HIGH-DOSE I-131 THERAPY FOR VARIED ASPECTS OF WELL-DIFFERENTIATED THYROID CARCINOMA

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ABSTRACT

Purpose: This study aimed to evaluate the response to high-dose RAI (100-200 mCi) in three groups of patients: with a thyroid remnant, high Tg/negative WBS, and with metastasis.

Materials and methods: We retrospectively chart-reviewed 159 patients who had been admitted and received high-dose RAI from October 1999 until August 2004 at our tertiary treatment center in southern Thailand. The indications for treatment included 1) a thyroid remnant after at least 2 OPD ablative doses, 2) high serum Tg with negative diagnostic WBS, and 3) I-131 avid metastasis.

Results: 45 of 79 patients receiving high-dose I-131 for thyroid remnant ablation were successfully ablated. 12 of 24 patients with high Tg/negative WBS showed I-131 uptake on post-therapy WBS, while 3 showed no uptake on subsequent WBS; none returned to a normalized Tg level. Of 54 patients who had I-131 uptake in their metastases, 24 achieved complete response.
There was no statistical difference in age, sex, histologic type, pre-treatment Tg level or accumulated small dose RAI between good and poor response groups.

Conclusions: 1)A thyroid remnant (after surgery and small dose RAI) could not be ablated with up to 250 mCi in 34/79 patients (43%). 2) In high Tg/negative WBS, high-dose RAI might improve sensitivity but without obvious benefit in therapeutic outcome. 3) 24 out of 54 metastases (44%) showed a positive response to high-dose RAI, particularly those exhibiting RAI uptake at a single site

WBS = Whole body Scan

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INTRODUCTION

I-131 is routinely used in the treatment of well -differentiated thyroid carcinoma (WDTC), however, there is no current consensus on many aspects.[1-4] Many previous studies have reported on the results of radioiodine (RAI) treatment, but they do not really present a coherent picture of the treatment due to differing details such as patient status, staging of disease, dosages of I-131 treatment and criteria for successful treatment. In this study, we retrospectively reviewed the data of 157 well-differentiated thyroid carcinoma patients who underwent high-dose RAI treatment at Songklanagarind Hospital to review the response to treatment for one of three indications: thyroid remnant, high Tg/negative WBS, and I-131 metastasis.

MATERIALS AND METHODS

From October 1999 to August 2004, 296 thyroid carcinoma patients received primary treatment (thyroid surgery and OPD ablative doses of RAI) and were admitted to an isolation room for high-dose RAI treatment. All patients were followed up at Songklanagarind Hospital in Hatyai, Thailand. We retrospectively chart-reviewed 157 patients who had undergone high-dose RAI for thyroid remnant ablation (n=79), diagnosis and therapy in the case of high Tg but negative WBS (n=24) and treatment of I-131 avid distant metastases (n=54). All patients had undergone a thyroidectomy with or without neck dissection and received at least 1 small OPD dose (30-50 mCi) of post-operative I-131 therapy. The first I-131 ablation was performed four to six weeks after surgery, with no thyroid hormone treatment given in the interim. Post-therapy I-131 WBS was performed 5-7 days after the I-131 treatment using a single-head gamma camera system (GCA-901 A/HG, Toshiba Corperation,® Japan). A follow up diagnostic WBS (3-10 mCi) was performed 6 months after each I-131 treatment. Each patient was instructed to cease taking thyroxine for 4 weeks before the I-131 administration for scanning or treatment. Long-term thyroxine replacement using levothyroxine was given after post-therapy scanning. Patients were asked to commence a low iodine diet 1 week prior to the scan.

Thyroid function tests, including TSH, serum thyroglobulin (Tg), anti-thyroglobulin antibody (anti-Tg Ab) and a chest radiograph, were performed prior to I-131 administration. I-131 was administered when the serum TSH level was at least 30 mIU/L. Serum Tg under TSH stimulation of 20 ng/ml or above was considered to be high and when found, was followed until normalized.

