Comparison of the Effectiveness Between a Single Low Dose and Fractionated Doses of Radioiodine in Ablation of Post-operative Thyroid Remnants

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Due to the lack of radiation isolation wards in most hospitals in Taiwan, high-dose (exceeding 30 mCi) radioiodine therapy is usually performed in a fractionated manner (successively administering multiple low doses). This study compared the ablating efficacies of post-operative thyroid remnants using a single low dose (30 mCi) and fractionated doses (four doses of 30 mCi given at weekly intervals) in 59 patients with differentiated thyroid cancer who received total or near-total thyroidectomy. Successful ablation was obtained in 20 of 38 patients (52.6%) treated with a single low dose compared with 14 of 21 patients (66.7%) treated in a fractionated manner. There was no statistically significant difference between these two treatment protocols ($P = 0.296$). As the fractionated-dose protocol has the drawbacks of a much longer hypothyroid state and a higher total expense, we suggest that a single low dose is more feasible than fractionated doses for outpatient ablation therapy.

Key words: thyroid carcinoma – postoperative ablation – radioiodine therapy – thyroid stunning

INTRODUCTION

Total or near-total thyroidectomy followed by iodine-131 ($^{131}$I) ablation therapy has been a widely accepted protocol in the management of well-differentiated thyroid carcinoma. The advantages of $^{131}$I therapy includes the following: (1) eradication of normal thyroid remnants, thereby increasing the sensitivity of subsequent $^{131}$I whole-body scanning and the specificity of serum thyroglobulin measurements for the detection of persistent or recurrent disease (1); (2) destruction of occult microscopic carcinoma by $^{131}$I, thereby reducing the incidence of recurrence and mortality (2,3); (3) a high dose of $^{131}$I permitting postablative whole-body scanning that is more sensitive for the detection of occult metastases (4). There is currently no standard therapeutic dose of $^{131}$I ablation for post-operative thyroid remnants (5,6). Despite reports of successful ablation rates as a result of low-dose (30 mCi) $^{131}$I therapy, there has been controversy (7,8), although low-dose $^{131}$I therapy has the advantages of outpatient administration, lower total expense and lower radiation exposure. Conversely, Doi and Woodhouse (9) performed a meta-analysis on 967 patients from 19 studies and revealed a statistically significant advantage for a single high dose (75–100 mCi) over a single low dose (30 mCi) of $^{131}$I therapy. They suggested routine use of high-dose $^{131}$I therapy for ablation of post-operative thyroid remnant.

In Taiwan, many hospitals, including medical centers, do not have radiation isolation beds. In these hospitals, a total high dosage was divided into multiple fractionated small sections in an attempt to avoid the necessity of hospitalizing patients. In our hospital, the post-operative ablation of thyroid remnants was also performed on an ambulatory basis using either a single dose of 30 mCi $^{131}$I or four successive doses of 30 mCi at weekly intervals (a total of 120 mCi). This study compared the efficacies of these two protocols.

SUBJECTS AND METHODS

PATIENTS

We retrospectively reviewed the records of patients with differentiated thyroid carcinoma referred to the Department of Nuclear Medicine of Changhua Christian Hospital for post-operative ablation of thyroid remnants. Fifty-nine patients included in the study matched the following criteria: (1) had undergone total or near-total thyroidectomy; (2) had evidence...
of thyroid remnants in the scintigram (WBS); (3) had no scintigraphic evidence of lymph node, lung or bone metastasis. Age, sex and histological type were recorded.

**Radioiodine Treatment**

$^{131}$I treatment was given orally 4–6 weeks after the operation and thyroxin supplement was not initiated until the completion of treatment. All patients were instructed to have a low iodine diet for at least 2 weeks. There were two protocols of ablation therapy, consisting of a single dose or four successive weekly 30 mCi $^{131}$I doses. The selection of ablative protocols was based on the size of primary tumor and presence or absence of lymph node metastasis in pathologic examinations. Thirty-eight (31 women, 7 men) patients were treated with a single low dose (30 mCi). A post-therapy WBS was obtained 7 days later using a large field-of-view gamma camera equipped with a high-energy parallel-hole collimator. Twenty-one (17 women, 4 men) patients were treated using the fractionated-dose protocol, which consisted of four successive weekly doses of 30 mCi (a total of 120 mCi). A WBS was obtained on the day of second dose prior to $^{131}$I administration.

**Follow-up and Criteria for Successful Ablation**

All patients received a diagnostic WBS at least 6 months after ablation therapy. Thyroid hormone withdrawal and low iodine diet protocols were applied as previously described. A diagnostic WBS was performed 48 hours after oral administration of $^{131}$I (2 mCi). Radioiodine ablation was considered successful if there was no activity demonstrated in the thyroid bed. If there was any activity in the thyroid bed, the single low-dose therapy would be repeated until successful ablation was achieved. The efficacies of the two protocols at achieving successful ablation of post-operative thyroid remnants were compared.

