Five-Year Survival Is Similar in Thyroid Cancer Patients with Distant Metastases Prepared for Radioactive Iodine Therapy with either Thyroid Hormone Withdrawal or Recombinant Human TSH

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Context: Elevated levels of TSH markedly enhance the effectiveness of radioiodine (RAI) therapy in metastatic thyroid cancer.

Objective: The objective of the study was to compare short-term overall survival in thyroid cancer patients with RAI-avid distant metastases prepared for RAI therapy with either traditional thyroid hormone withdrawal (THW) or recombinant human TSH (rhTSH) stimulation.

Design: This was a retrospective chart review.

Setting: The study was conducted at a tertiary care comprehensive cancer center.

Patients: Patients included 175 patients with RAI avid metastatic disease to lung and/or bone.

Interventions: In 58 patients, all RAI treatments (remnant ablation and therapy of metastatic disease) were done with rhTSH stimulation. In 35 patients, all RAI treatments were done after THW. In 82 patients, THW was used for initial RAI treatment(s) with subsequent administered activities given after rhTSH stimulation.

Main Outcome Measure: Overall survival was measured.

Results: After a median follow-up of 5.5 yr, there were no significant differences in overall survival between patients prepared for RAI therapy with rhTSH alone, THW alone, or THW followed by rhTSH (Kaplan-Meier analysis, \( P = 0.80 \)). In a multivariate analysis that included clinicopathological features and method of preparation (rhTSH or THW), only age at diagnosis was an independent predictor of overall survival.

Conclusions: Preparation for RAI therapy using either THW or rhTSH stimulation was associated with similar 5-yr overall survival rates in patients with RAI avid thyroid cancer metastases to lung or bone. (J Clin Endocrinol Metab 96: 2105–2111, 2011)
Patients and Methods

Patients

After obtaining appropriate Human Use Committee approval, we reviewed the clinical charts of all follicular cell-derived thyroid cancer patients referred to the Nuclear Medicine Department at Memorial Sloan Kettering Cancer Center between 1993 and 2010 for remnant ablation, therapy of distant metastases or for diagnostic RAI whole-body scanning (Dx-WBS). All patients receiving RAI therapy after either THW or rhTSH preparation with definite evidence of RAI avid DM to lungs and/or bones found on either the diagnostic (Dx-WBS) or posttherapy WBS (Rx-WBS) were included in this study. The Rx-WBS and Dx-WBS reports of all patients were reviewed; the actual whole-body scanning (WBS) imaging was available and reviewed in 89% of the patients. Nearly all patients (98%) had cross-sectional imaging of RAI avid metastatic lesions identified on WBS. Lung metastases were classified as micrometastases if all pulmonary lesions were 1 cm or less or macrometastases if any single lesion was greater than 1 cm.

Patients were excluded from analysis for the following reasons: 1) no visible (or only very faint) uptake of RAI in metastatic lesions on either a prior diagnostic or posttherapy scan; 2) uptake of RAI in only a small fraction (<10%) of multiple metastatic lesions; 3) patients with inadequate follow-up data; 4) age less than 20 yr old at diagnosis (because rhTSH preparation was rarely performed in younger patients with distant metastases); 5) patients with another concomitant primary cancer in which the status of the other cancer was unknown or active; 6) patients with DM to organs other than lungs and bones; and 7) patients with anaplastic thyroid carcinoma.

From 245 potential study subjects, 175 patients met the inclusion criteria. We excluded 15 patients with either no definite evidence (or <10% of metastatic lesions) being RAI avid, 13 patients with metastasis in other organs beyond lungs and bones, 15 patients younger than 20 yr old, five patients with a focus of anaplastic thyroid carcinoma within the primary tumor or the metastasis, 18 patients with inadequate follow-up information, and four patients with unknown status of another cancer.

Preparation for RAI treatment

All patients treated with RAI for distant metastases at our center were instructed in a low-iodine diet and underwent whole-body and blood RAI clearance dosimetry studies that were used to determine the maximal therapeutic activity that could be safely administered without expectant damage to the bone marrow (less than 2 Gy) or lungs (less than 80 mCi whole body retention at 48 h) as described previously (10). In 38 patients, one or more of their RAI therapies were done before referral to our center using THW preparation without dosimetry studies. Patients treated before 1998 underwent traditional THW in preparation for RAI scanning and therapy. After rhTSH became commercially available in 1998, the choice of preparation (rhTSH vs. THW) was an individualized decision between each treating physician and the patient with no preset criteria favoring either rhTSH or THW preparation.

