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# Prognostic Factors in Patients with Well-Differentiated Thyroid Cancer Presenting with Pulmonary Metastasis

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## ABSTRACT

**Purpose:** Survival outcomes in patients presenting with well-differentiated thyroid cancer with pulmonary metastasis are variable. The aim of this study was to evaluate prognostic factors for outcome in this patient population. **Methods:** A prospective registry database was searched to identify patients presenting with pulmonary metastasis from well-differentiated thyroid cancer. All patients underwent total thyroidectomy and postoperative I-131 therapy. Cox proportional hazards modeling was performed to evaluate prognostic factors for survival outcomes. **Results:** Forty (40) patients were identified with well-differentiated thyroid cancer involving the thyroid and metastatic to cervical lymph nodes and lung at initial diagnosis. The median follow-up was 9.7 years for those alive at last follow-up. Cox proportional hazards modeling evaluated age at diagnosis, gender, primary tumor size, and vascular invasion on cause-specific and progression-free survivals. Age at diagnosis was the only significant independent prognostic factor ( $p = 0.0035$ ). The 10-year cause-specific survivals were 100% in patient's  $\leq 40$  years, compared to 36% for those  $> 40$  years ( $p < 0.0001$ ). The corresponding 10-year progression-free survivals were 69% and 12% ( $p = 0.0003$ ). **Conclusions:** Patients  $\leq 40$  years of age presenting with pulmonary metastasis from well-differentiated thyroid cancer had an excellent prognosis. Older patients have a poor survival outcome. Postoperative I-131 therapy is recommended in all patients.

**Key words:** thyroid cancer, metastasis, pulmonary, I-131, lung

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All experiments in this study comply with the current laws of the country in which they were performed, inclusive of ethics approval.

## INTRODUCTION

Well-differentiated thyroid carcinoma affects both children and adults and is accompanied by distant metastasis at the time of diagnosis in a minority of cases.<sup>1-10</sup> Pulmonary metastases is the most common at diagnosis and is detected in 3%-20% of patients.<sup>11-15</sup> Pulmonary metastasis

is more common in children and young adults<sup>9</sup> and is associated with excellent survival after initial treatment or recurrence.<sup>16–18</sup> Poor long-term survival has been reported for older patients with metastatic well-differentiated thyroid cancer,<sup>8,10,14,15,19,20</sup> but age has not been shown to be an independent predictor of survival in other reports.<sup>1,6</sup> This analysis was performed to study the impact of prognostic factors at diagnosis on progression-free and cause-specific survivals in patients presenting with well-differentiated thyroid cancer and pulmonary metastasis.

## MATERIALS AND METHODS

A prospective registry of patients with thyroid cancer referred to the Mallinckrodt Institute of Radiology (MIR; Washington University School of Medicine, St. Louis, MO) from 1970 to 2006 was searched to identify patients with pulmonary metastasis at time of diagnosis. Approval from the Institutional Review Board (Washington University Human Research Protection Office) was obtained for this study. The registry included 1333 patients with newly diagnosed, well-differentiated papillary thyroid carcinoma. None of the patients had follicular carcinoma. Of these, 40 patients (3%) were identified with pulmonary metastasis detected on <sup>131</sup>I scintigraphy at the time of the initial thyroid cancer diagnosis and treatment. The size of the pulmonary metastases could not be determined, since the information was not recorded in the clinical records for all patients. None of these patients were known to have a history of prior radiation exposure.

All patients underwent a total thyroidectomy and received postoperative <sup>131</sup>I therapy, according to standard institutional practice. For adults, the general guideline was to administer 150–250 mCi of <sup>131</sup>I (5.55–967.25 GBq), and children usually received the corresponding dosage adjusted for body weight (3.57 mCi/kg, 0.13GBq/kg). Whole-body <sup>131</sup>I scintigraphy was performed 2–5 days after treatment. Repeat <sup>131</sup>I administration was performed for residual or recurrent disease. Patients received a mean <sup>131</sup>I-administered activity of 448 mCi (16.6 GBq) (maximum, 1400 mCi, 51.8 GBq). The presence of pulmonary metastasis and response to treatment were detected by whole-body scintigraphy with <sup>131</sup>I. Persistent and recurrence disease sites were detected by clinical examination, thyroglobulin assay, or I-131 scintigraphy. Follow-up I-131 scintigraphy was performed with 5 mCi I-131.

