

# Thyroid Carcinoma Metastasis to Skull with Infringement of Brain: Treatment with Radioiodine

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**Background:** Infringement by differentiated thyroid carcinoma on the brain is rare but, when suspected, the patient deserves special attention. A patient with an enlarging metastasis of thyroid carcinoma to the skull that was impinging on the brain illustrates diagnostic and therapeutic strategies applicable to the treatment of metastatic carcinoma.

**Methods:** A case study was performed. Computed tomography (CT) and magnetic resonance imaging (MRI) were done, serum thyroglobulin was measured, and tumor responses to thyroxine and <sup>131</sup>I treatments were monitored. Tumor dosimetry, enabled by scintigraphy with <sup>131</sup>I employing single photon emission tomography fused with CT (SPECT-CT), was performed.

**Results:** The metastasis was from a follicular variant of papillary thyroid carcinoma. During thyrotropin stimulation the tumor enlarged. The tumor decreased in volume after each of two <sup>131</sup>I therapies. Dosimetry indicated delivery of 1970 and 2870 cGy to the tumor and 35 and 42 cGy to the brain, respectively, in the two treatments. The patient has survived for more than 11 years since diagnosis.

**Conclusions:** A metastasis from a follicular variant of papillary carcinoma increased in volume during hypothyroidism producing more infringement on the brain. Beyond the effects of thyroxine therapy, <sup>131</sup>I treatments induced recession of tumor volume. In patients with metastases that concentrate <sup>131</sup>I, dosimetry with SPECT-CT can predict absorbed doses of radiation to the tumor and to the adjacent organs and thus lay a basis for data-based decisions on <sup>131</sup>I therapies. Therapy may induce prolonged survival in patients with metastases infringing on the brain.

## Introduction

**B**ONE IS THE ONLY SITE OF DISTANT METASTASIS in about 1.7% of patients with differentiated thyroid carcinoma (1), and the 5-year cause-specific survival for those with papillary carcinoma is about 10% (2). Skeletal deposits of neoplasm pose special hazards of fracture and, when adjacent to the central nervous system, neurologic impairment. In addition, stimulation by thyrotropin (TSH) may produce swelling of metastases and abrupt clinical deterioration. Radiation therapy, including that from radioiodine, adds danger of injury to the adjacent neural structures.

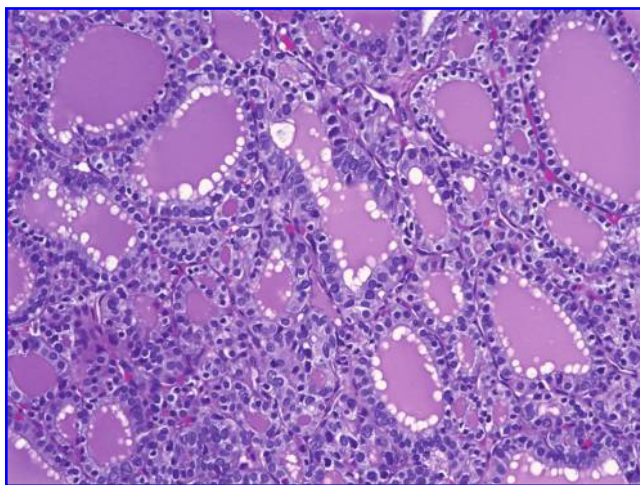
A case report exemplifies the concerns in treating a patient with a large papillary thyroid carcinoma that was impinging on the brain. Responses to <sup>131</sup>I treatments were monitored, and dosimetries of <sup>131</sup>I in the tumor and the adjacent brain tissue were assessed.

## Case Report

In 1997, at age 65 years, the patient developed a posterior head swelling. In another hospital, computed tomography (CT) and magnetic resonance imaging (MRI) images demonstrated a tumor, 8×4.8 cm, traversing the skull and intruding upon his brain, but he had no neurological symptoms. Biopsied tissue revealed what was ultimately defined as the follicular variant of papillary carcinoma (Fig. 1). Attempts at resection were foiled by copious bleeding. Embolization of tumor vessels failed to reduce the carcinoma. After a total thyroidectomy, scintigraphy during hypothyroidism portrayed <sup>131</sup>I concentration in the tumor but no other metastasis. The patient received 5.8 GBq (156 mCi) of <sup>131</sup>I as treatment; no symptoms ensued. The swelling subsided. A <sup>131</sup>I image in 2003 showed faint radioactivity in his posterior skull.