High-dose RAI therapy was considered if the radioiodine uptake was found within the thyroid bed or areas suggesting metastasis on the follow up diagnostic scan after at least 1 small OPD dose. The treatments administered ranged from 100-150 mCi for thyroid remnant ablation to 150-200 mCi for high Tg/negative WBS or distant metastases. The patients were admitted to an isolation room for 2 days and discharged after the exposure radiation at 1 m was below 5 mRem/hour.

Further radioiodine therapy was considered if radioiodine uptake could still be detected on the follow-up scan 6 months after the high-dose therapy. In some patients with very intense metastatic uptake and very high Tg, further high-dose therapy 4-6 months later was given unless a diagnostic WBS was done. In the high Tg/negative WBS group, if post-therapy WBS showed no uptake, there was no further I-131 treatment or follow up scanning.

Hospital records were reviewed and the following data were stored in the computer: age, gender, extent of surgery, histopathological type, primary tumor size, operative findings, pre-treatment Tg levels and anti-thyroglobulin antibody levels,

WDTC = Well-differentiated Thyroid Carcinoma
WBS = Whole body Scan

accumulated small I-131 doses, pre- and post-therapy WBS results and radiographic findings.

Data analysis was performed using SPSS version 11.0 and the results are presented as mean ± SD. A two-tailed unpaired t test was used to evaluate statistical significance.

DEFINITIONS

- **thyroid remnant:** positive I-131 uptake at thyroid bed in diagnostic WBS after receiving at least 2 doses of small OPD I-131 ablation
- **Tg0-max:** Pre-treatment serum Tg under TSH stimulation (TSH 30 mIU/L or above)
- **high Tg-max:** Serum Tg under TSH stimulation 20 ng/ml or above
- **complete response:** negative I-131 uptake at the primary lesion on subsequent diagnostic or post -therapy WBS after RAI treatment
- **partial response:** decrease in number or extent of I-131 uptake on subsequent diagnostic or post -therapy WBS after RAI treatment
- **no response:** unchanged or progressive I-131 uptake lesion on subsequent diagnostic or post -therapy WBS after RAI treatment
- **response by Tg:**
- **complete response:** at least 50% reduction of Tg-max compared to the pre-treatment level

no response: less than 50% reduction or increased level of Tg-max compared to the pre-treatment level

RESULTS

Among the 157 patients with thyroid cancer, there were 94 papillary carcinomas, 45 follicular carcinomas and 18 mixed papillary-follicular carcinomas. 112 patients were female with a mean age of 42 (± 15) years and 45 patients were male with a mean age of 43 (± 16) years at the time of diagnosis. Mean follow up period since the first high-dose RAI was 34 (range 7-116) months. The results of high-dose RAI treatment were evaluated in 3 groups according to the by indications for treatment.

Group 1) Thyroid remnant after OPD small ablative doses (n=79)

Following a post-operative small ablative dose, 79 patients, 58 females and 21 males, underwent high-dose I-131 treatment for thyroid remnant ablation. The mean ages of the complete response and no response groups were 44 (± 12) and 40 (± 12), respectively. Of the 79 patients who received a dose of 100-150 mCi for remnant ablation, 45 (57%) were successfully ablated with one or two doses of I-131. Of these 45, 27 were papillary (56% of all papillary carcinomas), 14 were follicular (64% of all follicular carcinomas) and 4 were mixed type (44% of all mixed papillary-follicular carcinomas). Table 1 shows the characteristics and successful rates of thyroid remnant ablation in these patients. There were no statistically significant differences in the success rates between the different ages ($p = 0.909$), sexes ($p = 0.593$), histological cell types ($p = 0.493$), pre-treatment Tg max's ($p = 0.167$) and accumulated small I-131 doses ($p = 0.681$).