Cause-specific survival is defined as death resulting from thyroid cancer. Progression-free survival is defined as the development of recurrent thyroid cancer. Cause-specific survival and progression-free survival were estimated by using the Kaplan-Meier method.<sup>21</sup> The equivalence of the survival estimates was evaluated by using the Mantel-Cox statistic.<sup>22</sup> Multivariate analysis was performed by using the Cox proportional hazards regression model.<sup>23</sup>

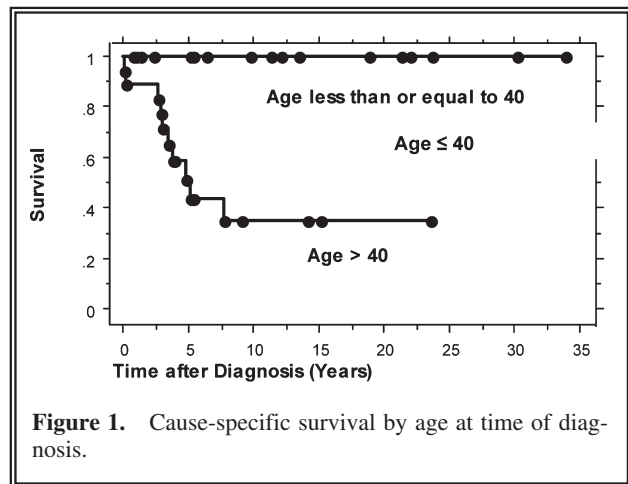
## RESULTS

### Patient Characteristics

The patient population consisted of 24 males and 16 females. Their median age was 38 years (range, 4–83). The tumor histologic type was well-differentiated thyroid cancer in all patients. None of the patients had poorly differentiated or anaplastic carcinoma. The mean and median follow-up times for all patients alive at the time of last follow-up were 12.3 and 9.7 years (range, 2–37).

### Prognostic Factors

All patients in this study were known to have metastasis to cervical lymph nodes and lung at the time of diagnosis. Other established prognostic factors were evaluated by Cox multivariate proportional hazards modeling. These factors included age at diagnosis, gender, primary tumor size, local soft-tissue invasion, and vascular invasion. Patient age was the only significant independent predictor of progression-free survival ( $p = 0.0061$ ) and of cause-specific survival ( $p =$



**Figure 1.** Cause-specific survival by age at time of diagnosis.

0.0035). Neither gender ( $p = 0.12$ ), primary tumor size ( $p = 0.15$ ), local soft tissue invasion ( $p = 0.19$ ), nor vascular invasion by tumor ( $p = 0.26$ ) were independent predictors of cause-specific survival in this model.

Because age at diagnosis was the only independent prognostic factor, its effect was further evaluated. The log-rank (Mantel-Cox) statistic was used to determine the cut-off age value that was strongly predictive of prognosis. It was found that patients  $\leq 40$  years had a significantly better outcome than those  $>40$  years (Figs. 1 and 2). The 10-year cause-specific survivals were 100% in patients  $\leq 40$  years, compared to 36% for those  $>40$  years ( $p < 0.0001$ ). The corresponding 10-year progression-free survivals were 69% and 12%, respectively ( $p = 0.0003$ ).

### Recurrence

Nineteen (19) of 40 patients had persistent lung metastasis or developed new sites of recurrence after  $^{131}\text{I}$  therapy. Recurrence sites are shown in Table 1. Persistent metastatic disease in the lung was the most common site of disease (13/19). Twenty-one (21) patients became disease free.

### DISCUSSION

The prognosis of patients presenting with pulmonary metastasis from well-differentiated thyroid cancer is variable after standard therapy. In the current study, cause-specific survivals were 100% for patients 40 years of age and younger and 36% in patients older than 40 years. Young

