

Low Dose ^{131}I Therapy in Differentiated Thyroid Cancer: An Initial Experience

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Received: June 18, 2010

Accepted: June 28, 2010

Abstract. Objective: Since the 1970s, low dose radioactive iodine-131 (RAI or ^{131}I) has been widely reported in the treatment of patients with differentiated thyroid cancer (DTC). However, the clinical outcomes, dosage of ^{131}I , and criteria for successful ablation differ in the various studies. The aim of this study was to assess the clinical outcome 18 months after RAI therapy in selected DTC patients, and to identify factors associated with a good response. **Methods:** In this experimental study, 105 subjects were randomly selected from patients with DTC referred to the Nuclear Medicine Department between December 2008 and April 2010 and who had indications for RAI therapy. Patients were randomly divided into 3 groups to receive an empiric low-dose therapy of either 30, 40, or 50 mCi of ^{131}I . For 18 months after treatment, at 6-month intervals, patients were monitored closely clinically, with serum thyroglobulin assays, and with ^{131}I whole-body scans. **Results:** Among 105 patients who completed followup, 86 % were successfully ablated with a single low dose of ^{131}I . There was no statistically-significant difference in ablation rates between the subgroups that receive 30,40, or 50 mCi of ^{131}I . The cumulative ablation rate was 99% in patients after the second dose of low dose therapy. **Conclusion:** If appropriate selection criteria are used in DTC, successful remnant ablation can be achieved with low doses of ^{131}I in the range of 30-to-50 mCi. No significant differences were found in results achieved with 30, 40, or 50 mCi of ^{131}I . As the majority of the DTC patients fall within the inclusion criteria of this study, they can be treated on an ambulatory basis with associated low cost, convenience, and a low whole-body radiation-absorbed dose of ^{131}I .

Keywords • Hyperthyroidism • Graves' disease • Radioiodine therapy • Outcome • Hypothyroidism

Introduction

The current accepted therapy for differentiated thyroid carcinoma is total thyroidectomy or near-total thyroidectomy followed by radioiodine (^{131}I) ablation of residual thyroid tissue, termed "remnant ablation." There are several arguments and compelling reasons for remnant ablation in cases of differentiated thyroid cancer, and these have been dealt with in detail elsewhere.^[21]

Although ^{131}I has been used for many years to ablate thyroid remnants following thyroid surgery, a single optimal ablation strategy is still not established. Varied reports on the amount of ^{131}I required to

achieve successful ablation, criteria for successful ablation, and long-term disease-free survival and recurrence rates show a considerable range.^[1,2]

In this context, multiple studies have established the adequacy of low dose ^{131}I in successfully ablating remnant thyroid in selected patients with a dose as small as 30-to-50 mCi.^[3-11] The proposed advantages of the dosage range are lower cost; minimizing whole-body radiation exposure, and hence lowering the potential risk of leukaemogenesis; and the practical advantage of economy and convenience of out-patient treatment in many countries. Thus, the objective of the present study was to determine successful ablation rates in selected differentiated thyroid cancer

patients with small single doses of ¹³¹I.

Patients and Methods

Study Design. One hundred and five patients with well-differentiated thyroid cancer were selected as study subjects. The patients had received 1110-to-1850 MBq of ¹³¹I for ablation of residual functioning thyroid tissue 1.5 months (median) after total or subtotal thyroidectomies performed between December 2008 and April 2010.

Inclusion Criteria. To be included in the study, patients were required to have disease that was limited to the thyroid bed, confirmed by clinical, radiological, peroperative, and postsurgical ¹³¹I scintigraphic examination. Patients were also required to have no evidence of extrathyroid or distant metastases at the time of presentation. The amount of thyroid tissue left behind or the completeness of surgery did not affect the dose of ¹³¹I given.

Exclusion Criteria. Patients with inadequate surgery were excluded. Inadequate surgery was qualitatively defined as significant bilateral thyroid uptake on the first ¹³¹I scan or > 5 cm initial tumour size on histological examination.

Patients were also excluded if they had any of a number of extrathyroid diseases: nodal or distant metastases, adverse histopathology-like Hürthle cell carcinoma, poorly differentiated carcinoma, insular carcinoma, medullary thyroid carcinoma, and the aggressive variant of papillary carcinoma. Moreover, if the first postoperative thyroid scan of a patient who had had a total thyroidectomy showed a substantial uptake in the thyroid bed, he or she was reclassified as having had a subtotal thyroidectomy and was excluded from the study.

