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Prospective randomized trial for evaluation of efficacy of low versus high dose I-131 for post operative remnant ablation in differentiated thyroid cancer

Sasitorn Sirisalipoch*
Vacharee Buachum* Panya Pasawang*
Supatporn Tepmongkol* Supot Boonvisut*

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Problem/background : *Radioiodine ablation of thyroid remnant following surgery has been found to decrease the risk of recurrence and death, and it also facilitates follow ups. However, there is some degree of controversy about the single optimal dose of I-131.*

Objectives : *1) To evaluate the efficacy of low (50 mCi) versus high (100 mCi) dose I-131 for remnant ablation in differentiated thyroid cancer and; 2) To search for factors associated with successful ablation.*

Design : *Prospective randomized clinical trial*

Setting : *Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine, Chulalongkorn University*

* Department of Radiology, Faculty of Medicine, Chulalongkorn University

Materials/methods : *One-hundred and thirty-eight cases, who underwent at least subtotal thyroidectomy and had no evidence of neither residual nor metastatic disease, were randomized to receive low (63 cases) and high (75 cases) dose of I-131. Baseline neck uptake and total body scan with 1 mCi of I-131 together with serum thyroxine (T4), thyroid stimulating hormone (TSH) and thyroglobulin (Tg) were performed. Six to eight months later, all subjects were reassessed using 3 mCi of I-131 after thyroxine withdrawal. The criteria for successful ablation were: 1) absence of visualized thyroid bed activity; or, 2) 48-72 hour-neck uptake of less than 0.2 % and serum thyroglobulin of less than 10 ng/ml.*

Results : *The overall successful ablation rate was 76.8 %. The high dose group had significant higher success rate than the low dose (86.7 % versus 65.1 %; p value = 0.003). Logistic regression analysis confirmed the significant influence of ablative dose on the successful outcome (odds ratio = 4.04; 95 % confidence interval; 1.64 - 9.93). Baseline T4 and TSH were also associated with success (odds ratio = 0.72; 95 % confidence interval; 0.59 - 0.88 and odds ratio = 1.02; 95 % confidence interval; 1.00 - 1.03 for T4 and TSH, respectively). We found no association of age, sex, tumor type, tumor size, baseline Tg, neck uptake, duration between surgery and radioiodine ablation, duration between diagnostic scan and radioiodine ablation, with successful ablation.*

Conclusion : *High dose I-131 (100 mCi) is more efficient than low dose (50 mCi) for remnant ablation. Besides high ablative dose, lower T4 and higher TSH are associated with successful outcome, this is likely due to good correlation with remnant mass.*

Keywords : *Thyroid cancer, I-131, Remnant ablation, Low dose, Prospective randomized trial.*

Reprint request : Sirisalipoch S. Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

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ศศิธร ศิริสาลิโภชน์, วัชรี บัวชุม, ปัญญา ภาสว่าง, สุภัทรพร เทพมงคล, สุพจน์ บุญวิสุทธิ์. การเปรียบเทียบผลการทำลายเนื้อเยื่อต่อมไทรอยด์ที่เหลือหลังจากการผ่าตัดด้วยสารรังสีไอโอดีน (I-131) ในปริมาณสูง 100 มิลลิคูรี และปริมาณต่ำ 50 มิลลิคูรี ในผู้ป่วยมะเร็งต่อมไทรอยด์ชนิด differentiated. จุฬาลงกรณ์เวชสาร 2549 ต.ค;50(10):695 – 706

เหตุผลของการทำวิจัย : *การให้สารรังสีไอโอดีน (I-131) เพื่อทำลายเนื้อเยื่อต่อมไทรอยด์ที่เหลือหลังจากการผ่าตัดในผู้ป่วยมะเร็งต่อมไทรอยด์ พบว่าสามารถลดอัตราการกลับเป็นซ้ำ และเพิ่มประสิทธิภาพในการติดตามการรักษา แต่ยังมีข้อถกเถียงในแง่ปริมาณสารรังสีไอโอดีนที่จะให้เพื่อการนี้*

วัตถุประสงค์ : *เพื่อเปรียบเทียบผลการทำลายเนื้อเยื่อต่อมไทรอยด์ที่เหลือหลังจากการผ่าตัดด้วยสารรังสีไอโอดีน (I-131) ในปริมาณสูง 100 มิลลิคูรี และปริมาณต่ำ 50 มิลลิคูรี ในผู้ป่วยมะเร็งต่อมไทรอยด์ และเพื่อศึกษาปัจจัยต่าง ๆ ที่อาจเกี่ยวข้องกับผลสำเร็จในการทำลายเนื้อเยื่อต่อมไทรอยด์ที่เหลือหลังจากการผ่าตัดด้วยสารรังสีไอโอดีน (I-131)*