In November 2006, progressive head swelling reappeared. In January 2007, MRI depicted a tumor of substantial size

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**FIG. 1.** Photomicrograph of tumor biopsy; original magnification,  $\times 200$ . Well-differentiated papillary carcinoma, follicular variant. The tumor has a pure follicular architecture while the tumor cells display the characteristic features of papillary carcinoma: nuclear enlargement and elongation and prominent nuclear grooves (6). Color image available online at [www.liebertonline.com/thy](http://www.liebertonline.com/thy).

extending across the posterior midline and infringing on the brain (Table 1, Fig. 2A). In March 2007, at the University of Michigan Health System, the patient appeared well except for the tumor. Neurologic examination detected only a slight left facial synkinesis. Medications were quinapril for hypertension, calcium supplement, and levo-thyroxine (Synthroid<sup>®</sup>,

Abbott Laboratories North Chicago, IL). Another attempt at surgical reduction provoked much bleeding. A biopsy was obtained, and the operation was then abandoned.

In July 2007, his thyroxine (0.2 mg/d) was withdrawn for 4–5 weeks. During this interval, his head swelling noticeably increased; his only other symptom was fatigue. At that time, CT demonstrated that the tumor had tripled its volume since January (Table 1, Fig. 3A). The images and dosimetric measurements were made after he ingested  $^{131}\text{I}$ , 37 MBq (1 mCi); these studies included single photon emission tomography fused with CT (SPECT-CT); the only abnormal focus of radioactivity was in the tumor (Table 1, Fig. 3B). SPECT-CT of his neck and thorax and whole body planar images disclosed no other tumor. He then received 7.4 GBq (200 mCi) of  $^{131}\text{I}$ ; 4 days later, images portrayed no additional focus of radioactivity within the patient. One day after treatment he resumed thyroxine therapy. Dexamethasone (5 mg four times a day) was initiated at the time of  $^{131}\text{I}$  treatment; the dose was tapered after 1 week. Other than anxiety from dexamethasone, no untoward symptoms developed.

By November, it was apparent to the patient and his physicians that the swelling was much reduced; the diminution of tumor size was documented on MRI images (Table 1, Fig. 2B). Thyroxine was again discontinued for 4–5 weeks, and noticeable swelling gradually recurred, but again the only other clinical change was fatigue. The investigations were repeated in December: on SPECT-CT the tumor was larger than in November, but smaller than in July; and serum thyroglobulin (Tg) concentrations (with absent Tg antibodies) followed a similar pattern (Table 1). A third therapy with  $^{131}\text{I}$ , 7.5 GBq (203 mCi) was administered along with dexamethasone at a lower dose than that following his treatment in July. Thyroxine

