

# Comparison between low and high radioactive iodine ( $^{131}\text{I}$ ) reablation dose in patients with papillary thyroid cancer

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**Aim** The aim of this study was to assess ablation outcome after a second ablation dose and compare the ablation rate after low and high reablation doses of iodine-131 ( $^{131}\text{I}$ ) after failure of the first ablation with 3700 MBq.

**Patients and methods** The study included 81 patients with papillary thyroid cancer; they failed to achieve complete ablation after a first ablative dose of 3700 MBq. Their first follow-up  $^{131}\text{I}$  whole-body scan carried out 6–9 months after ablation showed small residual functioning tissue in the thyroid bed, with no functioning metastases. This is associated with unsuppressed serum thyroglobulin level (Tg) higher than 2 ng/ml. The patients received a second ablation dose, which was low (1110 MBq) in 37 patients and high in the remaining 44 patients (2960 MBq in 36 patients and 3700 MBq in eight patients). A whole-body scan and Tg level assessment were carried out 6–9 months later. The criteria for complete ablation included absence of residual functioning thyroid tissue and a Tg level lower than 2 ng/ml.

**Results** The overall successful complete ablation rate after the second reablation dose was 75%. This was achieved in 27 of 37 patients (73%) who received a low reablation dose and in 34 of 44 patients (77%) who received a high

reablation dose; no statistically significant difference was found between the two groups ( $P > 0.05$ ).

**Conclusion** In patients with papillary thyroid cancer who failed to achieve complete ablation after the first ablation dose of 3700 MBq, the overall complete ablation rate after both a low and a high second  $^{131}\text{I}$  dose was 75%, with no statistically significant difference in ablation rate between low (1110 MBq) and high (2960 and 3700 MBq) doses (73 and 77%, respectively). *Nucl Med Commun* 36:114–119 © 2015 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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**Keywords:** complete successful ablation, papillary thyroid cancer, radioactive iodine remnant ablation, second reablative radioiodine dose

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## Introduction

Thyroid cancer accounts for 90% of all endocrine malignant tumors, with more deaths occurring annually in these patients compared with patients with other types of endocrine cancer. Most cases comprise differentiated subtypes, specifically papillary and follicular thyroid cancer [1]. The incidence of thyroid cancer has increased within the last decade, an increase that is accounted for mostly by differentiated tumors. Papillary thyroid carcinoma (PTC) is the most common type of differentiated thyroid cancer [2]. It has an excellent prognosis with a 20-year survival of 90% [3]. Surgery is the mainstay of treatment [4]. Total thyroidectomy is the recommended type of surgery [5], aiming to eradicate primary and nodal disease, minimize treatment-related morbidity, permit accurate staging of the disease, and facilitate radioiodine-131 therapy (RAI) and follow-up [4].

Postoperative RAI represents a cornerstone of differentiated thyroid cancer therapy [6]. It is considered the most effective biologically targeted and curative radiotherapeutic

modality [7]. The main goal of postoperative RAI is to destroy thyroid remnants, rendering malignant thyroid cells the only remaining source of thyroglobulin (Tg) production and iodine uptake and retention on diagnostic whole-body scan (WBS), thereby increasing the sensitivity and specificity of these follow-up tests [8].

Although iodine-131 ( $^{131}\text{I}$ ) has been used for over 60 years, a single optimal ablation strategy is still not established, with variable reports on the amount of  $^{131}\text{I}$  required to achieve successful ablation. The typical administered activities range from 30 to 100 mCi (1110–3700 MBq) and are the subject of ongoing debate [9]. The goal is to administer the lowest activity possible that will effectively eliminate residual normal thyroid tissue [4]. Some results showed that both low and high doses of  $^{131}\text{I}$  exhibit similar rates of successful remnant ablation and recurrence rates, whereas others showed that a high dose of  $^{131}\text{I}$  is more efficient than a low dose for ablation, especially after less than total thyroidectomy, if residual microscopic disease is suspected or documented,

or if there is a more aggressive tumor histology (e.g. tall cell, insular, columnar cell carcinoma) [4,10].