รูปแบบการวิจัย : *การวิจัยทางคลินิกแบบไปข้างหน้าโดยการสุ่ม*

สถานที่ทำการศึกษา : *สาขาเวชศาสตร์นิวเคลียร์ ภาควิชารังสีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

ตัวอย่าง/วิธีการศึกษา : *ผู้ป่วยทั้งสิ้น 138 คน ซึ่งได้รับการผ่าตัดต่อมไทรอยด์ (อย่างน้อยแบบ subtotal) ที่ไม่พบว่ามีโรคหลงเหลือเฉพาะที่ และไม่พบว่ามีการกระจายของโรค ถูกสุ่มให้ได้รับสารรังสีไอโอดีนปริมาณต่ำ 63 ราย และปริมาณสูง 75 ราย ทั้งหมดได้รับการตรวจ I-131 total body scan และ neck uptake รวมถึงตรวจเลือดเพื่อวัดระดับ thyroxine (T4), thyroid stimulating hormone (TSH) และ thyroglobulin (Tg) เป็นพื้นฐาน หลังจากนั้น 6 - 8 เดือนผู้ป่วยจะถูกประเมินผลการรักษาหลังจากงดไทรอยด์ฮอร์โมน โดยเกณฑ์การพิจารณาว่าประสบผลสำเร็จ ได้แก่ 1) ไม่เห็นว่ามีสารรังสีบริเวณ thyroid bed จากการทำ I-131 total body scan หรือ 2) neck uptake ที่ 48 - 72 ชั่วโมง น้อยกว่า 0.2 % และระดับ Tg ต่ำกว่า 10 ng/ml*

ผลการทดลอง : *อัตราการประสบผลสำเร็จในการทำลายเนื้อเยื่อต่อมไทรอยด์ที่เหลือหลังจากการผ่าตัดโดยรวมเท่ากับ 76.8 % โดยกลุ่มที่ได้รับสารรังสีไอโอดีนปริมาณสูงมีอัตราการประสบผลสำเร็จสูงกว่ากลุ่มที่ได้รับปริมาณต่ำ (86.7 % และ 65.1 %, P value 0.003) จาก logistic regression analysis ยืนยันว่าปริมาณสารรังสีไอโอดีนที่ให้มีผลต่ออัตราการประสบผลสำเร็จ (odds ratio 4.04, 95 % confidence interval; 1.64 - 9.93) นอกจากนี้ปัจจัยที่พบว่ามีผลต่ออัตราการประสบผลสำเร็จได้แก่ระดับ T4 (odds ratio 0.72, 95 % confidence interval; 0.59 - 0.88) และ TSH (odds ratio 1.02, 95 % confidence interval; 1.00 - 1.03) สำหรับปัจจัยอื่น ๆ ได้แก่อายุ, เพศ, ชนิดของเซลล์, ระดับ Tg, neck uptake, ระยะเวลาระหว่างการผ่าตัดและการให้สารรังสีไอโอดีน ตลอดจนระยะเวลาระหว่างการทำ total body scan และการให้สารรังสีไอโอดีน ไม่มีผลต่ออัตราการประสบผลสำเร็จ*

สรุป : *สารรังสีไอโอดีนปริมาณสูง 100 มิลลิคูรีให้ประสิทธิภาพในการทำลายเนื้อเยื่อไทรอยด์ที่เหลือหลังจากการผ่าตัดสูงกว่าสารรังสีไอโอดีนปริมาณต่ำ 50 มิลลิคูรี นอกจากนี้พบว่าระดับ T4 ที่ต่ำและระดับ TSH ที่สูง ก็มีผลต่ออัตราการประสบความสำเร็จ โดยน่าจะมีความสัมพันธ์เป็นอย่างดีกับขนาดของเนื้อเยื่อไทรอยด์ที่เหลือ*