**TABLE 1. THYROID METASTASIS**

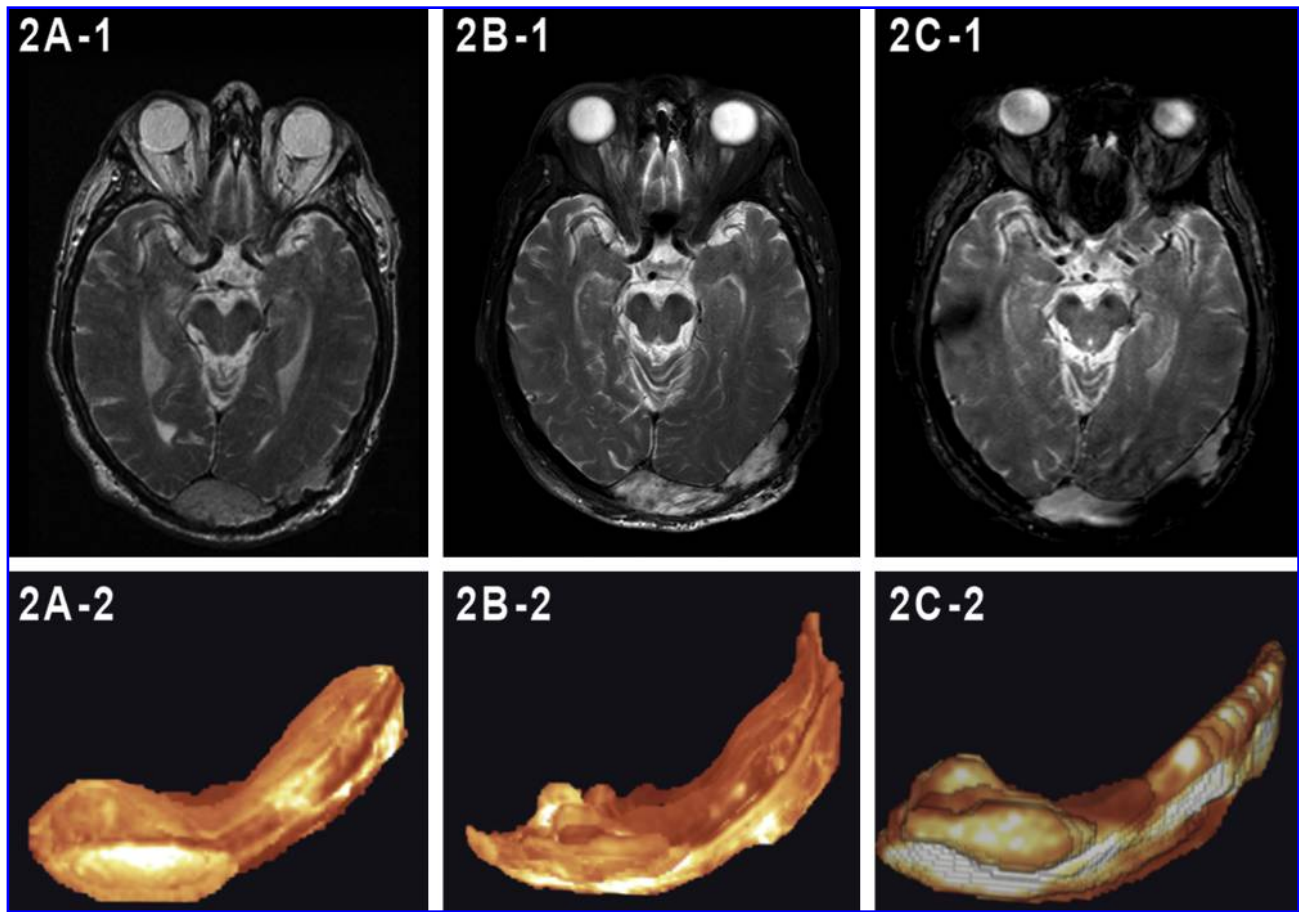
Date	Jan 07		Jul 07				Dec 07		Jun 08	Nov 08
	May 07	pre Rx	Rx	post Rx 4 days	post Rx 8 days	Nov 07	pre Rx	Rx		
TSH (mU/L)	0.4	75				0.4	84	0.1	2.1	
Tg (ng/mL)	6145	29124				3321	9140	530	1607	
Treatments										
thyroxine (mg/d)	0.2	0		0.2	0.2	0.2	0	0.228	0.228	
$^{131}\text{I}$ (GBq)			7.4				7.5			
Tumor Measurements										
volume method <sup>a</sup>	MRI	CT	CT	MRI	MRI	CT	MRI	MRI	MRI	
mL	74	219	216	169	121	155	110	72		
uptake $^{131}\text{I}$ (%)										
day 1							6			
day 2		4								
effective half life (d)										
from fractional uptakes <sup>b</sup>		1.7					1.7			
assumed <sup>c</sup>		3					3			
residence time (h)										
from fractional uptakes <sup>b</sup>		5.3					5.3			
assumed <sup>c</sup>		9.4					9.4			
absorbed dose (cGy)										
from fractional uptakes <sup>b</sup>		1970					2870			
assumed <sup>c</sup>		3470					5055			

<sup>a</sup>for details of method see text.

