Radioiodine ablation of thyroid tissue

The higher dose of I-131 (3700 MBq) resulted in a higher cumulative activity (median, 4810 vs. 3700 MBq, P < 0.0001) and more inpatient time (median 4 vs. 3 days) in comparison with the high-dose group. The covariate factors predicting the treatment response, in order of significance, were radioiodine dose, baseline Tg, baseline thyrotoxic state. Additional radioiodine doses were administered in cases showing no significant response to the first therapy. Finally, the initial outcome, the total hospitalization time, and the cumulative I-131 doses during the 12-month course of the study were compared between the subgroups.

Conclusion The higher dose of I-131 (3700 MBq) resulted in successful ablation more often than the low dose (1110 MBq).

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Keywords: ablation therapy, differentiated thyroid carcinoma, radioiodine

Introduction

Postoperative ablation of functioning thyroid tissue with iodine-131 may improve disease-free survival and long-term prognosis in patients with differentiated thyroid carcinoma (DTC) [1] It may also facilitate long-term surveillance of these patients as to the improvement of the sensitivity for an I-131 whole-body scan (WBS) and specificity for Tg measurements [2]. The optimal administered dose of I-131 to achieve successful ablation is still controversial. Many centers currently use 3700 MBq activity to achieve the highest rate of successful ablation. However, some potential complications such as salivary, lacrimal, or gonadal dysfunction and long-term potential carcinogenic effects may be related to the higher administered activity [3–6]. A single low dose (1100 MBq) of I-131 is thus being used in some centers to reduce the risk of short-term complications, the time of hospital stay, and the level of radiation exposure to the patients, environment, or health care providers. Interestingly, the reported rates of successful ablation with 1100 MBq activity are markedly variable, ranging from 10 to 84%, in patients who undergo a total thyroidectomy (TT) or near-total thyroidectomy (NTT) with no evidence of distant metastasis [7–12]. Several guidelines for postoperative thyroid ablation have been developed on the basis of individual experiences, retrospective case notes, prospective cohorts, or limited clinical trials, but with no consensus on the most appropriate dose of I-131 [13–16]. In fact, there is insufficient evidence to support a recommendation for or against a definite dose of I-131 for ablation therapy. Unfortunately, the retrospective investigations comparing different ablative doses may have selection biases, because a high or a low radioiodine dose may be preferred depending on the patient’s clinical

References


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risk and the physician’s judgment. Moreover, there are some confounding factors that differ in low-dose and high-dose groups and concomitantly affect the rates of successful ablation. The prospective cohort studies may also face these restraining factors [17–19]. Only a few reports in the existing literature, on the success rates of 1100 versus 3700 MBq, are based on randomized clinical trial (RCT) studies, but with poorly powered analyses and relatively small sample sizes ranging from 10 to 81 cases in each group [9,12,20–22]. A number of statistical estimations have pointed to the requirement of a much greater sample size to determine a statistically significant difference between high and low radioiodine doses in terms of successful ablation [12,23,24]. The available systematic reviews are also combinations of studies with very different designs and their results are still equivocal and inadequate to determine whether a low or a high administered radioiodine activity is more efficient [23,25]. A well controlled and adequately powered RCT was designed to compare the rate of successful ablation and/or recurrence after a high-dose or a low-dose radioiodine administration.

**Methods**

**Study population**

Three hundred and seventy-six patients with confirmed DTC who fulfilled the inclusion criteria after TT or NTT were consecutively recruited into this double-blind RCT. The project was approved by the Ethics Committee of Tehran University of Medical Sciences. An informed consent form was signed by each patient before entering the study. A proficient multidisciplinary team comprising of expert thorax surgeons, endocrinologists, nuclear medicine physicians, pathologists, and nurses was engaged in selecting and managing the patients. The study was also supported by a physicist, a radiochemist, a radioiodine technologist, a skilled technologist, and a research methodologist. TT or NTT was performed as an initial choice of surgery in cases with a presurgical proven diagnosis of DTC or as a complementary operation after lobectomy for patients with indeterminate presurgical biopsy. In addition, a prophylactic bilateral central (compartment VI) node dissection was performed for all patients with papillary carcinoma. In the patients with follicular neoplasm/carcinoma, this procedure was carried out only in the presence of macroscopic or ultrasound evidence of nodal disease [24]. Histological type of thyroid carcinoma was defined according to the WHO criteria [26]. Cases with a history of radioiodine ablation therapy, a postsurgical palpable mass in the thyroid bed, inoperable cervical lymph nodes in the neck, histopathological evidences of high risk and invasive tumors such as Hurthle cell or tall cell subtypes, capsular or vascular invasion or lymph node involvement, scintigraphic evidence of functioning metastasis, and pregnant or breastfeeding women were not included in the study. Patients in whom a distant functioning metastasis was found on postradioiodine therapy WBS or those who refused to comply with the regular care after ablation were also excluded from the study.