คำสำคัญ : *มะเร็งต่อมไทรอยด์, สารรังสีไอโอดีน, ปริมาณต่ำ, การวิจัยแบบไปข้างหน้า*

Differentiated thyroid cancer generally runs a very indolent course with excellent prognosis. The data from the Mayo Clinic revealed overall 20-year cancer-specific mortality rate of 5 % for papillary and 25 % for follicular types. [1] Although much prognostic difference between the low and high risk groups (distant metastasis, older age, larger tumor and local invasion) existed,[1-6] the best outcome resulted from near total thyroidectomy followed by I-131 and thyroid hormone therapy.[4] I-131 ablation of thyroid remnant following surgery has been found to decrease the risk of recurrence [2-6] and death [4-6], presumably through the destruction of microscopic tumors.[7] In addition, this will facilitate follow up with thyroglobulin and I-131 total body scan and some metastatic lesions might show up after ablative dose.[8,9] However, there is still certain degree of controversy about the optimal dose of I-131 for remnant ablation. Maxon *et al*. [10] proposed a complicated quantitative dosimetric approach with 80 % success rate, despite criticisms on the basis of dose calculation and threshold level.[11] Some preferred the conventional high doses (80 - 100 mCi or more), expecting more chance of success and possible treatment of undetected metastasis, with reported success rates between 60 - 90 %. [12-17] The low doses (30 - 50 mCi) have advantages of reduction of radiation burden to the whole body, and of course, the lower expense. The dose of 30 mCi was often selected because of outpatient treatment basis with varying success rates of 0 - 90 %.[11,15-27] However, there were only few small randomized trials.[15,16,20] Bal *et al*. [20] reported a plateau response when the doses were higher than 50 mCi. Also, Degroot *et al*. [25] found higher success rate with 50 mCi than with 30 mCi. The proposes of this study were: 1) to evaluate the efficacy of low (50 mCi) versus high (100 mCi) dose of I-131 for post operative remnant ablation in differentiated thyroid cancer; and, 2) to search for factors associated with successful ablation.

Materials and Methods

This study was performed under the International Atomic Energy Agency (IAEA) contract, from December 2000 to August 2003. One-hundred and forty-five patients with papillary or follicular thyroid carcinoma, who underwent at least subtotal thyroidectomy and were referred to our department for I-131 ablation, were enrolled in the prospective study. No one had evidence of neither residual unresected tumor nor any metastasis at the beginning. They were randomly selected to receive either 50 or 100 mCi of I-131 for remnant ablation. The randomization was done by the authors in the first year and later by the IAEA via electronic mail. Seven patients were excluded on the following conditions: having developed metastases (3), lost to follow up (2), had follow-up scan with Tc99m-MIBI instead of I-131 (1) and had previous I-131 treatment for hyperthyroidism (1).

Pre-treatment total body scan (TBS) was performed 4-6 weeks after surgery, together with baseline serum thyroxine (T4), thyroid stimulating hormone (TSH), thyroglobulin (Tg) and anti-thyroglobulin antibody (anti-Tg). Only few patients had thyroxine treatment after surgery that was replaced by triiodothyronine for four weeks and stopped for two weeks. The patients were informed to avoid iodine containing food and drugs. TBS with dual-headed gamma camera (Trionix, Biad XLT 20) and neck uptake with gamma probe (Biodex Medical Systems) were

performed 24 hours after giving I-131 tracer dose of 1 mCi. (The linearity of the gamma probe was tested with tracer doses up to 1.2 mCi, showing linear count rates.) The patients were admitted for I-131 treatment mostly within two weeks after diagnostic scan. Post-treatment TBS was also performed for detection of metastasis. Suppressive dose of thyroxine (150-200 microgram/day) were prescribed.

Follow-up TBS and neck uptake were performed 48-72 hours after giving 3 mCi of I-131, 6-8 months later with the same preparation as the first TBS. TSH level above 30 μU/ml was accepted as adequate stimulation. Ablation was considered successful when: 1) there was absence of visualized thyroid bed activity; or, 2) neck uptake was less than 0.2 % and serum Tg (off thyroxine) was less than 10 ng/ml. If the first ablation failed, the second dose of 100 mCi would be given.

Serum Tg was measured using immuno-radiometric assay (CIS bio international, France) with sensitivity of 0.5 ng/ml. Electrochemiluminescent method (Elecsys 1010, Roche Diagnostic GmbH, Mannheim) was used for serum T4 and TSH with sensitivity of 0.42 μg/dl and 0.005 μU/ml, respectively.

Statistical analysis was performed using t-test, chi-square test and logistic regression to identify factors influencing the successful outcome.

Results

In total, 138 patients completed the prospective study. Seventy-five were randomized to be treated with high dose and 63 with low dose I-131. All patient characteristics, as shown in table 1, were not significantly different between the two randomized groups. The overall successful ablation of the two groups was 76.8 % (106/138). Table 2 shows the success rate of each high and low dose group, with dividing into 3 subgroups by neck uptake range. The patient characteristics were compared between the success and the failure groups in table 3. Logistic regression analysis revealed variables associated with successful ablation in table 4.

Table 1. Patient characteristics of the two randomized groups.