<sup>b</sup>calculated from uptake at day 1 of 6% (Dec 07) and at day 2 of 4% (Jul 07).

<sup>c</sup>assumed effective half life of 3 days.

TSH, thyrotropin; Tg, thyroglobulin; MRI, magnetic resonance imaging; CT, computed tomography; Rx, treatment.



**FIG. 2.** MRI transaxial images of the patient’s head at the same anatomic level over time during thyroxine therapy. Tumor was electronically isolated. (A) January 2007; TSH (in May) 0.4 mU/L; 2A-1 MRI and 2A-2 tumor with volume of 74 mL; (B) November 2007 (following <sup>131</sup>I treatment in July); TSH 0.4 mU/L; 2B-1 MRI and 2B-2 tumor with volume of 121 mL. (C) November 2008 (following <sup>131</sup>I treatments in July and December 2007); TSH 2.1 mU/L; 2C-1 MRI and 2C-2 tumor with volume of 72 mL. Color image available online at [www.liebertonline.com/thy](http://www.liebertonline.com/thy).

was resumed, and because his cardiovascular status appeared stable, the prescription was increased to 0.225 mg/d. In June 2008, he was feeling quite well. Tumor volume and Tg level were each reduced below the values obtained in November 2007 (Table 1).

In November 2008, the tumor size was again smaller (Fig. 2C). He continued to feel well, and clinical evaluation including neurologic examination was unchanged. The level of Tg was higher than that in June 2008, but his TSH (2.1 mU/L) was no longer suppressed (Table 1). Thyroxine dose was further increased to 0.257 mg/d.

Additional <sup>131</sup>I treatment is possible and will depend upon the patient’s clinical course.

**Methods**

Before each of two therapies, diagnostic studies followed ingestion of 37 MBq (1 mCi) of <sup>131</sup>I.

*Body dosimetry*

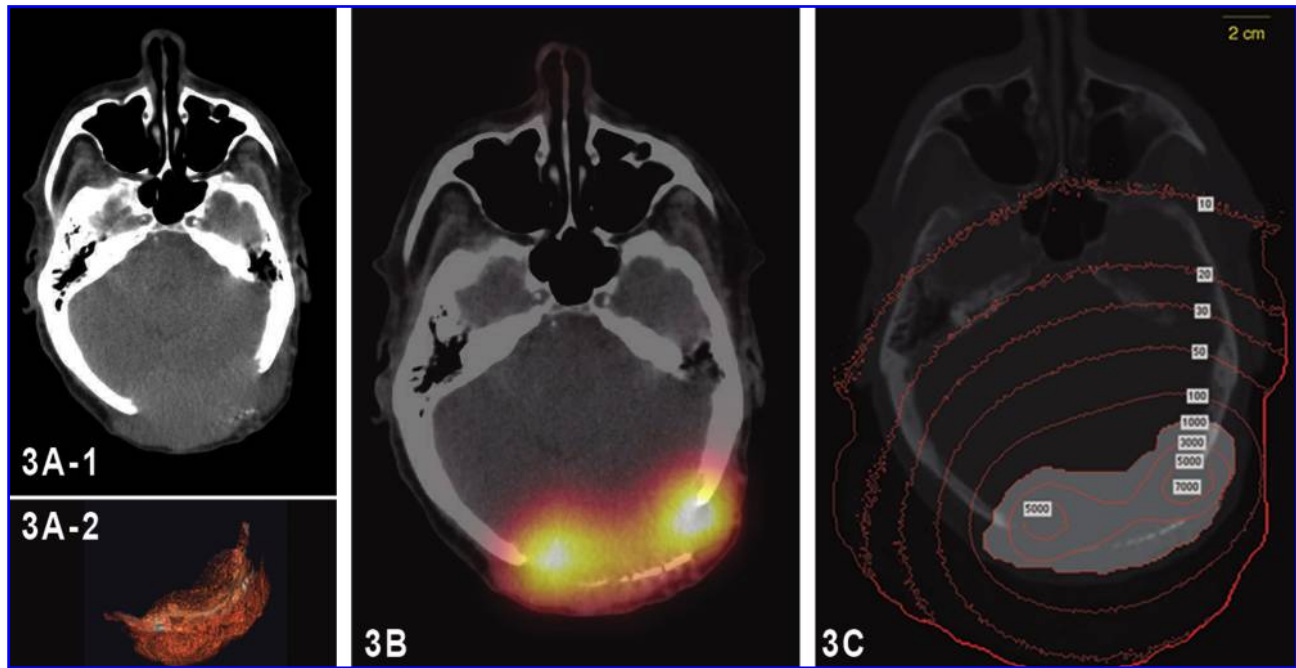
Whole body retention of <sup>131</sup>I after 2 days was determined by scintigraphic probe aimed at the patient’s body, 2.5 m distant, and related to the administered activity (3).