**Study procedures and measurements**

The interval between thyroid surgery and ablation therapy was 4–6 weeks for all patients. In the first two weeks, the patients received a dose of 50 μg/day liothyronine (T3). All participants were instructed to avoid radiographic contrast imaging, for 1 month, discontinue liothyronine consumption, for 2 weeks, and adhere to a low-iodine diet, for 1 week, before ablation therapy. At the end of this period (i.e. 4–6 weeks after surgery and 2–4 weeks following liothyronine withdrawal), a complete postoperative work-up including physical examination, blood cell counts, neck ultrasonography, baseline preablation WBS with I-131, serum TSH (TSH-off), and serum Tg (Tg-off) measurements was performed. Serum anti-Tg was also measured for patients with a Tg-off value less than 2 ng/ml [27]. All serum indices were measured by an immunoradiometric assay (IRMA). To find the middle ground between low sensitivity at lower doses [28] and possible stunning effect (i.e. temporary reduction of radioiodine trapping following exposure to diagnostic radioiodine) at higher doses [29], radioiodine activity in the range of 92–111 MBq was selected for WBS. Also, the time interval between the administration of diagnostic dose and hospitalization date was less than 48 h to further minimize the possibility of stunning effect. Imaging was carried out on the day of admission. A single-headed gamma camera (i.e. ADAC Argus, Milpitas, California, USA) equipped with a high-energy collimator, a photo peak of 364 keV with a symmetrical 20% window, and a 128 × 128 matrix size was used for imaging. Ten-minute overlapping spot views in anterior and posterior projections were obtained from the skull to the mid-thighs with the detector placed at a 10–15 cm fixed distance from the body surface on each view. The amount of preablation functioning remnant (FR) thyroid tissue was estimated on the basis of abnormal uptake in the thyroid bed and the anterior neck on I-131 WBS images. All images were interpreted on grayscale prints and the monitor screen and the magnitude of FR in the cervical region was graded by consensus of two experienced nuclear medicine physicians as absent, low, intermediate, and high FR using visual and semiquantitative evaluation methods. In the case of any disagreement, the opinion of a third nuclear medicine physician was obtained.

**Randomization, blinding, and interventions**

A total of 376 patients who initially fulfilled the inclusion criteria were assigned to participate in the study. All participants were randomly allocated, using the Un randomization method, into two groups to receive either 1110 MBq (group A) or 3700 MBq (group B) I-131 for post-thyroidectomy ablation therapy. The randomization program was prepared and applied by a trained technologist in Hot-Lab, where I-131 activities were measured and dispensed in coded vials, just before ablation therapy.
Subsequently, the patients were admitted to the nuclear medicine ward and received the doses in coded vials. Only the code on the vial, instead of the actual administered activity, was recorded on the patients’ files. Both the patients and the health care providers including physicians and nurses were thus unaware of the activity of I-131 administered during the management process.

The patients were discharged when radiation exposure was less than 50 μSv/h at one-meter distance. Liothyrone (T3) at a dose of 25–50 μg/day was started 24 h after radioiodine administration and a WBS was carried out by days 5–7 following admission.

