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# A Clinical Trial of Optimal Time Interval Between Ablation and Diagnostic Activity When a Pretherapy RAI Scanning Is Performed on Patients With Differentiated Thyroid Carcinoma

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**Abstract:** This article investigates the association of the time interval between the diagnostic dose and ablation with the stunning effect, when a 74 MBq $^{131}$I pretherapy scanning was performed on patients with differentiated thyroid carcinoma (DTC); the patients who were diagnosed as DTC and would be performed radioiodine (RAI) ablation of thyroid remnants or metastases were recruited during January 2011 and May 2012 in our hospital.

Thirty-seven patients with DTC who had the RAI ablation of thyroid remnants or metastases for the first time were recruited. All the patients received a dose of 1850 to 7400 MBq of $^{131}$I for ablation and a diagnostic scan was performed 24 hours after the administration of 74 MBq $^{131}$I before ablation. A posttherapy scan was performed 2 to 7 days after the ablation. The patients were broken down into 3 groups (G1, G2, and G3) according to the interval time between the diagnostic dose and therapy (1–3, 4–7, and >7 days). The fractional concentrations of $^{131}$I in remnants or functional metastases were quantified and expressed as therapeutic/diagnostic (Rx/Dx). The level of significance was set at 0.05.

Sixty-seven foci were found both on pretherapy and posttherapy scans, the mean ratio of Rx/Dx was $0.43 \pm 0.29$, and the ratio of 49 foci (73.13%) was <0.6. The ratios in G1, G2, and G3 were $0.46 \pm 0.29$, $0.29 \pm 0.18$, and $0.55 \pm 0.33$, respectively. The differences between G1 and G2, and G2 and G3 were statistically significant ($t = 2.40$, $P = 0.021$ and $t = 3.28$, $P = 0.002$), whereas the difference between G1 and G3 was not significant ($t = 1.01$, $P = 0.319$).

By a diagnostic scan of 74 MBq $^{131}$I, stunning prominently occurs with a time of 4 to 7 days between the diagnostic dose and ablation. We recommend that for less stunning effect, RAI ablation should be performed within 3 days or postponed until 1 week after the diagnostic dose administrated.

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**Abbreviations**: DTC = differentiated thyroid carcinoma, RAI = radioiodine, WBS = whole-body scan, TSH = thyroid-stimulating hormone.

## INTRODUCTION

The incidence of thyroid cancer is showing an increasing trend worldwide over the last 30 years.[1–4] Differentiated thyroid carcinoma (DTC), which includes papillary and follicular cancer, comprises the vast majority (90%) of all thyroid cancers.[5] DTC is typically managed initially with total or near total thyroidectomy. A diagnostic scan with $^{131}$I is usually obtained several weeks after surgery for DTC to demonstrate residual functioning thyroid remnant and/or metastases. Most protocols use a scanning dose of 74 to 185 Mq $^{131}$I followed by a whole-body diagnostic scan. Once the need for radioiodine (RAI) ablation is confirmed by the diagnostic scan, the patient receives an ablative dose of $^{131}$I ranging from 1850 to 7400 MBq depending on various factors, such as tumor size, histologic grade, presence of lymph nodes involvement, extrathyroidal extension, or distant metastases. The interval between the acquisition of the diagnostic scan and ablation can vary from several hours to several weeks.

However, recently, there is an increasing trend to avoid pretherapy RAI scans altogether or use $^{123}$I substituting for $^{131}$I because of the stunning effect by a diagnostic dose of $^{131}$I. Stunning is defined as a reduction in uptake of the $^{131}$I therapy dose induced by a pretherapy diagnostic activity.[6–9] There has been much controversy concerning the stunning effect reported in the literature.[6–15] Although many authors doubted whether stunning does exist, the evidence that stunning is a real phenomenon is now strong, albeit not yet conclusive. In special, the recent quantitive and in vitro studies all confirmed the existing of stunning.[6,16–19]

RAI whole-body scan (WBS) can provide the information on the presence of thyroid tissue, which may represent the normal thyroid remnant or the presence of residual DTC foci after operation.[20] The pretherapy RAI scanning is useful and necessary especially when the extent of the remnant cannot be accurately ascertained from the surgical report or neck ultrasonography, or when the results would alter either the decision to treat or the activity of RAI that is administered.[20]

Although some comparison studies show good concordance between $^{123}$I and $^{131}$I for tumor detection, optimal $^{123}$I activity and time to scan after $^{123}$I administration are not known.[21] Furthermore, $^{123}$I is expensive, is not universally available, and its short half-life (13 hours) makes handling this isotope logistically more difficult,[22] and stunning may also occur though to a lesser degree than with $^{131}$I.[16,23] In addition, some authors define $^{123}$I scan less sensitive and less accurate

than $^{131}$I WBS.[12] $^{131}$I has the advantages of widespread availability, low cost, and a half-life of 8 days, which could be administered for imaging conveniently at 48 to 72 hours after oral administration. The optimal target-to-background ratios in instances of weakly avid sites of remnant or tumor could be obtained at 3-day imaging time.[20] So, $^{131}$I is more appropriate for the pretherapy RAI WBS. As the pretherapy RAI scanning is necessary, and stunning does exist, how to perform the RAI ablation to reduce the stunning influence degree is more practical and more critical.