**Statistical Analysis**

The Chi-square test was used for statistical analyses of nominal data (sex, histological type, and successful ablation). The cardinal data (age) were expressed as mean ± standard deviation and were analyzed with Student t-test. A $P$-value of <0.05 was considered to be statistically significant.

**RESULTS**

Patient characteristics are summarized in the Table 1. There are no significant difference in terms of age, sex or histological types between the two groups treated with a single low dose or fractionated doses.

Successful ablation was achieved in 20 of 38 patients (52.6%) who received single low-dose therapy, and in 14 of 21 patients (66.7%) treated with fractionated doses. Even though the percentage of successful ablation in the fractionated group was slightly higher than that of the single low-dose group, there was no statistical difference between these two groups ($P = 0.296$).

**Table 1.** Clinical characteristics and results of the first ablation for patients received a single low dose (30 mCi) and fractionated doses (120 mCi)

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Single low dose</th>
<th>Fractionated doses</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.4 ± 15.4</td>
<td>46.6 ± 15.3</td>
<td>0.324 (NS)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>31 (81.6%)</td>
<td>17 (81.0%)</td>
<td>1.000 (NS)</td>
</tr>
<tr>
<td>Men</td>
<td>7 (18.4%)</td>
<td>4 (19.0%)</td>
<td>1.000 (NS)</td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>35 (92.1%)</td>
<td>19 (90.5%)</td>
<td>1.000 (NS)</td>
</tr>
<tr>
<td>and mixed type</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Follicular carcinoma</td>
<td>3 (7.9%)</td>
<td>2 (9.5%)</td>
<td>1.000 (NS)</td>
</tr>
<tr>
<td>Ablation results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful</td>
<td>20 (52.6%)</td>
<td>14 (66.7%)</td>
<td>0.296 (NS)</td>
</tr>
<tr>
<td>Failed</td>
<td>18 (47.4%)</td>
<td>7 (33.3%)</td>
<td>0.296 (NS)</td>
</tr>
</tbody>
</table>

*Student t-test was used for statistical analysis of cardinal data (age) between these two groups.
*Chi-square test was used for analysis of nominal data (sex, histological type, and successful ablation).

**DISCUSSION**

The production of thyroxine and other thyroid hormones almost ceases after thyroidectomy, and that of TSH is enhanced. Enhanced TSH subsequently increases the growth and iodine uptake of the thyroid remnant and metastatic tumor, thereby producing thyroid hormones from iodine. Radioactive iodine is active as radiation is absorbed by the remnant thyroid and metastatic tumor. The commencement of supplemental thyroxine therapy after a certain interval then reduces the already increased TSH level. It is a reasonable assumption that high-dose radioiodine will deliver a greater absorbed radiation dose to the thyroid remnant and occult functioning metastases than a lower dose (10), and consequently has higher ablation efficacy (11) with lower morbidity. In order to obviate the necessity of hospitalization and take advantage of high-dose ablation therapy, the protocols using two or more outpatient doses 2 days to 1 week apart have been suggested (12,13). In our institute, the high-dose therapy was divided into four weekly fractions of 30 mCi with a total of 120 mCi $^{131}$I therapy. In this manner, the supplement of thyroxine started after completion of the fourth dose of $^{131}$I.

The postponement of the interval for a further 3 weeks is the accepted standard after fractionated low-dose delivery when compared with that of single-dose delivery in Taiwan. Thus, fractionated low-dose delivery has the drawbacks of a long-lasting hypothyroid state that is sometimes poorly tolerated and may even be fatal (14), and of a potential risk of accelerated tumor growth as a result of stimulation by elevated TSH.

Thyroid stunning is a phenomenon defined as a decreased uptake of therapeutic dose of $^{131}$I by remnant thyroid tissue or functioning metastases shortly after a diagnostic, as well as therapeutic, dose administration (15). The degree of stunning...
appears to be related to the administered therapy activity (16). In Taiwan, the fractionated protocols delivered three or four therapeutic doses of $^{131}$I 1 week apart. Thus, the uptake of subsequent doses of $^{131}$I after initial dose may be significantly reduced by the ‘stunning effect’.

Our study first compared the efficacy of a single low dose and fractionated doses in post-operative ablation of thyroid remnants. The successful rate of ablation by fractionated doses is slightly higher than single low dose therapy (66.7% versus 52.6%). However, there is no statistically significant difference between these two groups ($P = 0.296$). This observation might reflect the influence of the stunning effect.

Our preliminary report had some limitations. First, this study was a retrospective one. Second, the sample size of the fractionated-dose group was smaller than that of single low-dose group. Therefore, a potential selection bias might exist.

In conclusion, there was no definitive benefit for fractionated doses over a single low dose in the outpatient therapy of post-operative thyroid ablation. Therefore, fractionated-dose treatment is not suggested for clinical use in the consideration of prolonged thyroxine withdrawal, stunning effect and higher cost. A single low dose resulted in a comparable success when compared with fractionated doses, and can be used as an alternative to high-dose ablation if radiation isolation beds are not available.

References