**Follow-up evaluation and outcome**

Following the first postablation WBS, thirty-five patients were excluded from the study according to the pre-defined exclusion criteria; 15 cases revealed mediastinal or distant metastasis on postradioiodine therapy WBS and 20 refused to further cooperate with the investigation team. The total exclusion rate in the postrandomization setting was thus 9.3% and this rate did not differ significantly between groups A and B (9.1 vs. 9.6%, respectively; \( P = 0.859 \)). The two groups did not differ in the postrandomization setting as to the age, sex, histopathology of tumor, post-thyroidectomy remnant tissue, type of surgery, and baseline Tg-off, anti-Tg, and TSH-off values at the time of admission (Table 1).

<table>
<thead>
<tr>
<th>Table 1 Baseline patients’ characteristics in the two studied groups</th>
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</thead>
<tbody>
<tr>
<td><strong>Baseline variables (unit)</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Median (range)</td>
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<tr>
<td>Age group N (%)</td>
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<tr>
<td>&lt;45 years</td>
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<tr>
<td>≥45 years</td>
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<tr>
<td>Sex N (%)</td>
</tr>
<tr>
<td>Females</td>
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<tr>
<td>Males</td>
</tr>
<tr>
<td>Type of surgery N (%)</td>
</tr>
<tr>
<td>Tumors</td>
</tr>
<tr>
<td>Histology N (%)</td>
</tr>
<tr>
<td>Papillary</td>
</tr>
<tr>
<td>Follicular or mixed</td>
</tr>
<tr>
<td>Functioning remnant N (%)</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Intermediate</td>
</tr>
<tr>
<td>Serum TSH (mIU/l)</td>
</tr>
<tr>
<td>Mean (SD)</td>
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<tr>
<td>Median (range)</td>
</tr>
<tr>
<td>Serum Tg-off (ng/ml)</td>
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<tr>
<td>&gt;4.5*</td>
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<tr>
<td>&lt;4.5*</td>
</tr>
</tbody>
</table>

**Criteria Definition**

- Major: Absence of functioning remnant on 131 I WBS (FR score = 0) Serum Tg-off < 2 ng/ml with anti-Tg-off < 100 IU/ml
- Minor: Reduction of functioning remnant to a score not less than 1 (FR score > 0) A minimum of 50% decrease in the Tg-off level, but not to a value less than 2 ng/ml Serum Tg-off < 2 ng/ml with anti-Tg-off > 100 IU/ml

All patients were then registered for an additional follow-up course of 6 months’ duration (i.e. second phase postablation follow-up) with exactly the same diagnostic measures as in the first phase. The outcome was subsequently reevaluated, at the end of the second post-therapeutic phase, that is, 12 months after the first radioiodine ablation.
therapy, to make a new decision on whether more treatment is required. The additional ablative dose of I-131 was administered if the participant did not meet the full criteria of ‘successful ablation’ at the end of the second post-ablation phase. This dose would be at least 3700 MBq or 25% higher than the last dose.

The main endpoint of the study was defined by a successful ablation rate. The secondary endpoints were the number of subsequent radioiodine treatments required, the summative time spent in the isolation ward, and the cumulative dose of I-131 administered in anticipation of achieving successful ablation or completing 12 months of surveillance.

Statistical methods and analyses
The sample size was restricted to 341 cases by applying the interim statistical analysis of success rates. The statistical software package, SPSS (i.e. version 16.0, Chicago, Illinois, USA), was also used for data analyses. The Kolmogorov–Smirnov test was used to determine whether quantitative data are normally distributed or not. For univariate analyses of differences between two groups, the Student t-test or Mann–Whitney U tests for quantitative variables with or without a normal distribution, χ² for categorical variables, and the Mantel–Haenszel statistic for control of the possible effect of confounders were applied. The RR of successful ablation for the low-dose to high-dose group and the corresponding 95% CI were also calculated.

For multivariate analysis, a binary logistic regression procedure with both forward and backward stepwise methods was carried out to determine which independent factors are most expected to predict successful ablation at the first postablative evaluation. Accordingly, the odds ratios of the successful versus unsuccessful ablation for independent predictors and the corresponding 95% CI were estimated. P values of less than 0.05 were considered significant.