*MRI and SPECT-CT*

MRI images were obtained on a Phillips 3.0 Tesla magnet (Siemens Medical Solutions, Malvern, PA) utilizing intravenous gadolinium (Magnevist) contrast medium Siemens Medical Solutions Malvern, PA. Two days after ingestion of diagnostic <sup>131</sup>I, co-registered SPECT-CT images were acquired on a Siemens Symbia T6 SPECT/CT dual-head gamma camera (Siemens Medical Solutions, Malvern, PA). No contrast medium was employed for the CT. Scintigraphic data were obtained using 64 steps (20 seconds/stop) in a noncircular orbit over 360°. Tomographic images were in a 128×128 matrix using 3-dimensional ordered-subset expectation maximization iterative reconstruction technique (eight iterations, four subsets), and a CT-based correction algorithm for attenuation was applied. CT images were made with parameters of 130 kV and 100 mAS; reconstruction was from 5 mm slices in a 512×512 matrix.

*Tumor volume*

In MRI and CT images, tumor volumetric measurements were obtained with Vitrea 2 software, version 4.1.1.0 (Vital Images, Inc., Minnetonka, MN). Free-hand sculpting



**FIG. 3.** Images in July 2007 1 day before  $^{131}\text{I}$  treatment. TSH 75 mU/L. CT transaxial images of the head were obtained at a different inclination from the MRI images in Fig. 2, but both CT and MRI portray tumor at maximum dimensions. (A1) 1, CT image and (A2) tumor with volume of 219 mL. (B) Single photon emission tomography fused with CT (SPECT-CT) demonstrating radioactivity concentration in tumor. (C) CT with superimposed iso-dose levels of cGy in the tumor (shaded) and brain. The absorbed dose to the brain is from gamma (photon radiation) emanating from the tumor. Mean radiation dose to the tumor was 1970 cGy. Color image available online at [www.liebertonline.com/thy](http://www.liebertonline.com/thy).

of the tumor boundaries excluded tumor from surrounding structures and the volume of the tumor was then generated for each time of imaging.

#### Tumor dosimetry

Radioactivity in the tumor was also determined by scintigraphic probe at 2.5 m and related to the administered activity of  $^{131}\text{I}$ , but acquisitions were not systematically planned. Before the first treatment, tumor activity was 4% at 2 days; and before the second treatment tumor activity was 6% at 1 day. The effective half life of  $^{131}\text{I}$  in the tumor was estimated from these two values.

Tumor time-activity measurements from the scintigraphic probe data (above) were combined with the 3D dose-rate distribution from a Monte Carlo based calculation to obtain the average absorbed dose to the tumor and brain. The Dose Planning Method (DPM), a Monte Carlo electron and photon transport program (4), was designed for radiation absorbed-dose computations in external beam radiotherapy; it was adapted and validated for applications in internal emitter therapy (5). In the present study, the inputs to DPM were the co-registered SPECT images, CT-derived density map, and the CT-defined masks for tumor and brain regions. The SPECT and CT matrix size was  $512 \times 512 \times 115$  with a voxel size of  $0.98 \text{ mm} \times 0.98 \text{ mm} \times 2 \text{ mm}$ . The field-of-view covered the brain and neck regions. The tumor and brain were outlined according to the contour seen on CT and independent of SPECT images. The output from DPM was the 3D absorbed dose-rate distribution, the absorbed dose-rate averaged over the tumor, and the absorbed dose-rate averaged over the brain.