rhTSH preparation

Whole-body and blood dosimetry studies were done as previously published (10). It is important to note that the rhTSH-stimulated RAI therapy described in this report incorporates two injections of rhTSH during wk 1 as preparation for dosimetry and an additional set of two injections during wk 2 before therapy. Briefly, while remaining on suppressive doses of levothyroxine, im injections of rhTSH (0.9 mg) were administered on d 1 and 2. On d 3, 1–5 mCi of 131-I was administered orally, and an additional set of two injections during wk 2 before therapy.
THW preparation

After levothyroxine withdrawal, most patients received T₃ for 2–4 wk before complete THW as previously described (10). In patients treated at our center whole-body and blood RAI clearance studies were done after a 1- to 5-mCi dose of 131-I. In 38 patients receiving RAI therapy outside our center, standard empiric dosing approaches were used. In either setting, a TSH level above 30 mIU/liter was required before therapy. The posttherapy scan was performed approximately 3–10 d after RAI administration.

Laboratory and pathology studies

Between 1994 and 1997, a variety of thyroglobulin assays were used with functional sensitivities of approximately 1 ng/ml. Starting in 1998, all Tg values were measured using the DynoTest-Tg5 immunoradiometric assay (Brahms Inc., Berlin, Germany; functional sensitivity 0.6 ng/ml normalized to CRM 457) (10). TSH was measured using Advia Centaur two-site sandwich immunoassay (Bayer Corp., Tarrytown, NY).

Statistical methods

The primary end point of the study was a comparison of overall survival between patients prepared for all their RAI treatments (remnant ablation and RAI therapies) with either rhTSH (n = 58) or THW (n = 35). As an additional comparison group, we describe the overall survival in a cohort of patients (n = 82) that had initial remnant ablation and or RAI therapies with THW who then had additional follow-up treatments with rhTSH.

Continuous data are presented as median and range values. Comparison between medians was performed using nonparametric tests (Mann-Whitney test). Categorical comparisons were performed with the Fisher’s exact test and χ² test. Kaplan-Meier analysis was performed for overall survival, comparing survival with the log rank test and using the Cox model for multivariate analysis. All the analyses were performed using SPSS software (version 16.0.1; SPSS Inc., Chicago, IL).

Results

Clinicopathological characteristics of the entire cohort

The clinical characteristics at the time of diagnosis of the 175 patients with RAI avid DM are summarized in Table 1. The median age was 56 yr (range 20–86 yr) and 53% of the patients were female. DM were diagnosed at the initial presentation of thyroid cancer in 60% of the patients (M1 patients). The locations of the DM were as follows: 53% only in lung, 28% only in bone, and 19% in lung and bone. Of the entire cohort, 35 patients had all RAI therapies (including radioactive iodine remnant ablation) done following THW (THW only), and 58 had all RAI therapies done after rhTSH stimulation (rhTSH only). The other 82 patients had initial RAI treatments done with THW with subsequent treatments done with rhTSH. The median follow-up time for the entire cohort was 5.5 yr (range 0.8–21 yr).

Clinicopathological features based on method of preparation

The clinical characteristics of patients based on the method of preparation for RAI treatment are given in Table 2. There are no statistically significant differences between the three groups in age, gender, M stage at the time of diagnosis of thyroid cancer, distribution of DM, size of lung metastases, and presence of multiple bone metastases. Because rhTSH became commercially available in 1998, the median follow-up was significantly longer in the THW-only group (6.9 yr) and in patients who received initial doses prepared with THW followed by rhTSH (6.9 yr) compared with the rhTSH-only group (3.4 yr, P < 0.05). There was no significant difference in the histotype between the two groups.

Patients prepared with THW followed by rhTSH treatments received a median of four treatments compared...
with only two treatments in both the rhTSH alone and the TWH alone. As a consequence, the cumulative administered activity was higher in this group than in either the TWH only or rhTSH-only groups (median 967 vs. 522 vs. 408 mCi, respectively, \( P < 0.05 \)). However, the median administered activity per treatment was higher in patients prepared with rhTSH only (median 263 mCi, range 30–514) than in patients prepared with TWH only (median 200 mCi, range 30–480; \( P = 0.038 \)). Patients prepared with TWH followed by rhTSH preparation received a median of 207 mCi after TWH (range 30–510 mCi) and a median of 315 mCi following rhTSH (range 10–521 mCi).