Results
Patients
In terms of postrandomization status, 341 patients (286 women, 55 men) were eligible for inclusion in the analysis (171 and 170 patients in groups A and B, respectively). The mean age of the patients was 39.41 ± 12.10; 12–78 years. In the first postsurgical assessment, the mean TSH-off was 43.53 ± 18.81 mIU/l and the median Tg-off value was 4.5 ng/ml, ranging from less than 1 to 221 ng/ml. The mean age, sex, type of surgery (i.e. TT or NTT), histopathology of the tumor (i.e. papillary or follicular), FR grade, Tg-off, Anti-Tg-off, and TSH-on in the baseline preablative study and the TSH-on in the postablation state did not differ between the two groups (Table 1).

Endpoints and outcomes
The rate of successful ablation at the end of the first postablative phase was 51.6% (176/341) in all patients, 39.2% (67/171) in group A, and 64.1% (109/170) in group B. Only one patient in group B (0.6%) and no patient in group A showed disease progression at the end of the first follow-up phase. The RR of having a successful ablation for the low-dose group (1100 MBq) to the high-dose group (3700 MBq) was 0.61 (95% CI, 0.49–0.76; P < 0.0001). Conversely, the RR of unsuccessful ablation after the first ablative dose of I-131 for group A (low dose) to group B (high dose) was 1.695 (95% CI, 1.54–2.14; P < 0.001).

Among the patients with unsuccessful ablation, 12 in group A and 15 in group B showed one major and one minor criteria of treatment response, out of which four patients (33.3%) in group A versus eight (53.3%) in group B showed evidence of successful ablation at the end of the second follow-up phase without any additional I-131 treatment. The total success rate of the first-dose ablation therapy at the end of the 12-month follow-up program was thus 41.5% in group A and 68.8% in group B (P < 0.0001).

According to the fixed criteria for retreatment, 92 patients in group A and 46 patients in group B were candidates for repeated radioiodine ablative therapy using high doses (i.e. at least 3700 MBq). Because of logistic limitations, two patients requiring additional ablative therapy in each group did not receive any further dose of I-131. Patients’ initial and subsequent outcomes following the first and the second ablative doses of I-131 is shown in Table 3. As can be seen in the table, the outcome and success rate of second-dose ablation therapy did not differ between the two groups of the study. The second dose, however, was not less than 3700 MBq.

During the 12-month follow-up, 100 patients (58.5%) in group A (low dose) and 51 patients (30.0%) in group B (high dose) were admitted more than once for radioiodine ablation therapy (P < 0.0001). The median cumulative dose of administered I-131 for all patients during this period was 3700 MBq. Ninety-eight patients (57.3%) of group A and 51 patients (30.0%) of group B received more than the median cumulative dose (P < 0.0001). The median and range of cumulative administered activity in each group are shown in Table 3. The total time spent in an isolation ward was 1–8 days for group A, with a median of 4 days, and 2–10 days for group B, with a median of 3 days. Also, 98 patients (57.3%) in group A versus 52 patients (30.6%) of group B revealed a cumulative time of isolation longer than 3 days (P < 0.0001).

Predicting factors
In a multivariate model, the dose of I-131, the baseline serum Tg-off value, the baseline TSH-off value, sex, and efficiency of TSH suppressive therapy during the follow-up phase were the significant factors that independently had an influence on the odds of successful ablation in our patients. The estimated OR (and CI) of each predicting factor for the first-dose successful ablation are shown.
in Table 4. The frequency of cases with TSH less than 25 mIU/l at the time of ablation therapy was 21.2% (36/171) and 23.6% (40/170) in the low-dose and the high-dose group, respectively (P = 0.583). Similarly, the distribution of the other mentioned predicting factors (baseline Tg, suppressed TSH, and sex) was comparable in the two studied groups (Table 1). We subsequently examined the independence of the relationship between baseline TSH or Tg values and successful ablation, controlling for the FR categories in both univariate and multivariate analyses. We found that the odds of successful ablation in our multivariate model were not significantly affected by any other categorical variables. Thus, the univariable risk estimates for Tg and TSH were not constant across the different levels of this factor. Also, the order of significance for these estimates was not changed after considering the interaction of TSH or Tg by FR categories. In addition, the risk estimates were not significantly affected by any other categorical variables entered into our model, including the histological type of tumor (papillary or follicular), age group (≥ 45 or < 45 years), and type of surgery (TT or NTT) in this specific population of patients.