A substantial amount of research has been performed on the adjuvant first dose of <sup>131</sup>I treatment; however, to our knowledge, few data are available on the optimal second administered activity of <sup>131</sup>I needed to completely ablate remnant thyroid tissue after the first dose and whether a low second dose is associated with rates of ablation success similar to or lower than the success rates with high-dose <sup>131</sup>I.

## Aim

The aim of the current study was to assess successful complete ablation after a second ablation dose of <sup>131</sup>I and to compare the success rate of low (1110 MBq) versus high (2960 and 3700 MBq) second reablation doses of <sup>131</sup>I in PTC patients who had failed to achieve complete ablation after a high first ablation dose of 3700 MBq.

## Patients and methods

The study included patients who had undergone total thyroidectomy for PTC and were referred to nuclear medicine units for remnant ablation during the period from January 2007 to December 2012. All patients had tumor between 1 and 4 cm in diameter, with no extra-thyroidal extension and no lymph nodal or distant metastases (T<sub>1</sub> and T<sub>2</sub>, N<sub>0</sub>, and M<sub>0</sub>). Patients who had incomplete free surgical margins were excluded from our study. Of 247 patients who fulfilled these criteria and presented for ablation during that period, 81 patients failed to achieve complete ablation after the first high ablation dose (3700 MBq). The criteria for failure of ablation are presence of residual functioning thyroid tissue in the neck with no lymph nodal or remote metastatic functioning thyroid tissue, together with stimulated serum Tg level higher than 2 ng/ml. Our institutional medical ethics committee approved the protocol, and informed consent from each individual patient was asked for before inclusion in the study.

First follow-up diagnostic WBS was performed 6–9 months after the first ablation dose using 3 mCi of <sup>131</sup>I; all patients were prepared in the same way for the administration of <sup>131</sup>I ablation therapy by withdrawal of thyroxine (LT<sub>4</sub>) medication for 3–4 weeks. In addition, patients were asked to follow a low-iodine diet 1 week before the scan. Blood samples were taken to measure serum Tg levels and thyroid-stimulating hormone (TSH) levels a few days before administration of the diagnostic dose. The TSH level had to be higher than 30 uIU/ml to receive the diagnostic dose. Three days after radioactive <sup>131</sup>I intake, WBS was performed using a dual-head gamma camera fitted with high-energy collimators and a bed speed of 6 cm/min for simultaneous anterior and posterior whole-body imaging. The energy window was set at 15%, centered on 364 keV with a 256 × 1024 size matrix. Additional spot views of the neck and chest were

also acquired. Images were interpreted qualitatively by visual assessment of the size and tracer uptake intensity of remnant thyroid tissue in the neck. Remnant functioning thyroid tissue in the neck with no lymph nodal or distant functioning metastases was noted in all patients; this is associated with stimulated serum Tg higher than 2 ng/ml. The aforementioned positive scan and serum Tg results represent important inclusion criteria. These patients were then scheduled for a second ablative dose of <sup>131</sup>I, which was given 8–12 weeks after the diagnostic WBS with the same preparation schedule. Patients were randomized into two groups on the basis of the administered dose:

Group 1 comprised 37 patients who received a low ablative dose (1110 MBq).

Group 2 comprised 44 patients who received a high ablative dose (80 and 100 mCi; of the 44 patients, 36 received 2960 MBq and eight received 3700 MBq).

