Do Negative ^{124}I Pretherapy Positron Emission Tomography Scans in Patients with Elevated Serum Thyroglobulin Levels Predict Negative ^{131}I Posttherapy Scans?

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Background: The management of patients with differentiated thyroid cancer (DTC) who have elevated serum thyroglobulin (Tg) levels and negative ^{131}I or ^{123}I scans is problematic, and the decision regarding whether or not to administer ^{131}I therapy (a “blind” therapy) is also problematic. While ^{124}I positron emission tomography (PET) imaging has been shown to detect more foci of residual thyroid tissue and/or metastases secondary to DTC than planar ^{131}I images, the utility of a negative ^{124}I PET scan in deciding whether or not to consider performing blind ^{131}I therapy is unknown. The objective of this study was to determine whether a negative ^{124}I pretherapy PET scan in patients with elevated serum Tg levels and negative ^{131}I or ^{123}I scans predicts a negative ^{131}I posttherapy scan.

Methods: Several prospective studies have been performed to compare the radiopharmacokinetics of ^{124}I PET versus ^{131}I planar imaging in patients who 1) had histologically proven DTC, 2) were suspected to have metastatic DTC (e.g., elevated Tg, positive recent fine-needle aspiration cytology, suspicious enlarging mass), and 3) had ^{131}I planar and ^{124}I PET imaging performed. Using these criteria, we retrospectively identified patients who had an elevated Tg, a negative diagnostic $^{131}\text{I}/^{123}\text{I}$ scan, a negative diagnostic ^{124}I PET scan, therapy with ^{131}I , a posttherapy ^{131}I scan, and a prior ^{131}I therapy with a subsequent positive post- ^{131}I therapy scan. For each scan, two readers categorized every focus of ^{131}I and ^{124}I uptake as positive for thyroid tissue/metastases or physiological.

Results: Twelve patients met the above criteria. Ten of these 12 patients (83%) had positive foci on ^{131}I posttherapy scan.

Conclusion: In our selected patient population, ^{131}I posttherapy scans are frequently positive in patients with elevated serum Tg levels, a negative diagnostic ^{131}I or ^{123}I scan, and a negative ^{124}I PET scan. Thus, for a patient with elevated serum Tg level, negative diagnostic ^{131}I planar scan, and a prior post- ^{131}I therapy scan that was positive, a negative ^{124}I PET scan will have a low predictive value for a negative post- ^{131}I therapy scan and should not be used to exclude the option of blind ^{131}I therapy.

Introduction

IMAGING OF THYROID CANCER WITH ^{124}I and a positron emission tomography (PET) scan has been demonstrated by several investigators to be superior to ^{131}I imaging (1–5). This superiority is due to a combination of factors, including improved spatial resolution, improved contrast resolution, tomographic imaging, and the ability to fuse the tomographic images with computed tomography (CT) and/or magnetic resonance imaging for better anatomical localization (1–5). While ^{124}I PET imaging has been shown to detect more foci of residual thyroid tissue and/or metastases secondary to differentiated thyroid cancer (DTC) than planar ^{131}I images,

the utility of a negative ^{124}I PET scan in deciding whether or not to consider performing “blind” ^{131}I therapy is unknown. The objective of this study was to determine whether a negative ^{124}I pretherapy PET scan in patients with elevated serum thyroglobulin (Tg) levels and negative ^{131}I or ^{123}I scans predicts a negative ^{131}I posttherapy scan.

Materials and Methods

Several prospective studies were conducted at MedStar Washington Hospital Center to compare the radiopharmacokinetics of ^{124}I vs ^{131}I in patients who 1) had histologically proven DTC, 2) were suspected of having metastatic DTC

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(e.g., elevated Tg, positive recent fine-needle aspiration cytology, a suspicious enlarging mass), and 3) were referred for ^{131}I whole-body dosimetry.