**Discussion**

In our study, even though high-risk patients were not included, ablation with 3700 MBq radiiodine was significantly more successful than ablation with 1100 MBq (success rates of 68 vs. 39%, respectively). The previously reported success rates for ablation therapy after TT or NTT using either low or high radiiodine doses have a wide range of 10–98% due to inconsistent definitions for successful ablation, variations in the extent of surgery, stage of primary disease, method of preablation preparations, use of on-T4 or off-T4 serum assays in the follow-up assessments, route of TSH stimulation, and timing between procedures [7–12,17,20–22,30–38] Only a few studies, considering all important factors, with definitive and constant baseline and endpoint diagnostic criteria have been conducted [23,39]. In our study, a strict definition for ‘successful ablation’ according to off-T4 serum Tg and Anti-Tg assays using highly sensitive IRMA methods, neck ultrasound, and I-131 WBS was used. In contrast, somewhat more lenient criteria were applied by many other studies for identifying patients with ‘successful ablation’ that predictably resulted in a higher success rate of ablation therapy at first glance, as indolent residual

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**Table 3** Initial and subsequent endpoints of the first and second ablative therapies with low and high doses of I-131

<table>
<thead>
<tr>
<th>Study groups</th>
<th>First dose success rate</th>
<th>Disease progression rate</th>
<th>Requirement for retreatment</th>
<th>Second dose success ratea</th>
<th>Recurrence rate</th>
<th>Final success rate</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>67/171 (88.1%)</td>
<td>0 (0.0%)</td>
<td>92/171 (53.8%)</td>
<td>71/171 (41.5%)</td>
<td>2/171 (1.2%)</td>
<td>99/171 (57.9%)</td>
<td>4810 (1110–12210)</td>
</tr>
<tr>
<td>Group B</td>
<td>109/170 (64.1%)</td>
<td>1/170 (0.6%)</td>
<td>46/170 (27.1%)</td>
<td>117/170 (41.1%)</td>
<td>17/140 (2.3%)</td>
<td>134/170 (78.8%)</td>
<td>3700 (3700–18500)</td>
</tr>
<tr>
<td>Difference</td>
<td>&lt;0.0001b</td>
<td>–</td>
<td>&lt;0.0001b</td>
<td>&lt;0.0001c</td>
<td>P &gt;0.05c</td>
<td>&lt;0.0001b</td>
<td>&lt;0.0001b</td>
</tr>
<tr>
<td>Total</td>
<td>176/341 (51.6%)</td>
<td>1/341 (0.3%)</td>
<td>138/341 (40.5%)</td>
<td>188/341 (55.1%)</td>
<td>45/134 (1.8%)</td>
<td>233/341 (68.3%)</td>
<td>3700 (1110–18500)</td>
</tr>
</tbody>
</table>

P values: a <0.0001, b <0.0001, c <0.0001

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**Table 4** Likelihood ratios of the independent predictors for achieving complete ablation of remnant thyroid tissue by the first dose of radiiodine therapy on the basis of a binary logistic regression procedure as a model for prediction of outcome

<table>
<thead>
<tr>
<th>Independent predicting factors</th>
<th>Odds of successful vs. unsuccessful ablation for the first value proportionate to the second value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictors of first-dose successful ablation</td>
<td>Odds (OR)</td>
</tr>
<tr>
<td>Dose of administered I-131: 3700 vs. 1110 (MBq)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline serum Tg: &gt;4.5 vs. ≤ 4.5 (ng/ml)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline serum TSH: &gt; 25 vs. ≤ 25 (mIU/l)</td>
<td>0.006</td>
</tr>
<tr>
<td>On-levothyroxine Serum TSH values: ≥ 0.3 vs. &lt; 0.3 (mIU/l)</td>
<td>0.033</td>
</tr>
<tr>
<td>Sex: female vs. male</td>
<td>0.032</td>
</tr>
<tr>
<td>The factors not associated with treatment response</td>
<td>Pathologic type of tumor: follicular vs. papillary</td>
</tr>
<tr>
<td>Age group: ≥ 45 vs. &lt;45 (years)</td>
<td>0.995</td>
</tr>
<tr>
<td>Baseline radiiodine uptake: high or intermediate vs. low</td>
<td>0.105</td>
</tr>
<tr>
<td>Type of thyroidectomy: TT vs. NTT</td>
<td>0.147</td>
</tr>
</tbody>
</table>