Patients in the first group received the ablative dose on an outpatient basis, whereas patients in the second group were admitted and received <sup>131</sup>I therapy – the patients were hospitalized for 3 days. Thyroxine (LT<sub>4</sub>) treatment was resumed on the fourth day and post-therapy WBS was performed for all patients 5–7 days after therapy to ensure proper tracer localization in residual functioning thyroid tissue in the neck and to confirm the absence of any cervical lymph nodal or distant functioning metastases. Diagnostic WBS was performed for all patients 6–9 months after the second ablative dose. Blood samples were taken to measure Tg levels and TSH a few days before administration of the diagnostic dose. On the third day after the administration of <sup>131</sup>I, diagnostic WBS was performed. Image interpretation was made qualitatively, and our criteria for complete successful remnant ablation were defined as absence of residual functioning thyroid tissue in the thyroid bed with no functioning metastases and stimulated Tg level lower than 2 ng/ml. Accordingly, two categories were identified, either complete or incomplete ablation. The former includes those with negative WBS and serum Tg lower than 2 ng/ml. The latter is defined by the presence of residual functioning thyroid tissue at the thyroid bed, together with elevated serum Tg higher than 2 ng/ml. Patients with a positive scan and negative serum Tg level or the reverse were excluded from the study.

## Statistical methods

Categorical data are represented as percentage. For comparison of percentage, the  $\chi^2$ -test was used. The Mann–Whitney *U*-test was used to compare numeric data. A *P* value of 0.05 was set as the threshold for statistical significance. SPSS, v.16 (SPSS, Chicago, Illinois, USA) was used for statistical analysis.

## Results

The study included 81 patients who met the inclusion criteria; of them, 72 (89%) were female and nine (11%) were male. The age range was 21–79 years, with a median age of 51.7 years. Of the 81 patients, 66 patients had tumor size from 1.5 to 4 cm, capsular and vascular invasion was reported in 52 and 37 patients, respectively, and multicentric tumor was found in 29 patients. Ablation was indicated in the majority of patients because of two or more factors (69 patients, 85%), whereas in the remaining 12 (15%) patients ablation was indicated for only one factor (Figs 1–3).

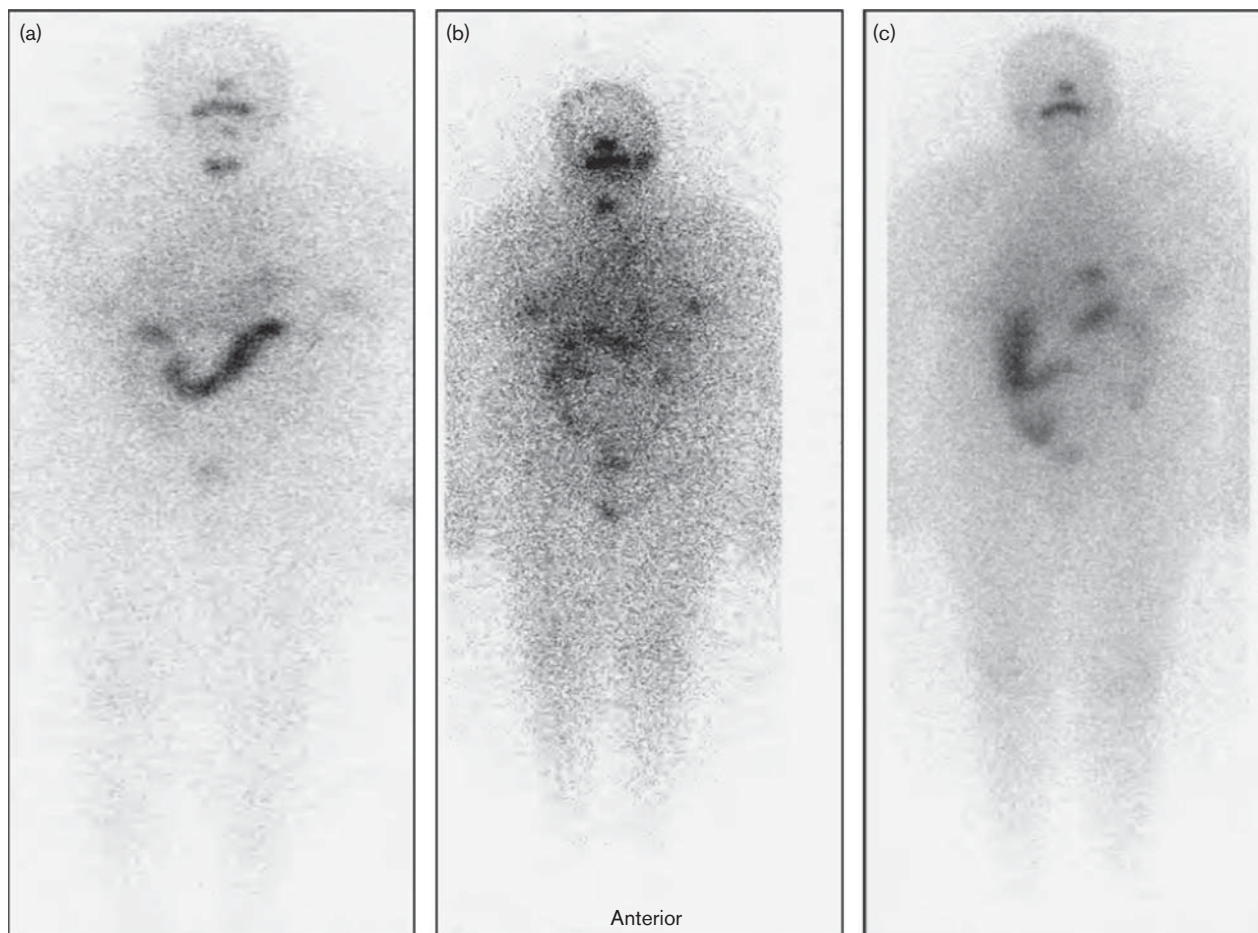
Successful complete ablation after the second application of  $^{131}\text{I}$  was reported in 61 of 81 patients (75%). Of the 37 patients who received the low reablation dose (1110 MBq) on an outpatient basis, 27 (73%) were completely ablated. This figure was 77% (34 of 44 patients) for patients treated on an inpatient basis with high-dose (2960 or 3700 MBq) reablation therapy. The difference was statistically insignificant ( $P > 0.05$ ) (Table 1).