From three databases, we identified all patients who had 1) an elevated Tg ($>2\text{ ng/mL}$), 2) a negative diagnostic ^{131}I planar scan, 3) a negative diagnostic ^{124}I PET scan, 4) therapy with ^{131}I , and 5) an ^{131}I posttherapy scan. All patients had undergone prior ^{131}I therapy with a subsequent positive post- ^{131}I therapy scan. Demographics including age, serum Tg, urine iodine, number of therapies, and total prescribed activity of therapeutic ^{131}I were tabulated. Patients were prepared by either thyroid hormone withdrawal (THW) or recombinant human thyrotropin (rhTSH) based on the clinical request from the patient's referring endocrinologist. Those patients prepared by THW discontinued their long-acting thyroid hormone medication, levothyroxine, 4–6 weeks prior to dosing for imaging and discontinued their short acting thyroid hormone medication (triiodothyronine) 2–3 weeks prior to dosing for imaging. Patients prepared by rhTSH received an intramuscular injection of 0.9 mg rhTSH on two consecutive days with administration of the radioiodine for imaging on the next day. All the patients underwent both ^{131}I whole-body scans and ^{124}I PET scans. Patients were also instructed to initiate a low-iodine diet beginning 2 weeks prior to the dosing for the diagnostic imaging, which continued until after they received the ^{131}I therapy. The imaging protocols for ^{131}I planar whole-body scans and ^{124}I PET-CT scans are presented in Tables 1 and 2, respectively, and have previously been described (5). Post-therapy ^{131}I scans were performed 5–7 days after ^{131}I therapy. All foci of uptake on each of the scans were categorized blindly by two physicians (D.V.N. and G.K.) using the following criteria: 1 = definite physiological uptake or artifact, 2 = most likely physiological uptake or artifact, 3 = indeterminate, 4 = most likely locoregional metastases and/or functioning residual thyroid tissue in the neck bed, 5 = most likely distant metastasis or metastases, or 6 = definite distant metastasis or metastases. Foci categorized as grade 1, 2, or 3 were considered negative for functioning metastases. Post- ^{131}I therapy scans were performed 7 days after ^{131}I administration. This study was approved by the Institutional Review Board, and all patients gave informed consent.

Results

From a total of 40 patients from the three databases, 28 patients either had a positive ^{131}I pretherapy scan, a positive

TABLE 2. IMAGING TECHNIQUE FOR ^{124}I PET-CT IMAGE ACQUISITION

- Prescribed activity: 63.9 MBq (1.7 mCi) ^{124}I (the range was within $\pm 10\%$ of the prescribed activity)
- GE Advance Nxi
 - Emission scans 5 min/bed position
 - Transmission scans 2.5 min/bed position
 - Processing: reconstruction OSEM (4.3 mm isotropic pixels) with SAC
- Philips Gemini TF 64
 - Emission scans 4 min/bed position.
 - 14–16 bed positions
 - CT attenuation scans, 120 kV, 30 mAs
 - Processing: reconstruction OSEM-TF with SAC using the CT data
- Imaging times: 24, 48, 72, 96, and 120 hours after administration of ^{124}I ; see prior publication (5)

CT, computed tomography; PET, positron emission tomography; OSEM, ordered subset expectation maximization; TF, time of flight; SAC, segmented attenuation correction.

^{124}I pretherapy scan, and/or did not have ^{131}I therapy. These patients were excluded from the study. The remaining 12 patients met the study criteria; five were women and seven were men. Seven of the 12 patients were prepared with rhTSH, and the remaining five patients were prepared by THW. Demographic data are presented in Table 3. The histopathology was papillary in nine, with one of these nine patients having tall cell variant, follicular in one, and follicular variant of papillary thyroid cancer in two. Of the 12 patients, 10 (83%) had positive foci on ^{131}I posttherapy scans (see Figs. 1–3), while two patients had negative ^{131}I posttherapy scans.

Discussion

Two difficult and controversial areas in the management of patients with DTC are the management of patients who have elevated serum Tg levels and negative radioiodine scans, and the administration of ^{131}I therapy in patients who have distant metastases identified by various methods, but have no observable radioiodine uptake on diagnostic radioiodine scans and are not manageable with site-specific treatment options. In these two groups of patients, the administration of ^{131}I therapy, which is frequently called blind ^{131}I therapy, has been performed. The arguments for such blind ^{131}I therapies are twofold. First, multiple authors (6–12) have reported that post- ^{131}I therapy scans after blind ^{131}I therapy may be positive in as many as 66% of patients, and therefore, because the metastases have function, those metastases may in fact respond to a therapy with ^{131}I . Secondly and more importantly, several investigators (13–18) have reported salutary responses to such therapy.

