis diagnosis; (iii) and late progressors: those who progressed five or more years after initial lung metastasis diagnosis. All analyses were performed using IBM SPSS Statistics for Windows v22.0.1 (IBM Corp., Armonk, NY). A *p*-value of ≤0.05 was considered statistically significant.

TABLE 1. CLINICAL CHARACTERISTICS OF THE COHORT

		N
Age at diagnosis (years)		199
<i>M</i> ± <i>SD</i>	50 ± 20	
Median	53	
Range	4–90	
Presence of distant metastasis at cancer diagnosis	58%	
Age at distant metastasis diagnosis		
<i>M</i> ± <i>SD</i>	52 ± 20	
Median	56	
Range	4–90	
Sex		
Female	53%	105
Histology		
All PTC, other than FV-PTC	43%	86
FV-PTC	17%	33
Hürthle cell	7%	14
Poorly differentiated	33%	66
Size of primary tumor (cm) (if known)		141
<i>M</i> ± <i>SD</i>	3.8 ± 2.5	
Median	3.4	
Range	0.3–16	
Thyroid cancer stage at diagnosis		193
I	17%	33
II	21%	40
III	9%	18
IV	53%	102
Extrathyroidal extension		138
None	28%	38
Minimal	49%	68
Gross	23%	32
Vascular invasion		137
None	28%	38
Present	72%	99
Initial thyroid surgery		199
Total	94%	186
Subtotal/hemithyroidectomy	6%	13
EBRT to neck		199
Yes	14%	28
Local recurrence before DM diagnosis in M0 patients		84
Yes	43%	36
Presence of extranodal extension		
Yes	45%	82
No	33%	59
Unknown	22%	40
RAI therapy	89%	177
First RAI therapy activity (mCi)		170
<i>M</i> ± <i>SD</i>	164 ± 91	
Median	150	
Range	29–501	
RAI avidity at time of DM diagnosis		199
RAI avid	67%	133
RAI refractory	33%	66
Number of additional RAI activities before end of follow-up		155
<i>M</i> ± <i>SD</i>	2 ± 1	
Median	2	
Range	1–6	

(continued)

TABLE 1. (CONTINUED)

		N
Cumulative dose of additional RAI activities (mCi)		
<i>M</i> ± <i>SD</i>	467 ± 329	
Median	387	
Range	73–1740	
Time to DP from last RAI activity (years)		96
<i>M</i> ± <i>SD</i>	2.3 ± 2.8	
Median	1.2	
Range	0–14	
FDG-PET avidity		123
PET (+)	42%	52
PET (–)	58%	71
DM distribution		
Lung only	79%	157
Lung and bone	18%	36
Lung and other (excluding bone)	3%	6
Lung metastasis size category		197
Micro (<1 cm)	75%	148
Macro (≥1 cm)	25%	49
Follow up since DM diagnosis (years)		
<i>M</i> ± <i>SD</i>	7.8 ± 5.1	
Median	6.9	
Range	0.3–30.5	
Clinical outcome at end of follow-up		
CR	7%	13
PR/SD	26%	51
DP	68%	135
Time to DP since DM diagnosis (years)		135
<i>M</i> ± <i>SD</i>	3.2 ± 3.2	
Median	2.0	
Range	0.2–16.6	
DP type		135
Size increase	17%	23
New lesions	15%	20
Both	68%	92
Status at end of follow-up		
Alive	54%	108
Dead	46%	91
Cause of death		74
Thyroid cancer	92%	68
Lung cancer	4%	3
Myelodysplastic syndrome	3%	2
Other	1%	1

SD, standard deviation; PTC, papillary thyroid carcinoma; FV-PTC, follicular variant of papillary thyroid carcinoma; EBRT, external beam radiation therapy; RAI, radioactive iodine; DM, distant metastasis; DP, disease progression; FDG-PET, fluorodeoxyglucose-positron emission tomography; CR, complete remission; PR, partial remission; SD, stable disease.