In the present study, a quantitive method[24] was applied to explore the association of the time interval between the diagnostic dose and therapy with the stunning effect when a 74 MBq $^{131}$I scanning dose was administered in order to find out an optimal time to perform ablation with less stunning.

## MATERIALS AND METHODS

The patients with DTC who were referred to our department between January 2010 and June 2012 for RAI ablation of thyroid remnants or metastases for the first time were retrospectively studied; 37 patients in total who had both pretherapy and posttherapy RAI WBS were adopted. The patients were excluded if they had diffused pulmonary metastasis or did not have or had only once RAI WBS or their clinical data was not sufficient. This study obtained the permission of the ethics board of the First Hospital of China Medical University, Shenyang, China.

The mean age of the patients (24 women and 13 men) was 44.4 (range 15–75) years. All patients had been performed total or near total thyroidectomy and surgically resected thyroid tissues were examined for definitive pathologic classification. Histologic subtypes in these patients consisted of 32 papillary (86.5%), 4 follicular (10.8%), and 1 mixed papillary follicular carcinoma (2.7%).

All carcinoma the patients received a pretherapy scan 1 to 32 days prior to the $^{131}$I ablation and were given a dose of 1850 to 7400 MBq of $^{131}$I for the ablation of thyroid remnants or/and functional metastases after pretherapy scan. If there were only remnants detected by the pretherapy scan, the patients would receive a dose of 1850 to 3700 MBq of $^{131}$I. If there were regional nodal or distant metastases detected by the pretherapy scan, the patients would receive a dose of 3700 to 7400 MBq of $^{131}$I. All doses of $^{131}$I were carrier free and ingested in liquid form. Patients on thyroid-stimulating hormone (TSH) repressive treatment after thyroidectomy were prepared by L-T4 withdrawal for at least 2 to 4 weeks to achieve serum TSH levels >30 mU/L before the pretherapy scan. Meanwhile, all patients were instructed to follow a low-iodine diet for 2 weeks and until 7 days after treatment with $^{131}$I. Thyroxine therapy was initiated 1 day after treatment.

The pretherapy scan was performed 24 hours after the administration of a diagnostic dose of $^{131}$I (74 MBq), and the posttherapy scan was performed 2 to 7 days after a therapeutic dose of $^{131}$I was administered.

There were 3 patients without foci found in pretherapy scan but with foci in posttherapy. So the data of these 3 patients were not analyzed further. The other 34 patients were further divided into 3 groups (G1, G2, and G3) according to the interval time between the diagnostic dose and therapy. Time intervals were 1 to 3, 4 to 7, and >7 days (8–32 days) for G1 ($n = 14$), G2 ($n = 13$), and G3 ($n = 7$), respectively (Table 1).

RAI WBS was obtained using dual-head Single Photon Emission Computer Tomography (Millennium VG, GE; Symbia 2, Siemens, Germany) equipped with a high-energy, parallel-hole collimator. All scans consisted of an anterior and posterior WBS and were acquired in a $256 \times 1024$ matrix and an energy window of 20% centered at 364 KeV, and the camera linear tracking speed was 13 cm/min for all the scans.

More than 2 experienced nuclear medicine physicians in the department interpreted all scans and confirmed the foci with high radioactivity uptake representing remnant thyroid tissues or functional metastases. The fractional concentrations of $^{131}$I in remnant thyroid tissues or functional metastases were expressed as ratios: therapeutic/diagnostic (Rx/Dx). Rx or Dx was expressed as the geometric mean (after background subtraction) divided by the administered dose of $^{131}$I and pixels to give a fractional concentration: counts per pixel per mCi (cpm/pixel/mCi and equivalent to cpm/pixel/37 MBq). Rectangular regions of interest were drawn around observable thyroid tissue or metastasis and around an area in the neck or the other side of the body devoid of $^{131}$I-concentrating tissues for background.

The Student *t* test and analysis of variance test was used for comparisons of numeric variables. The likelihood ratio $\chi^2$ test was used for categorical data. Computation of statistics was performed using SPSS 17.0, for Windows. The level of significance was set at 0.05.

All of the data were evaluated independently by 3 physicians. The final results were based on evaluations agreed upon by at least 2 physicians. Differences were adjudicated by a third reviewing physician.