Characteristics	High dose* (n=75)	Low dose* (n=63)	P value**
Age (years); range 16-69	41.6 ± 12.2	38.4 ± 12.3	0.12
Sex (famale/male)	65/10	53/10	0.66
Tumor type (papillary/follicular)	57/18	51/12	0.48
Tumor size (cm); range 1.0 - 6.5	3.0 ± 1.1	2.8 ± 1.0	0.14
T4 (μg/dl); range <0.4 - 7.0	2.7 ± 2.1	2.5 ± 2.1	0.53
TSH (μU/ml); range 3.2 - >100	55.8 ± 32.8	63.3 ± 34.4	0.20
Tg (ng/ml); range 0 -143	12.4 ± 17.0	13.1 ± 22.0	0.83
Neck uptake (%); range 0.8 - 36.3	14.3 ± 9.7	12.2 ± 8.6	0.18
Days between surgery and I-131 ablation; range 34 -146	60.1 + 18.1	63.8 + 20.8	0.27
Days between diagnostic scan and I-131 ablation; range 1 - 33	13.0 ± 7.7	12.6 ± 8.2	0.76

* Value expressed as mean ± standard deviation or ratio

** T-test or chi-square test

Table 2. Successful ablation rate of each high and low dose group.

% Baseline neck uptake (n)	% Successful ablation (n)		P value*
	High dose	Low dose	
< 10.0 % (62)	86.7 % (26/30)	68.8 % (22/32)	0.089
10.0 - 19.9 % (43)	91.7 % (22/24)	68.4 % (13/19)	0.048
≥ 20.0 % (33)	80.9 % (17/21)	50.0 % (6/12)	0.058
All (138)	86.7 % (65/75)	65.1 % (41/63)	0.003

*Chi-square test

Table 3. Thyroid ablation status versus patient characteristics.

Characteristics	Success* (n=106)	Failure* (n=32)	P value**
Age (years)	39.9 ± 12.8	41.0 ± 11.9	0.66
Sex (female/male)	90/16	28/4	0.73
Tumor type (papillary/follicular)	83/23	25/7	0.99
Tumor size (cm)	2.9 ± 1.0	2.9 ± 1.1	0.81
T4 (μg/dl)	2.3 ± 1.8	3.6 ± 2.5	0.01
TSH (μU/ml)	62.9 ± 31.5	47.2 ± 37.8	0.04
Tg (ng/ml)	12.6 ± 19.5	13.2 ± 19.3	0.89
Neck uptake (%)	12.6 ± 8.5	15.8 ± 11.4	0.15
Days between surgery and I-131 ablation	60.6 ± 17.9	63.5 ± 19.8	0.46
Days between diagnostic scan and I-131 ablation	13.1 ± 7.7	12.0 ± 8.6	0.53
Ablation dose (high/low)	65/41	10/22	0.003

* Value expressed as mean ± standard deviation or ratio

** T test or chi-square test

Table 4. Variables associated with successful ablation.

Variables in equations	P value	Adjusted odds ratio	95 % Confidence interval
T4	0.001	0.72	0.59 - 0.88
Ablation dose	0.002	4.04	1.64 - 9.93
TSH*	0.007	1.02	1.00 - 1.03
Ablation dose*	0.002	4.17	1.71 - 10.16

*When T4 was not considered a variable.

Discussion

Great variation in the reported success rates of low, or even high, doses of radioiodine ablation is likely due to different criteria of "successful" ablation and diagnostic doses of I-131[11-27] Other factors include extent of the surgery, the presence of residual unresected tumor, the preparation protocol and interval of follow up. Comtois *et al*. [22] and Kuni *et al*. [27] reported very low success rates of 27 % and 0 %, respectively, using rigid criteria of absent visualized thyroid bed activity and diagnostic I-131 dose of 5 mCi. While Snyder *et al*. [11] and Leung *et al*. [23], using 1 % neck uptake as the threshold below which successful ablation was considered and diagnostic I-131 doses of only 1 - 3 mCi, reported 80 – 90 % success rates of low dose (30 mCi) ablation. We decided to use the optimized criteria of less than 0.2 % neck uptake, the same as Bal *et al*. [20] and Degroot *et al*. [25], since it went along quite well with our visual assessment in considering success. Besides, we observed some background uptake, probably salivary gland activity, in patients without visualized thyroid bed activity. Serum Tg (off thyroxine) of less than 10 ng/ml was the additional criteria to increase specificity.