**Table 1.** Recurrence Sites

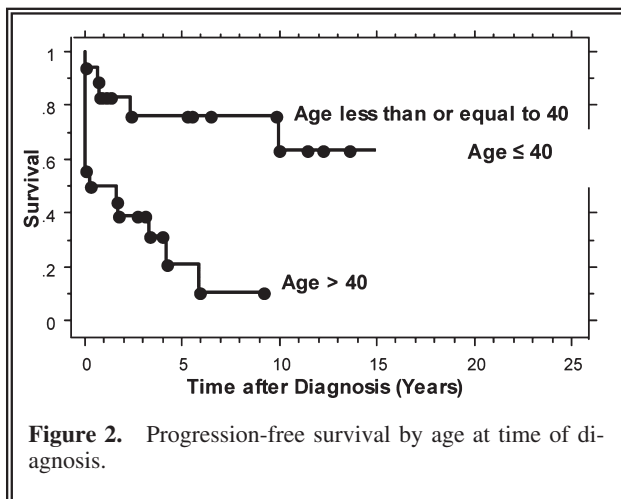
Recurrence site	Number of patients
Cervical LN	3
Lung	6
Cervical LN + lung	4
Cervical LN + lung + thyroid bed	3
Bone	3
Total	19 (53%)

LN, lymph node.

age has been reported to be a positive predictor of prolonged survival.<sup>2,8,10,14,15,19,20,24</sup> On the other hand, some recent reports have not found age to be a significant independent factor.<sup>1,6</sup> Most investigators report young age as a predictor of survival but fail to address the issue of what is the cut-off age for a poor prognosis. Our data demonstrate no cancer-related deaths for patients less than 40 years, whereas most patients older than 40 years will die from metastatic thyroid cancer.

Thyroid cancer has a favorable overall prognosis in children and young adults, despite a pattern of disseminated disease and frequent recurrence.<sup>16-18,25</sup> Cervical lymphadenopathy and distant metastasis are more common in children and adolescents than in adults. The inconsistency between extensive disease at presentation and positive outcome after therapy is characteristic of childhood well-differentiated thyroid cancer, but the reason for this apparently discordant behavior has not been described.<sup>25</sup>

Excellent outcome after aggressive treatment with thyroidectomy and  $^{131}\text{I}$  administration for young patients with metastatic well-differentiated thyroid cancer supports the use of  $^{131}\text{I}$  therapy in these patients. The positive survival results in younger patients may be explained by less aggressive tumor biology, but  $^{131}\text{I}$  therapy is recommended, based upon excellent survival rates achieved in patients with metastasis.<sup>25,26</sup> For older patients with pulmonary metastasis from well-differentiated thyroid cancer, survival may be improved through a similar approach, using  $^{131}\text{I}$  administration until complete remission of disease, with multiple treatments to high cumulative activities.<sup>19,27</sup> A treatment protocol that includes total thyroidectomy and postoperative  $^{131}\text{I}$  therapy reduces the rate of recurrence and allows for the early detection of pulmonary metastasis.<sup>28,29</sup>



**Figure 2.** Progression-free survival by age at time of diagnosis.

Uptake of  $^{131}\text{I}$  by pulmonary metastases from well-differentiated thyroid cancer has been shown to be an important factor associated with prolonged survival time.<sup>19,26</sup> This observation underscores the important role of  $^{131}\text{I}$  therapy in the successful treatment of disseminated well-differentiated thyroid cancer.  $^{131}\text{I}$  therapy decreases the tumor burden in patients with pulmonary metastasis from well-differentiated thyroid cancer<sup>30</sup> and should be administered to patients whose tumors concentrate  $^{131}\text{I}$ . Three-dimensional lung and bone marrow dosimetry may be performed for patients with  $^{131}\text{I}$ -avid pulmonary metastases from well-differentiated thyroid cancer.<sup>31,32</sup> Use of large cumulative activities has been reported with minimal clinical toxicity.<sup>29,33</sup> For older patients with metastatic well-differentiated thyroid cancer, the incorporation of systemic agents into therapeutic regimens may be a promising avenue for future research, given the availability of molecularly targeted drugs<sup>27</sup> and because of the suboptimal outcomes after standard treatment. Definitive proof of benefit of I-131 therapy for I-131-avid lung metastases is lacking because there is no group of “control” or untreated patients.

## CONCLUSIONS

In the current study of patients presenting with pulmonary metastasis from well-differentiated thyroid cancer, no deaths were observed in patients 40 years of age or younger, whereas pulmonary metastasis was associated with a poor prognosis in older patients. Total thyroidectomy and aggressive postoperative  $^{131}\text{I}$  therapy are recommended for all patients with pulmonary metastasis from well-differentiated thyroid cancer, and this treatment regimen provides optimal long-term survival for patients aged 40 years or younger.

## DISCLOSURE STATEMENT

There are no conflicts of interest associated with this manuscript by any of the authors.

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