However, published studies that have evaluated the results of blind ^{131}I therapy are significantly limited. In a review of the literature by Ma *et al.* (14), the published studies typically have low numbers of patients, are retrospective, have inadequate control groups, and predominantly use only a decrease in serum Tg as the response criterion. However, although Tg levels may significantly decrease, this does not necessarily indicate that any significant improvement such as increased survival or palliation has been achieved. Further study is clearly warranted using better criteria such as Response

TABLE 1. IMAGING TECHNIQUE FOR ^{131}I IMAGE ACQUISITION

- Prescribed activity: 74 MBq (2 mCi) of ^{131}I (range: 70–81.4 MBq [1.87–2.2 mCi])
- Whole-body imaging with
 - ADAC Genesys dual-head whole-body speed 4 cm/min; ^{131}I 364 keV, 20% window, or
 - Siemens E-cam dual-head whole-body speed 4 cm/min; ^{131}I 364 keV, 20% window
- Planar/pinhole with
 - Searle single head with an MIE computer. Planar and pinhole (aperture 6 mm) 1200 sec (20 min); ^{131}I 364 keV, 20% window
- Imaging times: 24, 48, 72, 96, and 120 hours after administration of ^{131}I ; see prior publication (5)

TABLE 3. PATIENT DEMOGRAPHICS

Statistics	Age, years (n = 12)	Tg (stimulated) (ng/mL) (n = 12)	Urine iodine (μ g/L) (n = 10)	Total no. of prior ^{131}I therapies	Cumulative activity, GBq (mCi)
Mean	55	376	79	2.25	19.6 (530)
SD	17	730	62	0.87	9.4 (254)
Median	58	60	56	2	18.0 (485)
Minimum	22	0.2	21	1	5.6 (151)
Maximum	84	2480	189	4	37.0 (1001)

Tg, thyroglobulin.

Evaluation Criteria in Solid Tumors (RECIST) criteria to evaluate whether or not blind ^{131}I therapy may significantly improve outcomes. However, other studies that attempt to identify those patients who will have functioning metastases on post- ^{131}I therapy before administration of blind ^{131}I therapy may prove to be valuable.

FIG. 1. Pretherapy anterior ^{124}I PET maximum intensity projection image that was attenuated corrected and obtained 48 hours after administration of ^{124}I in a patient diagnosed with differentiated thyroid cancer (DTC). The image demonstrates no abnormal focus of radioiodine uptake. Physiologic uptake of ^{124}I is noted in the nose, salivary glands, gastrointestinal tract, and urinary bladder.

With the initial reports of improved lesion detection of metastatic DTC with ^{124}I PET imaging (1–5), we reasoned that the evaluation of pretherapy ^{124}I PET imaging was a logical alternative to explore, with the hope of identifying prior to ^{131}I therapy those patients who would not demonstrate radioiodine uptake on their post- ^{131}I therapy scan, and therefore would not have any chance of benefitting from blind ^{131}I therapy. However, the results reported here indicate that ^{124}I PET, at least in the prescribed activities used, was not effective in achieving this goal in our select patient population.

In comparison to our results, Freudenberg *et al.* (18) also demonstrated a high frequency of negative pretherapy ^{124}I PET scans in patients with diffuse pulmonary metastases secondary to DTC. They evaluated the ability of ^{124}I PET imaging to detect diffuse iodine-avid pulmonary metastases that were detected on post- ^{131}I therapy scans but not on CT of the thorax (e.g., micronodular pulmonary disease). Of seven patients, only one patient was positive in the thorax on the pretherapy ^{124}I PET scan, which was performed 24 hours after administration of 24 ± 2 MBq (0.65 mCi) of ^{124}I . This time point was chosen because their patient data demonstrated that the maximum uptake of ^{124}I in DTC metastases occurred at about 24 hours postadministration. Thus, out of six patients with negative pretherapy ^{124}I PET scans for diffuse micronodular pulmonary metastases, all were positive on the post- ^{131}I therapy scan. Phan *et al.* (3) reported two patients with no uptake on the ^{124}I pretherapy scan, and both of these were negative on the patients' post- ^{131}I therapy scans.