Table 1 Characteristics and success rates of thyroid remnant ablation of well-differentiated thyroid cancer patients after high-dose I-131 therapy

	Complete response (N = 45)	No response (N = 34)	p value
Sex			
- Female (%)	32 (71%)	26 (76%)	0.593
- Male (%)	13 (29%)	8 (24%)	
Age at diagnosis (years)	44 ± 12	40 ± 12	0.909
Cell type			0.493
- Papillary	27 (60%)	21 (62%)	
- Follicular	14 (31%)	8 (23%)	
- Mixed papillary – follicular	4 (9%)	5 (15%)	
Tg0 max, ng/ml	71 ± 190	139 ± 238	0.167
Range	0-823	0-862	
Median	1.4	10	
Accumulated small dose	106 ± 91	119 ± 168	0.681
Number of treatment (median)	1	2	
other site uptake	11	14	0.085
- mediastinum	9	9	
- lung	1	2	
- mediastinum & lung	1	2	
- bone	-	1	
Number of surviving patients	45	34	-

Group 2) High serum Tg with negative WBS (n=24)

This group included 24 patients with persistently high serum Tg-max levels was based on a cut-off point of 20 ng/ml and a negative diagnostic I-131 WBS study. Patients with positive anti -thyroglobulin antibodies were excluded. Almost half of these patients still showed a negative WBS after administration of up to 50 mCi. Then an initial high-dose I-131 treatment of 150 mCi was administered to detect any I-131 uptake lesion. Follow up treatment results with a further post-therapy scan (in cases with positive uptake) and Tg-max response using the previously mentioned criteria were obtained.

Among the 24 patients who received high-dose I-131 for their high Tg level only, 10 showed I-131 uptake on the post-therapy scan and 2 showed questionable uptake. The sites of uptake on the post -therapy WBS are listed in Table 2. Further high-dose RAI treatment was administered in 9 patients of whom 4 showed complete resolution on a subsequent post-therapy scan. The remaining 5 patients still had unchanged uptake, although 3 of them received an accumulated I-131 dose of more than 1 Ci. There was no follow up WBS in 3 patients who had minimally positive uptake on the first high-dose WBS.

Table 2 The sites of I-131 uptake on the post-therapy scan of 12 patients with high Tg negative diagnostic WBS

Site of uptake at the 1st post therapy WBS	Uptake on high-dose RAI		Tg post therapy	
	Uptake	No uptake	Unchanged	Increase
Thyroid bed, n = 3	Possibly = 1 Not F/U = 1	0	1	2
Lung, n = 3	2	1	1	2
Questionable uptake at mediastinum, n = 2	Not FU = 1	1	0	2
Thyroid + mediastinum, n = 3	Not FU = 1	2	0	3
Mediastinum + LN, n = 1	1	0	1	0

Only 1 of these 12 patients (8.3%) showed significant reduction of the Tg-max level after one or more high-dose RAI treatments. The responses as indicated by I-131 uptake and Tg max level using a cut-off ? 50% reduction from pre-treatment levels is shown in Table 3. There was no significant difference of I-131 uptake on the first post-therapy WBS among different age groups (p = 0.124), sexes (p = 0.673), histological cell types (p= 0.165) or pre-treatment Tg-max levels (p = 0.781).

Table 3 Patient characteristics between those with positive and negative uptake on the first post-therapy WBS

	Uptake (N = 12)	No uptake (N = 12)	p value
Sex			
- Female (%)	7 (58%)	8 (67%)	0.673
- Male (%)	5 (42%)	4 (33%)	
Age at diagnosis (years)	38 ±14	43±16	0.124
Cell type			0.165
- Papillary	9 (75%)	6 (50%)	
- Follicular	1 (8%)	5 (42%)	
- Mixed papillary – follicular	2 (17%)	1 (8%)	
Tg max, ng/ml, mean ± SD	255±248	283±238	0.781
Range	44-697	15-708	
Median	127	235	
Accumulated small dose	191±362	220±126	0.798
High-dose RAI range	150-1024	150-660	0.192
Response of post-treatment Tg	1(8.3%)	0	-
Number of surviving patients	12	10	-

Group 3) Iodine-131 avid metastasis (n =54)

Among the 54 patients with positive I-131 uptake at their metastatic sites, 39 were female and 15 were male. 45 patients had single organ metastasis, in lung (n = 25), mediastinum (n = 10) or bone (n =

10) (Table 4). One patient with bony metastasis had multiple bones involvement, while the other 9 also had multiple organ metastases.