Results

Clinicopathologic characteristics of the cohort

The clinicopathologic characteristics of the 199 patients included in this analysis are summarized in Table 1. The patients had a median age of 56 years at the time of distant metastasis diagnosis (12 were <18 years of age at lung metastasis diagnosis), with papillary (60%) or poorly differentiated histologies (33%), and predominantly subcentimeter pulmonary metastases (75%). The majority had only lung

TABLE 2. CUMULATIVE PERCENTAGE OF PATIENTS WITH DISEASE PROGRESSION BY RAI AVIDITY

	All patients	RAI avid	RAI refractory
Year 1	17%	12%	29%
Year 2	35%	26%	53%
Year 5	55%	41%	83%
Year 10	65%	53%	91%

metastasis, with only 20% showing additional metastatic lesions outside the lung at the time of the diagnosis of the lung metastases. The median size of the primary tumor was 3.4 cm (range 0.3–16 cm). Only 9/141 patients with known primary tumor size had microscopic primary thyroid tumors (<1 cm): six were classified as papillary, and three were classified as poorly differentiated thyroid cancer.

At the time of initial metastasis diagnosis, close to two thirds of the tumor foci were classified as RAI avid (33% RAI refractory). Patients received as many as six additional RAI therapies after the initial metastasis diagnosis and prior to documented structural disease progression with a median of two additional RAI activities (cumulative RAI activities: median 387 mCi, range 73–1740 mCi). Of those who had FDG-PET scan available at diagnosis, 42% had FDG-PET-positive tumors.

Clinical outcomes

At final follow-up (a median of 6.9 years after identification of pulmonary metastases), 46% of the cohort had died (92% of the deaths were attributed to thyroid cancer). Only 7% of patients achieved a complete remission, with 25% having stable disease and 68% demonstrating disease progression both in terms of size and number of metastatic lesions, despite repeated doses of RAI (see Table 1). For those patients who progressed, the median time to progression was

FIG. 1. Progression-free survival and overall survival of patients with lung metastasis from thyroid cancer.

FIG. 2. Correlation between progression-free survival and overall survival.

two years, with 17% of patients progressing by the end of year 1, 35% by year 2, 55% by year 5, and 65% by year 10. The percentage of patients who progressed with time varied based on RAI avidity of the metastatic foci, with RAI refractory patients having more rapid progression at each time point than RAI-avid patients (see Table 2).

Survival analysis

Figure 1 depicts the Kaplan–Meier curves for OS and PFS in the cohort. The median OS was 10.45 years [confidence interval (CI) 8.91–11.99], while the median PFS was 3.65 years [CI 2.76–4.53]. A strong positive relationship was found between PFS and OS ($r^2 = 0.47$, $p < 0.001$; Fig. 2). PFS was significantly shorter in patients with RAI refractory disease, poorly differentiated/Hürthle cell histologies, male sex, FDG-avid metastatic foci, older age (>45 years), and pulmonary metastases >1 cm in size (see Fig. 3).

The OS and PFS were analyzed for patients presenting with lung-only metastasis ($n = 157$) and those with lung and bone metastasis ($n = 42$), and they were compared with the overall cohort. The OS was 10.45 years [CI 8.95–11.99] in the overall cohort, 11.24 years [CI 9.80–12.68] in patients with lung-only metastasis, and 6.01 years [CI 3.20–8.81] in patients with lung and bone involvement. Similarly, the PFS was shorter in patients with lung and bone metastasis (median 1.67 years [CI 1.37–1.97]) compared with those with lung-only metastasis (median 4.43 years [CI 3.08–5.77]) or the overall cohort (median 10.45 years [CI 8.96–11.99]).