de Pont *et al.* (19) compared "pretherapy" ^{124}I PET/CT scans to post- ^{131}I therapy single-photon emission computed tomography (SPECT)/CT and planar scans. It is our understanding that for the pretherapy ^{124}I PET/CT, the patient received the administration of ^{124}I the day after the ^{131}I therapy administration. They evaluated 20 patients, and interestingly, for the thyroid bed, the ^{124}I PET/CT identified one more focus than on the ^{131}I SPECT/CT, and three more foci than the ^{131}I planar image. For the paratracheal area, the ^{124}I PET/CT identified two more foci than on the ^{131}I SPECT-CT and four more foci than the ^{131}I planar image. Although the data from de Pont *et al.* (19) may imply that if the ^{124}I PET/CT had been performed prior to the ^{131}I therapy, it would have detected all lesions that would have been observed on the post- ^{131}I images, they only had two patients that were negative on the ^{124}I PET/CT. With this low number, one cannot conclude that a negative pre- ^{124}I therapy PET/CT at the prescribed activities administered accurately predicts that a post- ^{131}I therapy scan will be negative.

Several limitations of our study are noteworthy. First, this was a preliminary study and the sample size is small. A larger series is needed for validation. Second, the prescribed

FIG. 2. Anterior and posterior pre- ^{131}I therapy planar whole-body scan performed in the same patient as Figure 1. This image demonstrates no abnormal focus of radioiodine uptake. Physiologic uptake of ^{131}I is noted in the nose, oral cavity, gastrointestinal tract, and bladder.

activity of ^{124}I was low, only 62.9 MBq. The latter was required because of the restrictions of the Radioactive Drug Research Committee for allowable radiation absorbed dose to a volunteer, and further study is warranted to assess the effect of this activity on detectability. However, if higher prescribed activities of ^{124}I are used, the potential for stunning will also need to be evaluated. Third, post- ^{131}I therapy scanning was performed 7 days after ^{131}I therapy. Salvatori *et al.* (20) demonstrated in 124 patients that late scanning at 7 days after ^{131}I therapy may miss up to 7.5% of foci seen on an earlier scan 3 days posttherapy. However, this frequency is not significant enough to alter our conclusion. Fourth, a major limitation of this study is that the patient population is very select, and our data should not be generalized to larger and different patient populations with DTC.

So why are post- ^{131}I therapy scans typically superior to pre- ^{131}I therapy scans? As has been previously discussed (21), one proposed mechanism is a result of the higher prescribed activity of radioiodine administered for the therapy relative to that for the scan, and this has several advantages. First with a higher prescribed activity, the count rates are higher, and thus for an equivalent imaging time, a higher number of counts will

be obtained with the therapy prescribed activity relative to the diagnostic prescribed activity. This, in turn, improves counting statistics, which improves contrast resolution, helping to identify foci distinct from background radioactivity in the patient. Second, higher prescribed activities of therapies allow longer delayed imaging after administration, and this can improve the tumor to background ratios when imaging is performed 7 to 10 days later. Specifically, even though the tumor radioactivity may always be decreasing with time, if the background activity of the patient is clearing faster than the tumor, then the tumor to background ratio becomes larger, thereby allowing improved contrast resolution.

Conclusion

In our selected patient population, ^{131}I posttherapy scans are frequently positive in patients who have elevated serum Tg levels, a negative diagnostic ^{131}I planar scan, and a negative ^{124}I PET scan. In a patient with an elevated serum Tg blood level, a negative diagnostic ^{131}I planar scan, and a prior positive post- ^{131}I therapy scan, a negative ^{124}I PET scan has a low predictive value for a negative post- ^{131}I therapy scan.

FIG. 3. Image obtained in the same patient as shown in Figures 1 and 2. This image is an anterior and posterior posttherapy ^{131}I planar whole-body scan performed 7 days after a therapeutic dose of ^{131}I . Multiple foci of uptake in the mediastinum and left lung base are noted (arrows).

Acknowledgments

Biostatistical support for this project was funded in whole or in part with Federal funds (grant no. UL1RR031975) from the National Center for Research Resources (NCRR), National Institutes of Health (NIH), through the Clinical and Translational Science Awards Program (CTSA), a trademark of the Department of Health and Human Services, part of the Roadmap Initiative, “Re-Engineering the Clinical Research Enterprise.” This study was funded Genzyme, IBA, and Latham Fund.

Author Disclosure Statement

No competing financial interests exist.

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