Complete response using resolution of uptake at the primary lesion(s) on follow up WBS was achieved in 24 patients. Of these 24, 17 were papillary carcinomas (55% of all papillary carcinomas), 5 were follicular carcinomas (29% of all follicular carcinomas, and 2 were mixed (33% of all mixed papillary-follicular carcinomas). There were no statistically significant differences in the rates of successful treatment between different sexes ($p = 0.422$) histological types ($p = 0.474$), or Tg max's (0.183), but older age ($p = 0.018$) and higher accumulated small dose RAI ($p = 0.043$) were noted in patients with poor response to high-dose RAI treatment.

Among the 24 patients with good response to high-dose RAI treatment, 22 (92%) had single organ metastasis. Of 9 patients with multiple organ metastases, 2 showed complete response, 4 partial response and 1 no response. Of 26 patients with no response to RAI, 6 with co-existent lung and bony metastases died from cancer.

The responses to high-dose RAI in all 3 subgroups of 157 well-differentiated thyroid carcinoma patients are summarized in Table 5.

Table 4 Clinical features of WDTC patients with I-131 avid metastasis and responses to high-dose RAI

	Complete response (N = 24)	Partial response (N = 4)	No response (N = 26)	p value
Age at diagnosis (years)	36±16	40±14	45±15	0.018
Sex				0.422
- Female (%)	17	4	18	
- Male (%)	7	0	8	
Histology				0.474
- Papillary	17	1	13	
- Follicular	5	3	9	
- Mixed papillary – follicular	2	0	4	
Site of metastasis				
- Lung	11 (3)*	-	14 (3)*	
- Mediastinum	5 (0) *	-	5 (0) *	
- Bone	6 (1) *	-	4 (1)*	
- Multiple organs	2 (0) *	4 (1)*	3 (3)*	
Tg0 max, mean ± SD	143±214	282±208	366±308	0.183
range	0-711	92-490	0-837	
Median, ng/ml	12.5	273	490	
Accumulated small dose	432±286	104±228	662±338	0.043
Number of surviving patients	24	4	20	-

NB : ( )* = number of patients with newly detected I-131 uptake lesion on subsequent WBS after high-dose RAI therapy

Table 5 Summery of responses to high-dose RAI in all 3 subgroups of 157 well-differentiated thyroid carcinoma patients

Group	N Subjects	RAI dose, mCi	Tg range (mean) Ng/ml	Response		
				Complete	Partial	None
Remnant	79	98-1,401	0-862 (105)	45 (11)*	-	34 (14)*
High Tg	24	150-1,024	15-708 (269)	-	-	24 (12)*
Metastasis	54	135-1,330	0-837 (263)	24 (4)*	4 (1)*	26 (7)*

NB : ( )* = number of patients with newly detected I-131 uptake lesion on subsequent WBS after high-dose RAI therapy

DISCUSSION

Radioactive iodine-131 is used for post -operative thyroid remnant ablation and also for treatment of distant metastases in papillary and follicular thyroid cancer patients.[1-4] Although it is well known that I-131 plays a role in the treatment of thyroid cancer, there are still several controversial aspects to its use.[5-7]

I-131 therapy is given post-operatively for three reasons. First, it destroys any remaining normal thyroid tissue. Secondly, it increases the sensitivity of subsequent I-131 whole-body scanning and the specificity of measurement of the serum thyroglobulin for the detection of persistent or recurrent disease. Third, the use of a large amount of I-131 for therapy permits I-131 WBS, a sensitive test for detecting persistent carcinoma.[8]

One study reported that the remaining thyroid tissue can be destroyed with a single dose of I-131 in about 80% of patients, as defined by a diagnostic scan using 2 to 3 mCi of I-131 several months after the initial treatment, provided that the surgeon has left only a relatively small thyroid remnant. In this study, the first dose abolished thyroid uptake in 81% of patients given 30 mCi and 84% of those given 100 mCi.[9-11] The size of the thyroid remnant is also important. For example, in one study an average dose of 87 mCi was more effective in destroying the thyroid remnant after near-total thyroidectomy than less extensive surgery (90% vs. 22%). The remnant was destroyed successfully with I-131 in 94% of patients when the surgeon left less than 2 gm of thyroid tissue but in only 68% of patients in whom the remnant was larger.[11] Unfortunately, in our study the surgical data was incompletely recorded in many patients and an analysis of this parameter on response to treatment could not be carried out.