## Discussion

Postoperative thyroid remnant ablation is indicated in numerous patients with well-differentiated thyroid cancer [11]. Complete ablation is an independent variable that reduces locoregional recurrence, distant metastases, and cancer death. In addition, it significantly increases disease-free survival [12,13].

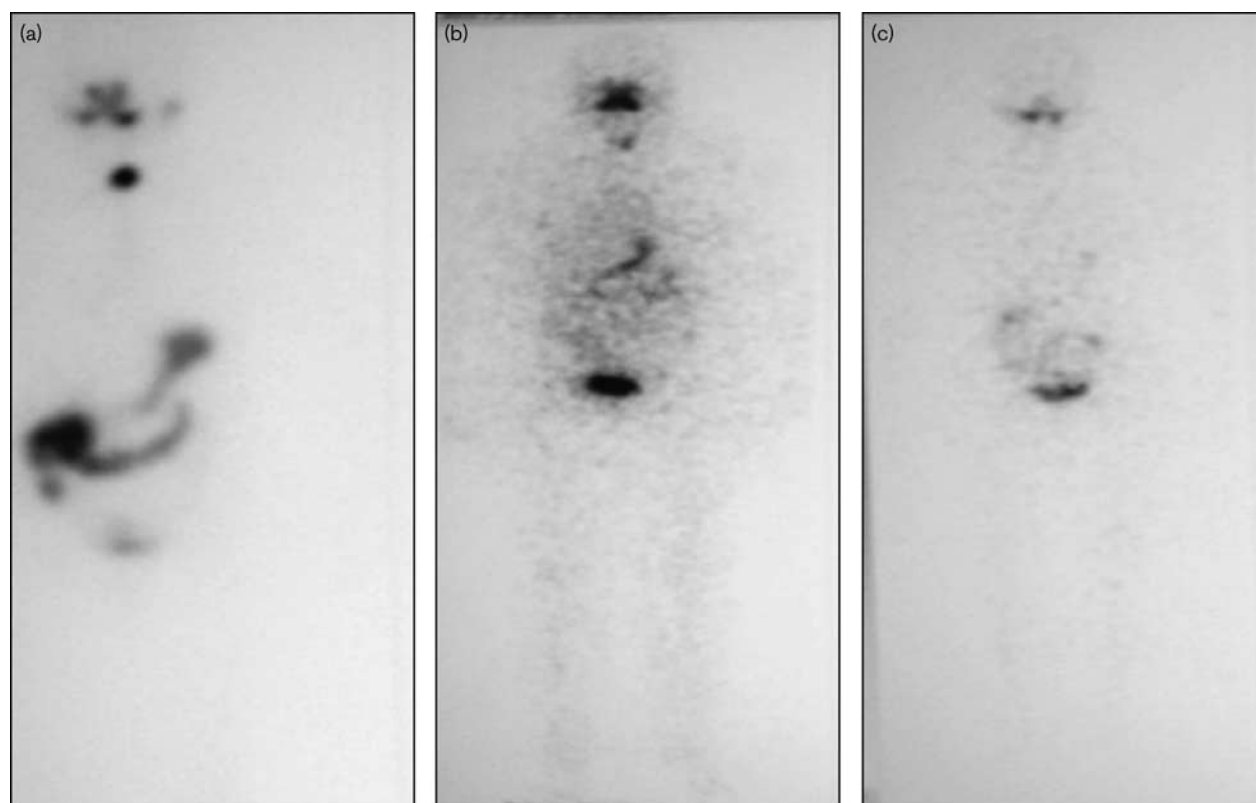
No single group achieved 100% ablation after the first application of  $^{131}\text{I}$ . Optimal  $^{131}\text{I}$  activity is usually determined empirically, ranging from 30 to 100 mCi (1110–3700 MBq) [9]. Many authors have reported 100 mCi (3700 MBq) as the usual first application of  $^{131}\text{I}$ , with an acceptable ablation outcome ranging from 50 to near 100% [8,14]. Gawkowska-Suwińska *et al.* [15], Verkooijen *et al.* [16], and Prpic *et al.* [17] reported satisfactory results for remnant ablation with all activities applied, which ranged from 30 mCi (1110 MBq) to 100 mCi (3700 MBq). However, they reported that the application of high doses is significantly more effective in thyroid remnant ablation compared with the administration

Fig. 1



(a) Postoperative diagnostic WBS. (b) Follow-up 6 months after 3700 MBq of  $^{131}\text{I}$  showing smaller residual disease. (c) Successful complete ablation 6 months after a second dose of 3700 MBq.  $^{131}\text{I}$ , iodine-131; WBS, whole-body scan.