CI, confidence interval; NTT, near-total thyroidectomy; OR, odds ratio; Tg, thyroglobulin; TSH, thyroid stimulating hormone; TT, total thyroidectomy.
tumors or minimal remnant thyroid tissues may be overlooked using the nonstringent criteria to define 'successful ablation'. Nevertheless, a temporary reduction of radioiodine uptake in thyroid remnant or residual thyroid cancer as a result of diagnostic radioiodine scan (stunning effect) may be another reason for the moderately low success rate [29]. However, on the basis of more recent evidence in the literature, the reported stunning phenomenon and its impact on the outcome of treatment seem to be overemphasized [40,41]. We have done our best to avoid this phenomenon using the lowest possible dose for a fairly sensitive diagnostic scan and by decreasing the time elapsed between the diagnostic and the therapeutic doses of I-131. According to current evidence, the administration of less than 111 MBq I-131 within 48 h before admission for ablation therapy, as was applied in our study, probably has minimal impact on the successful ablation rate in patients with thyroid cancer [29,40–42].

The rate of successful ablation in a study varied in ascending order with administered doses from 555 to 1100 MBq, whereas this rate fluctuated at doses between 1100 and 1850 MBq [11]. However, doses higher than 1850 MBq were not included in this trial and the number of patients in each group was low.

The currently available and fully published randomized trials that have compared the 1100 MBq activities with the 3700 MBq activities for ablation therapy consisted of four studies with a total of 297 cases [9,12,20,21]. None of these trials were able to show significant differences in the success rate of ablation favoring the high-dose group. As only 10–81 evaluable cases were included in each group of these studies, they have low statistical power to clarify the true difference in the success rates between groups [9,12,20,21]. Although the RR for unsuccessful ablation in the pooled data of all four trials tended to be greater after administration of low-dose I-131 (1.148), the 95% CI for RR (0.974–1.353), \( P = 0.1 \) was not significant [12] and was much less than that of our study (1.695 with 95% CI, 1.34–2.14; \( P < 0.001 \)). However, this meta-analysis is limited by a small number of cases, inconsistent definitions of successful ablation, and the differences of the populations among the studies, resulting in a low statistical power to detect a possible difference between groups.

Some other randomized trials have compared the doses of 1100 MBq with 1800 MBq [10,11,21] or 1800 MBq with 3700 MBq [21,22], of which some reported high doses are more successful for effectual ablation [10,22]. The results of a systematic review in 2000 by Doi and Woodhouse [30] demonstrated that the high-dose radioiodine is more favorable. They concluded that doses lower than 2775 MBq are not as effective as doses of approximately 3700 MBq in terms of successful remnant ablation. In contrast, another systematic review by Hackshaw et al. [23] suggested that the findings on published data are not sufficient to reliably determine whether a low or a high dose should be prescribed for radioiodine ablation therapy and more RCTs are needed to shed light on this issue. The pooled RR of having a successful ablation for low-dose versus high-dose I-131 therapy on the basis of the last meta-analysis of 2584 patients, in 22 combined datasets, was 0.73 (95% CI, 0.62–0.85) [25]. This result is relatively comparable with our finding (RR = 0.61, 95% CI, 0.49–0.76). However, 16 of the 22 studies in this meta-analysis were observational whereas the most appropriate evidence was presented by RCTs. For this reason, no definite recommendation for the preferred dose of I-131 has been made so far by the present guidelines. As indicated by our findings, 3700 MBq may be preferable to 1100 MBq even in a quite low-risk population of patients; however, further evidence may be required to confirm the generalizability of this conclusion to high-risk patients. To our knowledge, there are currently two other large RCTs in progress, one in the UK and the other in France, each with several hundred patients [23,39]. Although the preliminary findings of these two multicenter studies appear to be at variance to our findings, clear-cut and full detailed data on their methodologies, especially the exact methods of follow-up assessments and the definition of successful ablation, are not available in the current literature and their results are yet to be published.