In the present series, 79 of 157 thyroid cancer patients underwent high-dose (100-150 mCi) RAI therapy for thyroid remnant ablation after at least two small ablative doses. The thyroid remnant of 57% (45/79) of these patients could be ablated by giving one or two doses of high-dose RAI. Only 37% (29/79) of these patients with a thyroid remnant could be cured with a single dose of RAI and another 20% with a double doses.

The successful rate of thyroid remnant ablation in our series was much lower than earlier reports. One important difference in our study was the smaller dose of RAI. Our patients had persistent thyroid remnant after receiving at least two small doses

I-131 (mean accumulated dose = 110 mCi). We hypothesize that small doses I-131 given previously might have had some effect on the biochemical properties of the thyrocyte, resulting in decreasing the ability of the radioiodine trapping mechanism and so negatively affecting the treatment response. This defect of thyrocyte ability should not have been the 'thyroid stunning' effect because all patients had an interval of at least 4-6 months between each I-131 administration. However, there was no significant difference of accumulated small dose I-131 between those who were successfully ablated and those who were not ($p = 0.681$).

In one study in 2001 by Arslan et al.,[9] the total I-131 dose needed for successful ablation was significantly higher in males ($p = 0.003$). This finding suggested that sex might play a role in successful I-131 ablation. In our series, however, we found no significant difference in the sexes between the two response groups, and our findings are similar to a study of 544 patients performed by Lin et al.[11] In their study, factors identified as influencing response to I-131 therapy included age, clinical stage, survival, recurrence, extent of surgery and the post operative serum Tg level; sex was not a factor in this study. In our study, patients who were successfully ablated had lower pre-treatment Tg level (mean 71 ±190) in comparison with those who were not (mean 139±238). However, there was no statistically significant difference ($p = 0.167$), possibly due to the relatively wide range of Tg levels. Further study on significance of high Tg level and response to RAI treatment might be important in the management, e.g. selecting early high-dose RAI treatment instead of waiting until no response after 2 small doses in patients with initially high Tg.

Arslan et al.[9] also reported that 19 of 218 patients (7.8%) showed metastasis on a post-therapy scan and successful treatment was achieved in 11 of the 19 (57.8%). 25 of 79 (32%) thyroid remnant patients which in our study showed metastasis on their subsequent post-therapy scan, most commonly at the mediastinum. This high rate could be due to the initial small dose of I-131 treatment destroying some of the residual thyrocyte and increasing the ability of I-131 uptake at the metastatic site. The pre-treatment Tg level in these patients was significantly higher than in those without metastasis (179 vs. 69 ng/ml, $p = 0.051$). The successful rate of treatment in these patients was 71% (17/19).

In 10-15% of the patients, detectable increase in serum Tg levels were found despite a negative WBS.[12] This discrepancy was mainly due to a metastasis being able to produce Tg but having iodine uptake too low to be visualized on a diagnostic WBS, either because the mechanism of iodine trapping was defective or the mass of neoplastic tissue was small. However, false negative WBS's can be caused by technical factors such as an excessive iodine pool, poor instrumentation, or inadequate serum TSH elevation.[12] We are confident that our patients did not represent false negative WBS's, because more than 50% of the diagnostic WBS's remained negative with I-131 dose up to 50 mCi.