### Survival analysis and structural response to therapy based on method of preparation

There was no significant difference in overall survival between patients receiving all RAI treatments with TWH-only, rhTSH-only, or initial treatments with TWH followed by subsequent treatments with rhTSH stimulation \( (P = 0.8) \). A multivariate analysis that included age at
Discussion

This is the first report to demonstrate very similar five overall survival rates in thyroid cancer patients with RAI avid distant metastases prepared with either traditional THW or a four-injection, rhTSH-stimulated, dosimetry-guided treatment protocol. Furthermore, the method of preparation (rhTSH vs. TWH) had no impact on overall survival in a multivariate analysis. These data suggest that rhTSH may have a role as an adjunct to RAI therapy of distant metastases in addition to its role in diagnostic testing (whole body RAI scanning and/or stimulated Tg) and remnant ablation.

Although much longer studies will be needed to assess the impact of preparation methods on long-term survival, initial observations over the first 5 yr of follow-up are an important starting point. Analysis of both the Surveillance Epidemiology and End Results data (11) and the 53,856 cases in the National Cancer Data Base (12) demonstrates a 50% mortality in American Joint Committee on Cancer (AJCC) stage IV patients over the first 5 yr of follow-up. Because 41% of our rhTSH-only and 49% of our TWH-only patients were stage IV, it is likely that if major differences in short-term overall survival existed between these two groups, we would have detected either a trend or statistical difference over this initial 5-yr follow-up period. Furthermore, analysis of the Kaplan-Meier curve presented in the Durante series (1) shows a 5-yr survival rate of approximately 75–80% in patients with RAI avid distant metastases in which all RAI treatments were given after traditional THW. This rate is nearly identical to the 5-yr survival rates of 75–80% that we report with TWH when followed up over the next several decades.

Our findings suggesting that rhTSH preparation is an effective adjunct to RAI in the therapy of distant metastatic lesions is consistent with previous studies demonstrating similar effectiveness in destroying small-volume metastatic disease found incidentally at the time of radioactive iodine remnant ablation (4, 5). Furthermore, the
similar rates of recurrence seen with either THW or rhTSH preparation for radioactive iodine remnant ablation also suggests a therapeutic benefit that goes beyond simply destroying residual normal thyroid bed tissue.

Our findings are also consistent with previously reported series examining the clinical effectiveness of rhTSH stimulation before therapy of metastatic disease, usually in the setting of compassionate use in patients unable to increase endogenous TSH or in whom THW was deemed too risky. In a report on European patients, Luster et al. (13) showed that from 115 patients in which clinical outcome could be analyzed, 2% achieved complete remission, 36% partial response, and 27% disease stabilization. Robbins et al. (9) reported the effect of RAI treatment after rhTSH preparation as part of the Thyrogen Compassionate Use Program in 115 patients from the United States and Canada with metastatic disease. Clinical outcome was assessed by the serum Tg level trend, which was lower than baseline in 75% of patients assessed at 12 months. The results in both of these retrospective studies suggest that rhTSH-stimulated RAI therapy does have a therapeutic effect on RAI avid metastatic disease and is therefore consistent with our findings of similar rates of overall survival in both groups.

As with any retrospective study, there are several important limitations that must be considered. First and foremost is the potential for a selection bias that might result in patients with higher-risk disease being offered THW rather than rhTSH. Although we cannot rule out a subtle selection bias, comparison of the standard clinicopathological features between patients prepared with THW and rhTSH failed to identify significant differences. Prospective, randomized studies would be necessary to address this potential bias.

The other important limitation of this study is that our results are dependent on a series of four rhTSH injections (d 1, 2, 8, and 9) before administration of the therapeutic activity of RAI. Although we have previously published that a two-dose rhTSH regimen is associated with similar rates of successful ablation and recurrence as a four-dose regimen, the efficacy of a two-injection approach (d 1 and 2 with RAI therapy on d 3) in the treatment of macroscopic metastatic disease cannot be determined from our data (14). Additionally, because we routinely obtain whole-body and blood RAI clearance studies before therapy, we usually administer rather large activities of RAI as demonstrated by the median administered activity in the rhTSH cohort of 263 mCi. Therefore, our data cannot be used to determine whether a treatment approach using two injections of rhTSH followed by empiric 150- to 200-mCi dosing of RAI would result in similar clinical benefit. Unfortunately, the number of patients treated with rhTSH alone are too small to allow for a meaningful evaluation of the minimum empirical administered activity required to achieve the same results we achieved using our dosimetry guided approach.

In conclusion, in this retrospective study, the 5-yr overall survival is similar in thyroid cancer patients with RAI avid distant metastases prepared with whole-body and blood dosimetry with either thyroid hormone withdrawal or recombinant human TSH before receiving RAI. Therefore, a four-injection, rhTSH-stimulated, dosimetry-guided approach to the therapy of patients with RAI avid metastatic lesions appears to be an effective alternative to traditional THW-stimulated RAI treatments.

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