For this case report, the University of Michigan Internal Review Board waived any requirement for consent.

## Results

### Histopathology

The thyroid metastasis biopsy in March 2007 exhibited a follicular-patterned neoplasm with many colloid-filled follicles. At higher magnification, the characteristic nuclear features of papillary carcinoma were fully developed, including nuclear enlargement and elongation and numerous nuclear grooves. Thus, the diagnosis of well-differentiated papillary carcinoma, follicular variant was rendered (6).

### Body dosimetry

At 2 days, levels of body retention of the diagnostic  $^{131}\text{I}$  were 20% and 23% before the treatments with  $^{131}\text{I}$  in July and December 2007, respectively. Each was in a range wherein high activities of  $^{131}\text{I}$  were unlikely to induce body and bone marrow toxicity (4). Complete blood counts were normal in July and December 2007.

### Tumor images, volumes, and serum Tg

According to the patient, the tumor was enlarging over the months since late 2006. Between January and July 2007, the expansion was from 74 to 219 mL, and there was more infringement of brain (Table 1; Figs. 2A and 3A). However, it is not clear how much of the amplification took place during the 4–5 weeks of thyroxine deprivation and consequential rise in serum TSH level in preparation for  $^{131}\text{I}$  treatment in July.



Concentration of Tg rose from a May 2007 baseline of 6145 to 29,124 ng/mL in July (Table 1).

Thyroxine therapy was instituted the day after the July 2007  $^{131}\text{I}$  treatment. Four days post-treatment, SPECT-CT evaluation of the distribution of  $^{131}\text{I}$ , and CT showed the tumor volume unchanged. But 8 days after treatment, MRI disclosed a decrease in tumor volume to 169 mL (Table 1). With continued thyroxine therapy and diminution of TSH, the tumor declined to 121 mL in November 2007.

After thyroxine was discontinued for 4–5 weeks in December 2007, the carcinoma again enlarged, but only to 155 mL (128%), and, under the same level and duration of TSH stimulation, the tumor volume was 71% of that before the  $^{131}\text{I}$  treatment in July (Table 1). Compared to the baseline in May 2007, Tg decreased in November 2007 to 3321 ng/mL, but again rose to 9140 ng/mL (275%) in December 2007. Still, the Tg in December was less (31%) than in July (Table 1). These changes from July were attributed to the  $^{131}\text{I}$  radiation.

Subsequent to the  $^{131}\text{I}$  treatment in December 2007 and with resumption of thyroxine therapy, the tumor abated from 121 mL in November 2007 to 110 mL (91%) in June and to 72 mL (60%) in November 2008, respectively (Table 1, Fig. 2C). From November 2007, Tg declined from 3321 to 530 ng/mL (16%) in June, but it increased to 1607 ng/mL in November 2008; the latter Tg value was associated with a slight rise in TSH (Table 1). These decrements in tumor volume and Tg level were attributed to the  $^{131}\text{I}$  treatment in December.

It was clear that, on each occasion, cessation of thyroxine therapy was followed by enlargement of the tumor and infringement of the brain concomitant with the rise in serum TSH. However, an inherent growth of tumor between January 2007 and before the hypothyroidism in July 2007, may have accounted for a substantial component in the volume before the  $^{131}\text{I}$  treatment in July. Thus, despite evidence for  $^{131}\text{I}$  treatment effects (see above), no difference in tumor size was found between January 2007 and November 2008 (Table 1). Comparing the baseline Tg concentration in May 2007 (6145 ng/mL) with the Tg concentration in November 2008 (1607 ng/mL) gives evidence of  $^{131}\text{I}$  reductive effects and supports this explanation for the discrepancy between the observed tumor diminution after each  $^{131}\text{I}$  therapy but an absence of overall tumor change from January 2007 to November 2008. It is not clear whether the change in volume 8 days after  $^{131}\text{I}$  treatment and resumption of thyroxine therapy (Table 1) was a consequence of radiation-induced tumor dissolution, TSH decline, or both.