A limitation of our study, however, is that we did not deal with short-term or long-standing adverse effects of higher radioiodine activity. Although the higher administered activity may be associated with nausea and taste disorders, these problems are easily manageable and often disappear in a few days [12]. More salivary gland dysfunction may also be noted with higher doses of I-131; however, dry mouth has not been reported to be dose-dependent [3]. In addition, dry eye or reduction in tear secretion [4,43] as well as transient gonadal dysfunction especially in male patients have been reported following high-dose radioiodine therapy [5,44]; however, no definite finding is available on the threshold dose leading to these complications. Furthermore, regarding our previous studies, no clear evidence in favor of a higher risk of infertility, spontaneous abortion, congenital anomalies, and second primary malignancy has been found following the first dose of therapy [5,45,46].

Even though a higher dose may primarily lead to a higher cost of admission, patient’s trouble in the isolation ward, and minimally increased side effects, we should first and foremost consider the therapeutic outcome in selecting an optimal radioiodine ablative dose. An undesirable outcome following low-dose therapy may lead to a potential need for repeated radioiodine administration, a longer cumulative isolation time, and higher cumulative administered activity. A lower dose of radioiodine may be
used only in selected cases. However, we really need long-term follow-up to detect the rate of delayed recurrences after different ablation doses. A recent retrospective study of the patients who had received different ablation doses, on the basis of the preablative risk of recurrence, revealed that higher doses of radioiodine were associated with a higher rate of successful ablation than the smaller dose, whereas successful ablation was not associated with a reduction in clinical recurrences in each dose group [47]. At present, the investigation of the long-term outcome of patients with early successful ablation after high-dose versus low-dose therapy is prospectively under way in our institute.

Considering the fact that patients with inadequate surgical treatment or histopathologic evidence of high-risk disease were not included in our study, we attempted to construct a multivariate model on the basis of other categorical factors for predicting the first-dose outcome of ablation therapy in low-risk patients. The radioiodine dose, baseline Tg, baseline TSH, effective suppressive therapy, and sex were found to be significant independent predictors of successful ablation in our study. For instance, keeping all other predictors such as administered activity, sex, baseline, and suppressed TSH constant in this model, the patients with postsurgical Tg equal to or less than 4.5 ng/ml had 2.9 times better chance of complete ablation than those with Tg greater than 4.5 ng/ml. However, no difference in the first-dose outcome between papillary or follicular subtypes, different age groups, TT or NTT procedures, and scintigraphic grades of FR was observed in our study. In another study, the tumor size, type of surgery, postsurgical radioiodine uptake, and administered activity for ablation therapy were the most important factors affecting the first-dose outcome [11]. However, in this study, about 28% of the patients underwent inadequate surgery (subtotal-thyroidectomy or hemi-thyroidectomy) and some important factors such as baseline Tg and baseline or suppressed TSH values were not included in the model of predicting covariates. In the group with adequate surgery (TT or NTT), only the dose of I-131 (>925 MBq), tumor size (<5 cm), and post-thyroidectomy percent uptake (<10%) were found to be significant predictors of successful ablation [11].

In conclusion, a higher (3700 MBq) activity of I-131 is more effective than 1100 MBq for post-thyroidectomy ablative therapy in a low-risk group of DTC patients. This would be highly beneficial for patients in terms of the initial outcome, total isolation time, and cumulative dose of I-131.

## Acknowledgements
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## Conflicts of interest
There are no conflicts of interest.

## References
21. Bal C, Padhy AK, Jana S, Pant GS, Basu AK. Prospective randomized clinical trial to evaluate the optimal dose of (131I) for remnant ablation in
27. Spencer CA. Challenges of serum thyroglobulin (Tg) measurement in the presence of Tg autoantibodies. J Clin Endocrinol Metab 2004; 89:3702–3704.