There is still considerable controversy concerning the use of I-131 therapy in patients with true negative scans and a high serum Tg level. Some reports have suggested a benefit from empiric therapy for scan-negative, Tg-positive WDTC patients. Positive I-131 uptake on post-therapy scan could be detected 10-50% of these patients. Reduction in Tg level and disappearance of I-131 uptake in subsequent post-therapy scan could be achieved after treatment.[11, 13-15] However, many studies do not support benefits of empiric high-dose I-131 therapy in these patients.[7, 12, 17-19]

In a review article in 2001, Mazzaferri and Kloos[20] reported on 10 Tg-positive, diagnostic WBS -negative patients with serum Tg levels more than 15 ng/ml. Eight of these patients had evidence of metastasis on their post-therapy scan and 3 had a

WDTC = Well-differentiated Thyroid Carcinoma

subsequent negative post-therapy scan, with reduction of serum Tg to 5 ng/ml. A more recent report by Pacini et al.[12] compared the results of 28 untreated patients with 42 treated patients. The authors found a positive post-therapy WBS in 71% with reduction in Tg and disappearance of lung uptake with repeated therapy. They recommended treating all Tg-positive, WBS-negative cases once with 100 mCi of I-131 and continuing therapy until post-therapy WBS becomes negative.

In our present study of 24 patients treated with RAI who had detectable Tg and negative diagnostic WBS, 10 showed definite positive uptake on the post-therapy scan and 2 showed suspected I-131 uptake at the mediastinum. On a subsequent post-therapy scan, 4 of 9 (44%) who had a follow up post-therapy WBS showed complete remission. However, only 1 of these 12 patients with positive uptake on their post-therapy scan showed significant reduction of Tg level during the follow up period (based on at least a 50% reduction from the pre-treatment level). Our results suggest that in patients with a positive post-therapy scan, high-dose radioiodine treatment can be used as a diagnostic tool to identify tumor location. However, the beneficial therapeutic effect of this therapy remains unclear and has no obvious effect on survival. We would not advise the continuation of radioiodine therapy in patients with negative post-therapeutic WBS, unless a positive response is observed in individual cases, to prevent unnecessary radiation exposure to the patients.

I-131 therapy has been used to control distant metastasis from WDTC for more than 50 years.[21,22] In our series, the most common distant metastatic sites were lung, bone and mediastinum. A previous report by Brown et al.[23] on 235 patients who were treated for WDTC, of whom 42 had distant metastases and received I-131 therapy. 54% of the patients whose metastasis was confined to the lungs were alive without disease at a 10 year-follow up. Similar findings were reported by Schlumberger et al.,[24] who found that 46% of 394 patients with distant metastases who were treated with I-131 had complete resolution of uptake and excellent long-term survival.

In our series, the success rate based on complete resolution of uptake after high-dose treatment in patients whose metastasis was confined to either the mediastinum or a single bone was 50% for both, and only slightly lower in patients with lung metastasis (44%). The rate of successful treatment was significantly lower in those with multiple organ metastases, as only 2 of 9 patients (22%) showed successful treatment. Of 54 patients with metastasis, 2 with co-existing lung and bony metastases which had not responded to RAI treatment died from cancer.

The successful treatment rate in our patients was possibly false high, however, as based on the criteria we used to define success. The response to treatment was assessed based on the resolution of uptake at the primary detected lesion only, not all uptake of which some may appear on a subsequent scan. However, we nonetheless feel that a successful response to I-131 treatment can be achieved in as many as 40-50% of patients with single organ metastasis, with a poorer outcome in patients with multiple organ metastases.

CONCLUSION

I-131 has a major impact on the progressive control and cure of thyroid carcinoma, however it is not a panacea. The rate of unsuccessful thyroid remnant ablation with high-dose RAI is as high as 50%, depending on negative I-131 uptake at thyroid bed on post-therapeutic scan. In high Tg/negative WBS, high-dose RAI might improve sensitivity but without obvious benefit in therapeutic outcome. High-dose RAI therapy has some benefit in controlling metastasis, though there is lesser response where there is multiple organs involvement. Pre -treatment Tg level is not a significant factor in

predicting response to RAI, and further investigation is needed on the factors predicting response to treatment.

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This research methodology has been approved by the Ethics Committee on Human Research, Faculty of Medicine, Prince of Songkla University.

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