Fig. 2



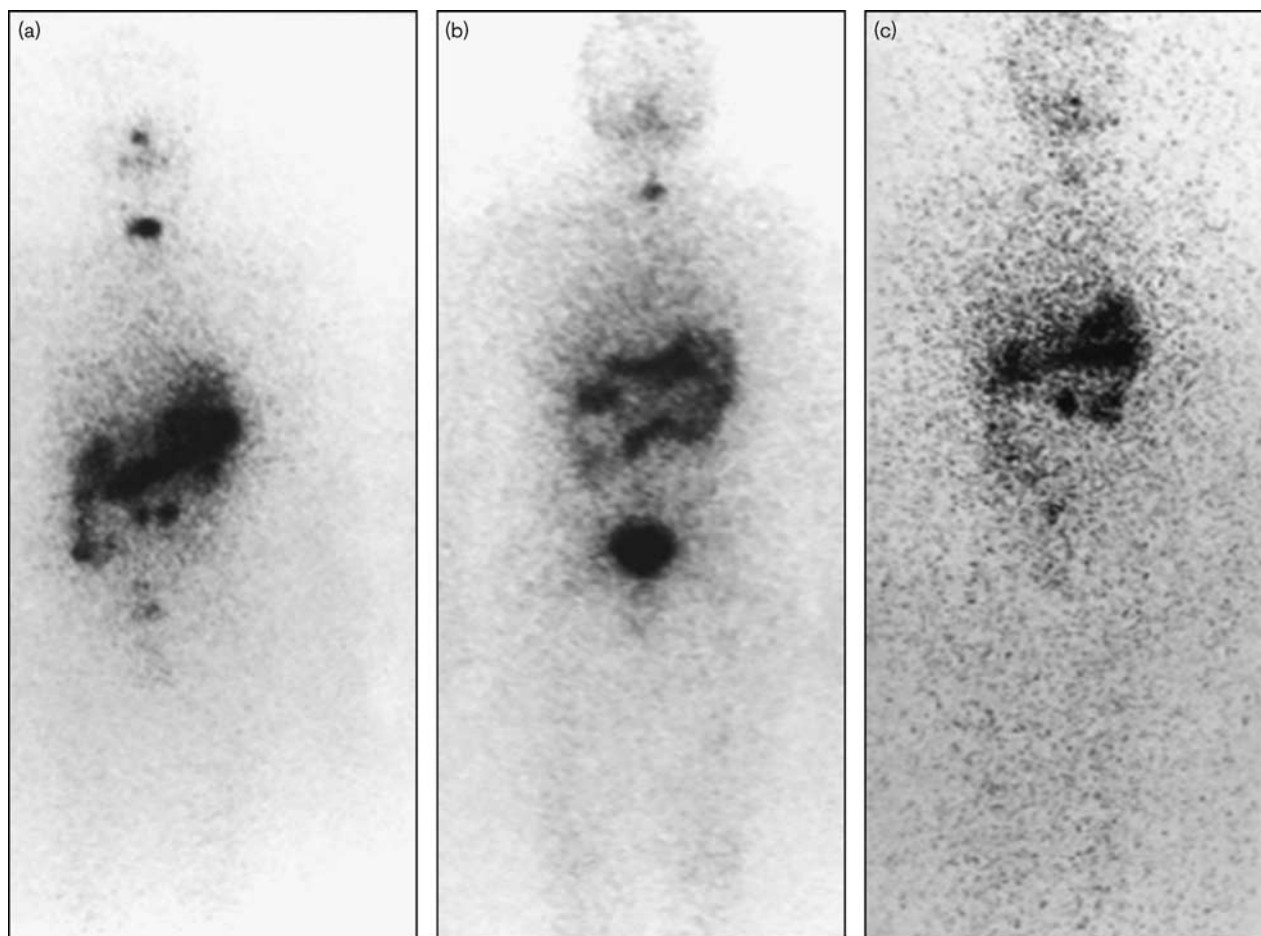
(a) Postoperative diagnostic WBS. (b) Follow-up 6 months after 3700 MBq of  $^{131}\text{I}$  showing small residual disease. (c) Successful complete ablation 7 months after a second dose of 1110 MBq.  $^{131}\text{I}$ , iodine-131; WBS, whole-body scan.

of low doses. The latter authors [17] reported an ablation outcome of 89.7% for 100 mCi (3700 MBq). In our experience, our group reported in 2012 an ablation outcome of 64% after a first dose of 3700 MBq [18], whereas in the current study the second  $^{131}\text{I}$  application had an overall successful outcome of 75%. The difference in ablation outcomes reported by different authors is actually related to multiple factors that affect the ablation outcome and are interlinked with each other. These include remnant size, the given  $^{131}\text{I}$  dose, stunning effect [19,20],  $^{131}\text{I}$  uptake, tumor stage, and the histopathology of non-neoplastic thyroid tissue [14]. These factors are associated with the biological variable that differs from one individual to another, with different radiosensitivities of thyroid tissue to  $^{131}\text{I}$ ; it may be attributed to the fact that thyroid remnants have different levels of expression of sodium iodide symporter [12,21].