## RESULTS

As shown in Table 1, no significant difference was found between the 3 groups with regard to age, sex, histological subtype, tumor stage, number and size of foci (remnants and metastases), operation mode, serum TSH and thyroglobulin levels at the time of the RAI administration, the number of antithyroglobulin antibody presence, ablation dose of $^{131}$I, as well as the time interval between ablation and posttherapy scan ($P > 0.05$).

A total of 72 foci were identified by posttherapy scans, of which 53 were remnants and 19 were metastases. Five foci in 3 patients were found only in posttherapy scan that could not get the ratio of Rx/Dx; finally, 67 foci that were found both on pretherapy and posttherapy scans were analyzed. The mean ratio of Rx/Dx in 67 foci was $0.43 \pm 0.29$; the ratio of 49 foci (73.13%) was <0.6. The ratios in groups G1, G2, and G3 were $0.46 \pm 0.29$, $0.29 \pm 0.18$, and $0.55 \pm 0.33$, respectively. The differences between G1 and G2, and G2 and G3 were statistically significant ($t = 2.40$, $P = 0.021$ and $t = 3.28$, $P = 0.002$), whereas the difference between G1 and G3 was not significant ($t = 1.01$, $P = 0.319$).

## DISCUSSION

Thyroid stunning is a radiobiological phenomenon in which a dose of $^{131}$I used for diagnostic purposes before RAI therapy decreases the trapping or retention of $^{131}$I by normal thyroid tissue or functional metastasis. There has been much debate in the literature over the existence of the stunning phenomenon[6–15,25–28] as it was first described in 1951 by Rawson et al.[29] Although it is albeit not yet conclusive, more and more authors approved stunning phenomenon on the basis of the quantitive and in vitro studies, even if opinions on treatment results remain inconsistent. Some studies about the treatment results on stunning are completely contradictory, and the reasons might be due to the incongruous clinical information, such as the administered

**TABLE 1.** Clinical Characteristics of Groups G1, G2, and G3

| Clinical Characteristics | G1 | G2 | G3 | *P* Value |
|---|---|---|---|---|
| Number of patients | 14 | 13 | 7 | — |
| Age, y | 46.50 ± 12.86 (28–75) | 43.00 ± 13.18 (26–67) | 48.57 ± 13.06 (33–68) | 0.627 |
| Sex (woman/men) | 10/4 | 8/5 | 4/3 | 0.775 |
| Histologic subtype (papillary/follicular/ mixed papillary follicular) | 12/1/1 | 12/1/0 | 5/2/0 | 0.437 |
| Tumor stage | | | | |
| Stage I | 6 | 7 | 2 | 0.380 |
| Stage II | 2 | 0 | 1 | |
| Stage III | 0 | 0 | 1 | |
| Stage IV | 6 | 6 | 3 | |
| Number of foci (remnants/metastases) | 25 (19/6) | 22 (18/4) | 20 (13/7) | 0.448 |
| Size of foci, pixels | 144.20 ± 74.96 (59–378) | 183.04 ± 142.20 (58–674) | 140.10 ± 45.79 (79–270) | 0.275 |
| Operation mode (total/near total thyroidectomy) | 11/3 | 11/2 | 3/4 | 0.112 |
| TSH, mU/L, at the time of administration of radioiodine | 49.47 ± 31.21 (30–100) | 41.94 ± 32.27 (30–100) | 57.03 ± 35.97 (30–93) | 0.607 |
| Tg, ng/mL, at the time of administration of radioiodine | 51.47 ± 105.95 (0.2–300) | 49.52 ± 109.37 (0.2–300) | 94.76 ± 140.78 (0.75–300) | 0.665 |
| Number of TGAb present | 2 | 2 | 0 | — |
| Ablation dose of $^{131}$I, MBq | 4492.86 ± 1398.47 (3700–7400) | 4553.85 ± 1221.42 (1850–7400) | 5285.71 ± 1664.51 (3700–7400) | 0.440 |
| Time between ablation and posttherapy scan, d | 2.79 ± 0.70 (2–4) | 3.31 ± 1.70 (2–7) | 3.29 ± 1.80 (2–7) | 0.578 |

Tg = thyroglobulin, TGAb = Antithyroglobulin antibody, TSH = thyroid-stimulating hormone.

activity for pretherapy scan, delay between diagnostic scan and treatment, time between treatment and posttherapy scanning, levels of TSH and serum iodine at time of diagnostic testing versus treatment, and others.[30] Additionally, the overdose RAI for ablation might be one of the reasons that no difference was found between the groups with or without pretherapy scan even if the stunning did act. Recently, 2 strictly performed, randomized, prospective studies by Schlumberger et al[31] and Mallick et al[32] showed a low dose of RAI (1.1 GBq) to be as effective as a high dose (3.7 GBq) for the management of low-risk thyroid cancer. This might explain, at least partially, why the ablation rates of 3.7 GBq $^{131}$I were similar in the 2 groups with diagnostic studies of either $^{123}$I (14.8 MBq) or $^{131}$I (74 MBq) on patients with nonmetastatic DTC from a prospective study too,[33] though stunning effect might exist in fact. In future, the further research work should be done to evaluate the treatment effect by comparing the outcomes of a low dose of RAI.