Patients demonstrating rapid structural disease progression (within a year of the diagnosis of pulmonary metastases) were more likely to be FDG avid and RAI refractory than patients who demonstrated late progression (progression developed more than five years after diagnosis of pulmonary metastases; see Table 3). Mortality tended to be higher in the rapid progressors (66%) than in the late progressors (44%; $p < 0.085$). Otherwise, there were no significant differences between rapid and late progressors based on age, sex, primary histology, RAI activity given for ablation/adjuvant therapy, or size of pulmonary lesions (see Table 3). The similar death rate noted in the rapid and slow progressors is explained by the relative short median time to progression in this group as opposed to those with late progression. The results did not change when only patients with RAI-avid disease were selected and the analysis was repeated.

FIG. 3. Progression-free survival based on clinicopathologic factors.

Discussion

This study retrospectively describes the natural history, time to progression, and risk factors for structural disease progression of lung metastasis in a large cohort of FCDTC patients who had not been treated with conventional chemotherapy or molecular therapies. As such, this cohort can serve as a historical control group describing the expected outcomes in patients with pulmonary metastases treated with thyroidectomy, RAI, and TSH suppressive therapy. Consistent with previous reports, 46% of the cohort had died after a median of 6.9 years, reflecting the poor prognosis often associated with distant metastases.

Chopra *et al.* examined the outcomes of patients with metastatic thyroid cancer (3). The study was enriched with patients with lung metastasis detected by post-therapy scan without clear evidence of structural correlate on initial computed tomography scan of the chest or chest roentgerogram. Cross-sectional imaging was not used to assess response. Thus, the patient outcomes of these cohorts are not comparable. In addition, disease-specific survival was obtained only on those patients who presumably achieved remission. Similar to the present results, older patients with macronodular lung metastasis were more likely to progress.

Even though the OS in this cohort of FCDTC patients was a median of 10 years, the median PFS from the time of diagnosis of the pulmonary metastases was much shorter at

3.65 years. Patients with RAI-avid metastatic thyroid cancer at diagnosis progressed at a slower pace than those with RAI refractory thyroid cancer. However, RAI avidity was not the only predictive factor for PFS. The PFS was shorter in patients with RAI refractory disease, poorly differentiated/Hürthle cell histologies, male sex, FDG avid metastatic foci, older age (>45 years), and pulmonary metastases >1 cm in size. In general, PFS was more than five years from the time of diagnosis of pulmonary metastases in RAI-avid tumors, FDG negative tumors, subcentimeter pulmonary nodules, and younger patients (see Fig. 3). Conversely, PFS was in the 1–1.5-year range in patients with RAI refractory disease, FDG-avid disease, larger pulmonary nodules, and older patients (>45 years). Furthermore, consistent with the authors' prior studies (2), patients with RAI refractory FDG-avid disease had the most rapid progression and highest disease-specific mortality (see Table 3). Consideration should be made early on to treat these patients with potentially more effective multitarget kinase inhibitor therapy.

Twelve patients were <18 years of age at lung metastasis diagnosis, and 4/12 had disease progression during the course of their follow-up. However, none had disease progression less than a year from the time of thyroid cancer metastasis diagnosis. Patients with lung and bone metastasis fared worse than those with lung-only metastasis did. As such, both the OS and PFS were shorter in patients with osseous metastasis as opposed to those with isolated lung metastasis.