In clinical practice, patients who fail to be completely ablated after the first  $^{131}\text{I}$  dose should receive a second  $^{131}\text{I}$  application to achieve complete remnant ablation [22]. Prpic *et al.* [17] stated that the administration of 30–50 mCi (110–1850 MBq), 75 mCi (2775 MBq), or 100 mCi (3700 MBq) as a second  $^{131}\text{I}$  application results in

similar and almost equal ablation outcomes. This is in agreement with our results in which no significant difference was found in ablation outcomes between low and high doses on the second application of  $^{131}\text{I}$ . We report a successful ablation rate of 73% after a second reablative  $^{131}\text{I}$  dose of 1110 MBq versus 77% after a high dose of 2960 or 3700 MBq, with no significant difference between the two groups ( $P > 0.05$ ). This can be partially explained by the change in size of remnant thyroid tissue, which is expected to become significantly smaller after a high first  $^{131}\text{I}$  dose. This diminution of remnant size is of significant magnitude and abolishes to a great extent the effect of the dose given as the second  $^{131}\text{I}$  application. This explanation is reinforced by what was reported in 2007 by Hackshaw *et al.* [23] for the first application of  $^{131}\text{I}$ . They stated that a low activity may have a similar successful ablation rate to high activity in patients with small remnants. Therefore, we ensure that this is also more applicable to the second  $^{131}\text{I}$  reablative dose as it is usually the case to have a small thyroid remnant after a high first ablation dose. Besides, the already known different cell radiosensitivities could be partially responsible for incomplete response to the first ablation dose with a persistent larger number of radio-resistant cells. The latter

Fig. 3



(a) Postoperative diagnostic WBS. (b) Follow-up WBS 7 months after 3700 MBq of  $^{131}\text{I}$  showing small residual disease. (c) Follow-up 6 months after 2960 MBq of a second ablative dose with persistent small residual disease.  $^{131}\text{I}$ , iodine-131; WBS, whole-body scan.

**Table 1 Ablation outcome after low and high second ablation doses of iodine-131**

Reablation dose	Incomplete ablation [n (%)]	Complete ablation [n (%)]	Total [n (%)]
Low dose (1110 MBq)	10/37 (27)	27/37 (73)	37 (100)
High dose (2960 or 3700 MBq)	10/44 (23)	34/44 (77)	44 (100)

needs a second dose of whatever activity to achieve complete ablation outcome.

We report a complete response to low and high reablation doses of 73 and 77%, respectively, with an overall complete ablation of 75% (61/81). These figures are comparable to our previous report of 72% response to a second ablation dose of 30 mCi (1110 MBq) [18]. In the study by Prpic *et al.* [17], who reviewed the results of 58 patients who received only 100 mCi (3700 MBq) of  $^{131}\text{I}$  as a first application of  $^{131}\text{I}$ , as in our study, complete

ablation occurred in 52 patients after the first dose (89.7%), whereas a second application of  $^{131}\text{I}$  in the six patients who failed to be completely ablated resulted in complete ablation in four patients, achieving a successful ablation outcome in 66.7% on second application of  $^{131}\text{I}$ , which is comparable to our figures. However, none of the studies achieved complete ablation in all patients. This was expected because of the presence of many factors affecting ablation outcome, and thus the diminution in size after the first high dose and the different  $^{131}\text{I}$  activities used as a second ablation dose are not solely responsible for the ablation outcome and do not abort the effects of the remaining multiple factors affecting the ablation result, failing to achieve successful complete ablation in all patients.

### Conclusion and recommendations

In patients with PTC after a first high ablative dose (3700 MBq) of  $^{131}\text{I}$ , ablation outcome after both low and

high doses of a second application of <sup>131</sup>I is 75%. No significant difference in ablation outcome was found between low dose (1110 MBq) and high dose (2960 and 3700 MBq) after the second dose of <sup>131</sup>I, with an ablation outcome of 73 and 77%, respectively. It is recommended to give 1110 MBq of <sup>131</sup>I as a second reablative dose on an outpatient basis, making therapy more convenient with fewer early side effects, less financial burden, and reduced radiation exposure to patients, relatives, and the environment, providing benefits to both patients and healthcare providers without affecting the outcome.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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