In the Society of Nuclear Medicine and Molecular Imaging Practice Guideline for Therapy of Thyroid Disease with $^{131}$I 3.0*,[34] which was published in October 2012, routine preablation plannar scintigraphy was recommended for guiding $^{131}$I therapy because it can change the preablation staging. A small minority of patients will not need $^{131}$I ablation for no remnant or because an area that seemed to concentrate iodine was a physiologic variant such as thymus, asymmetric salivary gland uptake, or dental inflammation.[34] The preablation scanning may change the staging when DTC foci are present and hence alter the activity of therapeutic $^{131}$I.[34] And regional nodal and distant metastases in the lung, bone, or brain may be detected, not only resulting in a reevaluation of the use or dosage of $^{131}$I but also, with brain metastases, bringing about consideration of whether corticosteroid administration is required.[34] As the pretherapy scan was useful, and the stunning effect did work, how to minimize the effect was more important.

In the present study, a quantitative method by calculating the fractional concentrations of $^{131}$I in thyroid remnants or functional metastases was used to evaluate the thyroid stunning followed by a 74 MBq $^{131}$I scanning dose, which was easy and convenient for practice in daily work. Time interval between the diagnostic dose and therapy is an important factor for the occurrence of thyroid stunning. In the present study, the ratio of Rx/Dx was used to investigate the association of the time interval between the diagnostic dose and therapy with stunning effect. The mean value of Rx/Dx was 0.43, and 73% of all values were <0.6. This level of Rx/Dx was likely that when the relative radioactivity (in thyroid tissues compared with background) on therapeutic images is <60% of that on diagnostic images, there will be an appearance of stunning.[23] The results were similar with the study by Sisson et al,[24] which used the same quantitative method.

The mean ratios of Rx/Dx in patients with short time interval (1–3 days) and long time interval (8–32 days) were higher than that in patients with medium time interval (4–7 days). Our results indicated that the stunning was more obvious during 4 to 7 days after a diagnostic dose administered. Together with the study by Huic et al,[11] who used a diagnostic $^{131}$I dose of 74 MBq and performed ablation with 4.4 GBq of $^{131}$I, and finally showed a 79.6% reduction in whole-body $^{131}$I uptake for patients with <7-day interval compared with only a 59.6% reduction for patients with >7-day interval, we believe

thyroid stunning occurs less prominently over 7 days after a diagnostic dose administered. In the present study, we also compared the stunning effect during 1 to 3 and 4 to 7 days, and found the stunning during 4 to 7 days was more obvious. An experiment about stunning in vitro by Lundh et al[16] gave us a strong support to our results. It showed that the transepithelial transport of iodide (monitored by $^{125}I^{-}$) started to decrease 1 to 2 days after irradiation and was suppressed most significantly after 5 to 7 days, and the expression of Na(+)/I(−) symporter (NIS) messenger RNA (mRNA) was investigated too; the results showed that there was no reduction in NIS mRNA expression 24 hours after radiation but by 5 days it had fallen to 80%. NIS expression did not recover in cells exposed to $^{131}I$ during the interval studied (7 days). But it is a pity that no in vitro study showed the change over 7 days after irradiation.

In the study by Bajén et al,[14] diagnostic scans were obtained with 185 MBq $^{131}I$; 7.2 weeks afterward, the patients received 489 ablative treatments with 4 GBq $^{131}I$. Their results suggested that a stunning effect did not exist for a diagnostic dose of $^{131}I$ as large as 185 MBq. This might be due to, at least in part, the long interval time between the diagnostic scan and therapy.

In our study, the patients of G3 mostly had ablation 2 to 4 weeks after diagnostic dose administered except 1 patient on the 8th day. The number of cases was too small to analyze the data about $<2$ and $>2$ weeks. Therefore, a large cohort study should be performed for further analyzing the stunning effect with the time interval $<2$ and $>2$ weeks in future.

## CONCLUSION

By a diagnostic scan of 74 MBq $^{131}I$, stunning prominently occurs with a time of 4 to 7 days between the diagnostic dose and ablation. We recommend that for less stunning effect, RAI ablation should be performed within 3 days after the administration of diagnostic dose or postponed until 1 week later, preferably after 2 weeks.

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