The median duration of the illness before surgery was 29 months; the range was 1-to-370 months). Mean tumor size was 3.8 ± 1.2 cm. The large tumor size was probably due to late referral to surgery. The initial surgical intervention was not uniform due to different surgical units operating upon the patients. The surgical procedure followed was near total thyroidectomy or total thyroidectomy in all of the patients. The histopathological diagnosis was established in all patients and classified according to the World Health Organization criteria.^[12] Eighty four patients (80%) had papillary thyroid carcinoma, and 21 (20%) had follicular thyroid carcinoma.

The interval between surgery and referral to the Department of Nuclear Medicine for remnant ablation ranged from 2 days to 2 months with a median value of 1 month. Postsurgical whole body scans were performed with 0.8-to-1.0 mCi of ¹³¹I after

keeping patients off L-thyroxin for 4-to-6 weeks. Preablation serum TSH values among patients ranged between 25 and 98 μ IU/ml (mean = 54 ± 14). Although patients were not prescribed special low-iodine diets, they were advised not to take in foods or drugs known to be rich in iodine or to undergo contrast CT scans. The patients were given oral ¹³¹I as NaI therapeutic capsules with dosages of 30-to-50 mCi. Informed consents were obtained from all adult patients before administration of ¹³¹I.

After ¹³¹I therapy, all patients underwent post-therapy whole body scans. The purpose was to look for any nodal or distant metastases missed on the previous postsurgical low-dose whole body scans.

The patients were then advised to take levothyroxine (2 μ g/kg body weight) daily on an empty stomach as suppressive therapy. This was continued until 6 months later when diagnostic ¹³¹I whole body studies were repeated. The preparation for the 6-month post-therapy evaluation was similar to that for the preablation scan. No recombinant human TSH was used in this study. All patients were prepared by conventional methods with serum TSH levels more than 30 μ IU/mL.

The repeated diagnostic studies consisted of 2-to-3 mCi ¹³¹I whole body scans and serum thyroglobulin assays. The criteria for successful ablation were as follows: a negative ¹³¹I whole body scan and thyroglobulin less than or equal to 1 ng/mL. If patients met these criteria, they were classified as having achieved complete remnant ablation. If, however, after the first posttherapeutic evaluation, a patient did not meet the criteria for complete thyroid ablation, then additional ¹³¹I treatment (30-to-50 mCi) was administered. Repeat ¹³¹I doses were administered until thyroid ablation was achieved. Afterward, annual check-ups were planned for thyroglobulin estimation.

Results

The mean age of the patients was 39 ± 12.7 years with a female-to-male ratio of 2.6. The mean tumor size was 3.8 ± 1.2 cm. Successful remnant ablation was achieved with one dose of ¹³¹I in 90 (86%) of the 105 patients. Their mean thyroglobulin level was 0.5 ± 0.1 ng/mL. The remaining patients showed partial ablation, objectively assessed by reductions in scan uptake intensity or number of foci and low thyroglobulin levels.

There was no statistically significant difference in the first-dose outcome (remnant ablation) between patients receiving 30 mCi of ¹³¹I (44% of patients), 40 mCi (32% of patients), or 50 mCi (24% of patients). Remnant ablation rates were almost identical

between patients administered 30, 40 and 50 mCi of ¹³¹I (84%, 92%, and 88% ablation rates, respectively). No statistically significant associations were found between successful ablation rates and mean group differences in tumor size and other demographical factors.

Two doses of ¹³¹I were administered to 15 patients. The rate of successful remnant ablation after the second dose of ¹³¹I was 99%. All patients were followed up for 18 months. So far, no cases of local recurrence or nodal or distant metastasis have been observed in the study cohort. Also, no deaths have

Table I. Demographic data, clinical profiles, and treatment outcomes of all patients.

Parameters	Total	30 mCi	40 mCi	50 mCi
Age (years) ¹	39 ± 12.7	37.5±11.6	41±13.6	39.9 ± 13.7
Sex (female:male)	2.6:1	2.7:1	2.4:1	3:1
Median duration of illness (months)	18	20	18	16
Tumor size (cm) ¹	3.8 ± 1.2	4.5 ± 1.6	3.6 ± 1.7	5.1 ± 2.1
Surgery NTT ²	105	46	34	25
Histopathology³				
Papillary	84	36	22	18
Follicular	21	10	12	7
Successful ablation ¹ (% of patients)	90 (86%)	39 (84%)	31(92%)	22 (88%)
Patients requiring second dose	15	7	3	3
Cumulative ablation after 2 nd dose 1 (% of patients)	104 (99%)	45 (97.8%)	34 (100%)	25 (100%)

¹ Age and tumor size are given in terms of mean ± SD; duration of illness is given as median

² Near total thyroidectomy

³ Number of patients.

occurred.