Our patients had wide variation of baseline neck uptake (0.8 - 36.3 %), TSH (3.2 - more than 100 μU/ml) and also T4 (less than 0.4 - 7.0 μg/dl), reflecting varying and quite large remnant sizes compared to most studies. This may be one of the possible explanations for the different outcome in some aspects. With our criteria and protocol, we found that the high dose (100 mCi) I-131 was more efficient than the low dose (50 mCi) for remnant ablation, unlike the previous prospective studies by Johansen *et al*. [15] and Creutzig *et al*. [16] who reported no advantage of 100 mCi over 30 mCi of I-131 for remnant ablation. Our result, however, does not support the study of Bal *et al*. [20], who found plateauing of the dose response curve with the doses beyond 50 mCi. Using the same criteria as us for successful ablation, Degroot *et al*. [25] who reported very high success rate of low doses (30 and 50 mCi) with data showing very low neck uptake (0.2 – 6 %) and consistently high TSH (more than 30 μU/ml). However, our result is in accordance with the meta-analysis of Doi and Woodhouse,[28] which revealed a statistically significant advantage for a single high (75 - 100 mCi) over a single low (30 mCi) dose.

We found higher success rate using high dose than low dose even in cases with low neck uptake i.e. less than 10 %, although the subgroup population were quite small and did not show statistic significance. The factors found to be associated with successful outcome are I-131 dose, baseline T4 and TSH, but not neck uptake and the others. Logistic regression analysis confirmed the significant influence of ablative dose on the outcome with 4 times more chance of success using the high dose rather than the low dose. Baseline serum T4 and TSH were also associated with successful ablation with 1.4 times more chance of success with each 1 unit (μg/dl) of T4 decrease and 1.2 times with 10 units (μU/ml) of TSH increase. This is likely due to good correlation between T4, TSH and the remnant mass, which was almost constantly reported to be the factor affecting ablation outcome.[10-12,29] Doi and Woodhouse[28] also showed that significantly greater proportion of patients were successfully ablated, either with high or low doses, if they underwent near-total as opposed to sub-total thyroidectomy with relative risk of 1.4. Neck uptake should also correlate well with the remnant mass, but it can be affected by other factors, especially iodide pool. Vermiglio *et al*.[18] reported high success rate in the patients from iodine-deficient area with neck uptake up to 30 %. They hypothesized that increasing uptake of radioiodine by thyroid remnants could result in overestimation of their sizes. Our patients were referred from many parts of the country, including iodine-rich seaside and iodine-deficient highland, thus there should be much variation in their iodide pools. Our data do not support tailoring the dose according to the baseline neck uptake, i.e., using the low dose with low neck uptake, as suggested by Hodgson *et al*.[30] and Logue *et al*.[31] As previously mentioned, their patients had obviously lower uptake and higher TSH than ours, which might explain the different results. Hodgson[30] adjusted the doses of 30-100 mCi for his patients with neck uptake up to only 8 %, using 2 % interval. Logue [31] used higher dose range with most of the patients receiving 100-150 mCi. The group with less than 5 % uptake had ablative dose of less than 100 mCi, but the exact or average dose for this group was not stated.

While we found significant correlation between TSH (also T4) and successful ablation, Muratet *et al.* [32] and Karam *et al*.[33] did not. This might be due to higher and less variation of TSH levels in their population, which were almost all higher than 50 μU/ml and 30 μU/ml in Muratet's and Karam's studies, respectively. Besides, they used uniformly high doses which might overcome the effect.

Our data revealed no influence of age, sex, tumor type, tumor size and baseline serum Tg on the successful outcome, similar to others.[12,19-22,32,33] There was no correlation of duration between surgery and I-131 ablation with the success. Thus, our timing should be adequate to stimulate maximum effectiveness of I-131 treatment with the average of 60 days and the minimum of 34 days after surgery. We used only 1 mCi of I-131 for diagnostic scan, believing there would be no clinical stunning effect.[34] Although quantitative study did show evidence of stunning, even with very low tracer doses.[35] As Hilditch *et al.* [36] suggested that stunning appeared to increase severity the longer the time interval between diagnostic and therapeutic doses up to 25 days. We found no evidence of this effect in our study, as diagnostic/therapeutic interval did not correlate with the success.

As we found significant higher efficacy of single high dose I-131 than single low dose for remnant ablation, the effect on long-term treatment outcome needs further study. We would not suggest that low dose I-131 for remnant ablation should be abandoned. It may be considered for low risk patients, i.e., young age patients with small papillary cancer, since benefit of I-131 remnant ablation in this group is questionable [37] and radiation burden and/or expense are in concerned.

Conclusion

According to our prospective randomized study in 138 differentiated thyroid cancer patients, high dose I-131 (100 mCi) is more efficient than low dose (50 mCi) for remnant ablation. Besides high ablative dose, lower T4 and higher TSH are also associated with successful ablation, this is most likely due to good correlation with remnant mass.

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