#### *Tumor dosimetry*

Dosimetry was carried out retrospectively; some measurements, particularly tumor uptakes of  $^{131}\text{I}$ , had not been made systematically. Yet, with certain assumptions, predictions of absorbed doses of radiation can be reasonably estimated. Assuming that tumor uptake of the administered  $^{131}\text{I}$  activity of 6% of the administered activity on day 1 (as measured in December 2007) and of 4% on day 2 (as measured on July 2007) were representative of the values before each treatment, then an effective half life of  $^{131}\text{I}$  can be assumed, from a mono-exponential fit, to be 1.7 days (Table 1). When this estimate is applied to the  $^{131}\text{I}$  treatment in July 2007, a residence time was calculated, and with the tumor volume and treatment activity the tumor absorbed dose was estimated

to be 1970 cGy (rad). The cGy seemed low for the amount of tumor diminution so an additional effective half life was assumed to be 3 days (Table 1). From this assumption, the absorbed dose was proportionally increased to 3470 cGy. The radioactivity concentrations in the tumor in July are portrayed in Fig. 3B,C.

Similar calculations and assumptions were made for the  $^{131}\text{I}$  treatment in December 2007. The absorbed doses of radiation for the effective half lives of 1.7 and 3 days were, respectively, 2870 and 5055 cGy (Table 1). The absorbed doses were higher in December because the tumor volume was smaller, the concentration of  $^{131}\text{I}$  was then proportionally larger, and the estimated/assumed effective half lives were unchanged.

#### *Brain dosimetry*

CT images indicated that the tumor was separated from the brain by meninges. Thus, very little of beta electron energies, which are deposited largely within 2 mm of disintegrations, would reach the brain. Radiation to the brain was assumed to be from the gamma photons of  $^{131}\text{I}$  emanating from the tumor, and estimations were then made of the absorbed doses. During the July  $^{131}\text{I}$  treatment, the overall brain received a mean of 35 cGy; at 1–2 cm distance from the tumor, 100 cGy was imparted (Fig. 3C). From the December treatment, a mean of 42 cGy was delivered to the brain.

#### **Discussion**

Distant metastases are rare from the follicular variant of papillary carcinoma; in 37 patients none exhibited distant metastases (7). Care must be taken to distinguish this variant from follicular carcinoma; the diagnosis in our patient is established by the presence of the nuclear changes characteristic of the variant (6). The large follicles filled with colloid may predispose to  $^{131}\text{I}$  concentration and retention. Our patient's clinical course was unusual for papillary carcinomas because he developed a single metastasis.

From the outset, swelling from a skull metastasis was apparent to the patient and readily appreciated on clinical examination as well as on MRI and CT images. Our observations confirm that, consequential to TSH stimulation, well-differentiated thyroid carcinomas can expand within a few weeks. Because the patient's skull was not intact, there was ample room for decompression during hypothyroidism. With resumption of thyroxine therapy, both tumor volume and Tg concentration receded. The risks of thyroxine in superphysiologic doses (e.g., atrial fibrillation) must be weighed against the obvious benefits on tumor suppression; possibly TSH levels of 0.2–0.4 mU/L will be optimal. In our patient, there appeared to be no immediate tumor expansion following  $^{131}\text{I}$  therapy. Whether the steroid therapy suppressed tumor swelling in response to the radiation was impossible to assess.

If one concludes that the carcinoma in our patient grew between the MRI assessment in January 2007 and before thyroxine cessation in July 2007, then there is reasonable evidence that each of the two  $^{131}\text{I}$  treatments diminished tumor volume. At each time point the percentage change in Tg exceeded that of tumor volume, making Tg a more sensitive index of tumor modulation. Since tumor volume contracted between June and November 2008, while the Tg level rose, the

Tg reflected a recent alteration, one related to the slight rise in TSH or to tumor resurgence.

Quantifying absorbed radiation in the tumors has generally eluded therapists in the past, but with the development of scintigraphic images fused with CT, dosimetry of  $^{131}\text{I}$  in metastases and their environs is now possible (4). The radiation imparted to the tumor of our patient was calculated to be 1970 cGy in the July treatment and 2870 cGy in December. These estimates were less, but possibly more accurate, than the absorbed doses (measured by two-dimensional planar scintigraphy) that were deemed effective in eliminating thyroid metastases; i.e., >8000 cGy (8) and >2900 cGy (9). In addition, 7700–14,000 cGy have reduced goiter volumes (10).