TABLE 3. PATIENT CHARACTERISTICS BY TIME OF DISEASE PROGRESSION GROUPS

	<i>Rapid DP</i> (median 0.6 years), N = 32	<i>Slow DP</i> (median 2.1 years), N = 76	<i>Late DP</i> (median 7.8 years), N = 27	p-Value
<i>Age at TC Dx</i>				NS
<i>M ± SD</i>	51 ± 13	59 ± 16	51 ± 20	
Median	52	62	58	
Range	26–74	12–74	490	
<i>DM at TC Dx</i>				NS
Yes	47%	51%	59%	
<i>Age at DM Dx</i>				NS
<i>M ± SD</i>	54 ± 12	62 ± 16	53 ± 19	
Median	55	65	59	
Range	34–76	16–87	478	
<i>Sex</i>				NS
Female	44%	51%	33%	
<i>Age group at DM Dx</i>				NS
<45 years	28%	12%	26%	
≥45 years	72%	88%	74%	
<i>Primary tumor size (cm)</i>				NS
<i>M ± SD</i>	3.8 ± 1.8	4.4 ± 2.9	4.1 ± 3.2	
Median	3.5	3.8	3.8	
Range	1.1–7.5	0.3–16.0	0.7–14.5	
<i>Histology groups</i>				NS
Papillary	40%	38%	67%	
Follicular/Hürthle cell	22%	11%	15%	
Poorly differentiated	38%	51%	18%	
<i>Extrathyroidal extension</i>				NS
No	35%	27%	43%	
Minimal	43%	41%	36%	
Gross	22%	32%	21%	
<i>Vascular invasion</i>				NS
Yes	78%	78%	71%	
No	22%	22%	29%	
<i>Thyroid surgery</i>				NS
Total	94%	92%	89%	
Subtotal	6%	8%	11%	
<i>EBRT neck</i>				NS
Yes	19%	23%	15%	
<i>RAI ablation</i>				NS
Yes	84%	91%	89%	
<i>RAI ablation activity (mCi)</i>				NS
<i>M ± SD</i>	171 ± 78	166 ± 107	169 ± 98	
Median	157	150	154	
Range	29–323	29–501	50–442	
<i>RAI avidity at DM Dx</i>				0.008
Yes	44%	51%	78%	
No	56%	49%	22%	
<i>FDG-PET avidity at DM Dx</i>				0.010
Yes	64%	52%	21%	
No	36%	48%	79%	
<i>Lung size category</i>				0.036
Micro (<1 cm)	56%	64%	82%	
Macro (≥1 cm)	44%	36%	18%	
<i>Follow-up since DM Dx (years)</i>				<0.001
<i>M ± SD</i>	4.3 ± 3.1	6.7 ± 3.2	12.0 ± 5.1	
Median	3.5	6.5	10.0	
Range	0.3–11.4	0.7–14.7	4.2–22.8	
<i>Time to DP since DM Dx (years)</i>				<0.001
<i>M ± SD</i>	0.6 ± 0.2	2.4 ± 1.1	8.5 ± 3.3	
Median	0.6	2.1	7.8	
Range	0.2–1.0	1.0–4.8	5.1–16.6	
<i>Status at end follow-up</i>				0.085
Alive	34%	32%	56%	
Dead	66%	68%	44%	

p-Value is a comparison of those who progressed in less than one year to those who progressed in more than five years.
TC, thyroid cancer; DM, distant metastasis; EBRT, external beam radiation therapy; DP, disease progression; Dx, diagnosis.

As shown in Figure 2, there is a strong positive correlation between OS and PFS in this cohort of patients with pulmonary metastases. These data validate the assumption that PFS is a reasonable surrogate marker for OS in most patients with metastatic thyroid cancer.

This study is limited by its retrospective design and the potential for selection bias. As such, patients referred to the center tend to have more aggressive thyroid cancer with shorter PFS than the general thyroid cancer population. In addition, patients were followed at the discretion of their treating physician with the follow-up and imaging intervals not standardized. As such, the precise time to progression may have been less than was measured. Furthermore, patients were excluded who were treated directly with chemotherapy or molecular targeted therapy. This may have potentially biased the results toward a better OS and PFS, given the likely more aggressive behavior of those malignancies.

In conclusion, most patients presenting with distant metastatic thyroid cancer will progress using standard-of-care approaches. This does not only occur in the patients with RAI refractory disease, but also in those with RAI-avid tumors. The exception is younger patients presenting with low tumor burden and who are likely to respond well to repeat RAI therapies with prolonged remission and very low disease-specific mortality. Therefore, additional studies are needed to define treatments/interventions to improve the PFS in most patients with distant metastasis for FCDTC.

Author Disclosure Statement

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