Discussion

There are multiple reports attesting to the efficacy of low-dose (30-to-50 mCi) ablative therapy for thyroid remnants since 1970's. One of the first reports of such therapy emphasized its effectiveness relative to the standard higher dose of ¹³¹I.^[3]

The initial belief and practice was that a higher dose of ¹³¹I should be administered as it more effectively achieved complete ablation with a single administration. Proponents of this higher-dose ¹³¹I remnant ablation argued that administering larger doses also ablated possible micrometastatic deposits. Their corollary argument was that lower doses were less effective in ablating the micrometastases not visualized in a posttherapy whole body scans, and thereby possibly led to a higher recurrence rate and metastases.^[10] However, Mazzaferri and Kloos^[11] addressed these arguments and found no difference in 30-year recurrence rates (4% and 6%, respectively; *P* = 0.1) between low-dose (29–to-50 mCi) and high-

dose (51–to-200 mCi) ¹³¹I remnant ablation groups.

The present study provides additional data on the effectiveness of the 30-to-50 mCi dose range. Our results show that a single 30-to-50 mCi dose resulted in successful ablation in 86% of the patients at 1 year post iodine therapy. A single low dose of ¹³¹I was sufficient in the majority of the cases to render the followup ¹³¹I scan negative and to provide considerably lower thyroglobulin levels.

A negative ¹³¹I scan and low thyroglobulin level would be reasonable criteria of successful therapy if the only concern were the detection of iodine-retaining malignant thyroid tissue. It is likely, however, that more complete ablation of non-neoplastic thyroid tissue is necessary to afford the advantages of decreased recurrences of thyroid carcinoma and increased patient survival.^[11,13-17]

Our experience in following patients with minimally positive scans indicates that some may become negative without further ¹³¹I therapy. Nevertheless, since 30 mCi is the largest dose usually approved for outpatients in many countries, it may be reasonable to combine the therapeutic and diagnostic efficacy of

30-mCi doses for ablation of thyroid remnants. The benefits of low-dose therapy, in addition to economy and convenience, relate primarily to a reduced total radiation exposure to extrathyroidal target organs. This reduction pertains mainly to the 86% of patients in whom ablation is achieved with a single 30-mCi dose.

However, repeated low-dose exposures, which allow for tissue repair mechanisms to proceed in the interim, may cause less biologic damage than the same total dose delivered at one time. Therefore, even patients requiring two such doses may benefit. The risk of leukemia and ovarian injury after thyroid ablation doses under 150 mCi is unknown, but is probably very small. Pochin^[18] reported four cases of leukemia in 140 patients who received an average total dose of 735 mCi. Pochin's leukemia cases received 1130-to-1715 mCi, and other cases gathered from the literature by Brincker et al.^[19] received 261-to-1600 mCi. Regarding ovarian injury, Sarkar et al.^[20] followed 33 young patients for an average of 19 years following treatment with 80-to-691mCi (mean of 196 mCi). The investigators found no evidence of radiation-induced problems in fertility or in the offspring of the young adults.

Despite the lack of evidence of injury with doses below 150 mCi, it seems prudent to mitigate radiation exposure by using the minimal effective dose to achieve the desired purpose. But disadvantages of low-dose therapy have been reported. First, about half of the patients require more treatment, resulting in more periods of T₃ withdrawal and hypothyroidism, and a longer time required to achieve ablation. Second, unrecognized metastases may be in adequately irradiated. This may reduce the function of the neoplastic cells but not their growth. A long-term, prospective randomized controlled study is needed to evaluate the importance of these factors in the efficacy of low-dose ablation therapy.

Our results suggest that use of a single low dose in the proper clinical setting results in successful ablation in a majority of patients. Thus, single low-dose therapy is a reasonable approach to ablation therapy, especially in young subjects with well-differentiated thyroid cancer. Our results also suggest that a minimally positive whole body scan 6 months after a therapeutic dose of ¹³¹I is an indication for further follow-up rather than immediate further treatment.

Conclusion

If appropriate selection criteria are used in differentiated thyroid cancer, successful remnant abla-

tion can be achieved with low doses, in the range of 30-to-50 mCi. No significant differences were found in results achieved with 30, 40, or 50 mCi of ¹³¹I. The majority of differentiated thyroid cancer patients fall within the inclusion criteria of this study. Because of this, patients can be treated on an ambulatory basis with associated low cost, convenience, and low whole-body radiation-absorbed doses.

Limitations of Study

Patients with incomplete initial surgery, poorly differentiated tumors, aggressive histology, or metastatic disease were not included in this study. Results of this study therefore cannot be extrapolated to this population of patients, and high-dose ablation therapy may be preferable for them.

In addition, treatment outcomes and recurrence rates among patients who met the inclusion criteria for this study would best be assessed through long-term followup.

Disclosure

No financial support or grants were available to conduct or complete the study.

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