Radiation from  $^{131}\text{I}$  imparted to the brain was from the gamma photons and relatively weak ( $\leq 100$  cGy). Patients have tolerated external beam radiation to brain metastases from breast carcinoma when 2000 cGy were delivered in two treatments over a week (11). Unless tumor and neuronal cells are in intimate contact,  $^{131}\text{I}$  radiation to the brain from treatment of thyroid metastases is likely to be inconsequential even when higher absorbed doses are delivered to the thyroid carcinomas.

In an evaluation of 988 patients with differentiated thyroid carcinoma, 20% of the 85 with distant metastases exhibited these only in bone (1.7% of all patients) (1). In the same category, those with papillary carcinoma had a 5-year cause-specific survival of 10% (2). Similar findings have subsequently appeared in two publications on patients with distant metastases from differentiated thyroid carcinoma. Only bone metastases were found in 25% of 444 patients (12) and in 24% of 111 patients (13). Of those with only bone metastases, 72% manifested  $^{131}\text{I}$ -concentrating tumors (12) and the 10-year cause-specific survival was 25% (13). Bone metastases that result in fracture undoubtedly contributed to the mortality. Tumors infringing on brain are rare but may be more hazardous.

Our patient exemplifies the potential for differentiated thyroid carcinomas to expand during TSH stimulation. As a warning, in seven patients who had intracerebral metastases, marked neurological symptoms developed during hypothyroidism (14–18). It is not known if the gradual changes during hypothyroidism could be more easily managed than the abrupt swelling of metastases that will follow recombinant human TSH (rhTSH) injections. If rhTSH is employed, the patient should be placed under continuous observation since within hours after single injections of rhTSH, thyroid gland enlargements were observed: 24% in goitrous tissues following 0.3 mg (19) and 36% in normal tissues after 0.9 mg (20). Also, goiter volumes have increased following  $^{131}\text{I}$  radiation (21), and in the same circumstances tumor enlargement could also occur. Because devastating tumor volume increments may follow TSH stimulation (14,16), surgical decompression of metastases near or in the brain should be considered before diagnostic investigations and therapy with  $^{131}\text{I}$  are undertaken.

If one assumes that a functioning metastasis of well-differentiated thyroid carcinoma is treatable by  $^{131}\text{I}$ , then dosimetry of normal tissues will likely provide the upper limit of prescribed activity (3,22). With SPECT-CT, accurate dosimetry of tumor and surrounding organs is now feasible, and results from these measurements may determine the amount of radioactivity necessary for beneficial effect. If the absorbed dose of radiation from  $^{131}\text{I}$  is found to be inadequate to the

task, consideration can be given to external beam radiation. As in our patient, steroid therapy has been administered with the hope of reducing tumor swelling (14,16), but the efficacy of this measure in reducing TSH-stimulated tumor swelling is unknown.

In summary, we present a patient who is unusual in many respects. A large solitary metastasis from follicular variant of papillary thyroid carcinoma infringed on his brain. The tumor enlarged during hypothyroidism but produced no symptoms probably because a skull defect allowed decompression; great care must be taken to avoid the devastating consequences of tumor swelling from TSH stimulation in patients with brain metastases. The tumor decreased in volume and in release of Tg after two treatments with  $^{131}\text{I}$ ; thyroxine therapy produced added benefit. Dosimetry, enabled by SPECT-CT, determined that with each  $^{131}\text{I}$  treatment >1900 cGy of absorbed radiation was imparted to the tumor and  $\leq 42$  cGy to the brain. However, patients suspected of metastases adjacent to or involving neural tissues must be evaluated with cognizance of the pitfalls from TSH stimulation. Since the tumor was diminished by  $^{131}\text{I}$  treatments and by thyroxine therapy, it is probable that each modality played a role in the patient's survival of more than 11 years. In the future, tumor dosimetry may determine how much  $^{131}\text{I}$  is required to reduce and eliminate thyroid carcinoma.

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#### Disclosure Statement

No competing financial interests exist.

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