A RETROSPECTIVE STUDY ON POST- OPERATIVE THYROID REMNANT ABLATION IN DIFFERENTIATED THYROID CANCER BY I-131: COMPARISON BETWEEN SUCCESS OF LOW AND HIGH DOSE.

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ABSTRACT

The first and most important step in the management of differentiated thyroid carcinoma is to reduce the chance of recurrence and death. I-131 ablation represents the most specific anti-neoplastic measures in differentiated thyroid cancer. Ablation of thyroid tissue remnant with radioactive iodine (I-131) reduces the risk of recurrence and increases the survival rate.

We studied retrospectively thyroid remnant ablation with low and high dose of I-131 and compare their success. Total 54 patients of low-dose group treated with 20-50 mCi of I-131 and 159 patients of high dose group treated with 100 mCi of I-131 were included in this study. After first dose both group shows variable success (33% versus 62% low dose versus high dose respectively) but nearly similar success in both groups after second dose (81% versus 77% respectively).

From our study it can be concluded that the use of two low doses at 6-12 months interval could be an acceptable and effective method to ablate post-operative thyroid remnant, particularly the young subjects or in the situation of limited hospital bed.

Besides minimizing the whole body and gonadal irradiation exposure, the advantages are more convenience and reduce the expenses with a dose that can be given as an outpatient. In spite of all advantages the disadvantages are that about half of the patients will require more than one dose to ablate and delay in achieving complete ablation.

INTRODUCTION

The First and most important step in the post-operative management of patient with differentiated thyroid cancer is to analyze the factors that affect the risk of recurrence and death.

Post-operative thyroid remnant (POTR) of nonmalignant thyroid tissue always presents after surgery. I-131 treatment for post-operative thyroid remnant in differentiated thyroid cancer represents one of the more specific anti-neoplastic measures. I-131 has been used for more than half a century to ablate POTR following surgery. I-131 ablation probably decrease the risk of recurrence by destruction of microscopic metastases which are known to be present in both the opposite thyroid lobe and ipsilateral lymph

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nodes in 90% of patient with papillary thyroid cancer.[1] Upto 60% of all thyroid cancer and 80% of all differentiated thyroid cancer are treatable with I-131, after removal of most of the thyroid tissue with tumor.

Elimination of residual normal thyroid with its relatively high uptake of I-131 should increase uptake of I-131 in metastases by making more I-131 available to them.[2]

Patients with residual normal thyroid often have detectable thyroglobulin (Tg) even when TSH is totally suppressed while those who have undergone successful ablation usually have low or undetectable Tg, so then it become more sensitive in detecting recurrences in the later group.[3]

There is still much controversy regarding the optimal dose of I-131, required to achieve a successful ablation. Dose of 50-150 mCi are now customarily used to ablate thyroid remnant.

Regarding the efficacy of low dose ablation of POTR in patient with differentiated thyroid cancer, a variable success rate has been reported with empirical low dose therapy. The interest in using low dose lies in the prospect of out patient (OPD) treatment, attendant economy and convenience, decreased risk of leukaemogenesis and extra-thyroidal organ damage from lower whole body radiation exposure. These are among theoretical advantage and may be of special concern in young patients with better prognostic value.

MATERIALS AND METHODS

A retrospective study was done on two groups of patients of differentiated thyroid cancer, treated with low and high dose of I-131, who received I-131 ablation dose for POTR ablation at the Nuclear Medicine section of Radiology Department of Chulalongkorn University.

In the first group (group-A) the patients were treated with low-dose (20-50 mCi) of I-131 in the period of 1980-1988 and in the other group (group-B) the patients were treated with 100 mCi in the recent year of 1996-1999.

Patients included in the study were all had biopsy proven well-differentiated thyroid carcinoma, had history of total/subtotal or at least partial thyroidectomy, treated with I-131 for POTR ablation and had at least 12 months follow-up after ablation.

Patients excluded from the study are those who had inoperable local disease, loco-regional recurrence on presentation, histologic type other than papillary and follicular and those who had history of external radiation. Patients having distant metastases were also excluded but patient with capsular invasion and local lymph-node involvement were included and only one patient with mediastinal mass was included in the low dose group.

All patients performed I-131 whole body imaging after surgery to look for post-operative thyroid remnants (POTR) and metastases, about 6-8 weeks following surgery. This period allows time for the patient to recover from surgery, establishment of vascularity to the site of operation and for circulating T4 to fall to undetectable level and for any stable iodine used in the setting of surgery to be utilized or excreted. I-131 neck and whole body imaging was performed 48 hours after administration of a diagnostic dose (1-2 mCi) of I-131 using Gamma camera or rectilinear scanner. Post therapy scan were done usually on the 2nd to 4th day for low dose group and on the 5th -7th day on the high dose group.

The criteria for complete ablation considered in this study were the absence of any visible I-131 concentrating tissue on whole body scan with serum Tg of less than 10 ng/ml, after oral thyroxin was taken out from the maintenance doses.

A few days after I-131 ablation dose, patients were started on thyroxin which was taken until 6 week before the next follow up, when T3 will be started for another 4 weeks then no supplement for the last 2 weeks before performing the follow up scan. Patients were then advised to come after 6 months for follow up I-131 whole body scan and serum TSH, T4 and TG levels. Occasionally in few cases Tl-201 scan, 99mTc-MIBI scan, CT scan and CXR were done when Tg level and I-131 TBS were not correlating clinically.

Chi-square test was used to compare success rate of ablation in two groups.

RESULTS

Characteristics of subjects included into this study is presented in table 1. In group-A (low-dose group), total 54 patients were included, with the age range of 8-68 years, 13 male and 41 female, with histopathologic type of 19 papillary, 24 follicular, and 11 mixed cell type. Among these patients 34 had near total thyroidectomy (NTT), 16 had subtotal thyroidectomy (STT) and 4 had partial thyroidectomy, 14 patients had local lymph node metastases. Duration of follow-up ranges from 12 months to 16 years.

In group-B (high-dose group), total 159 patients were included, with age range of 17-84 years, 18 male and 141 female, with histopathologic type of 106 papillary, 29 follicular and 24 mixed cell type. All these patients have NTT and reported no local or distant metastases. Duration of follow-up ranges from 12 to 30 months.

There is marked difference in successful ablation of two groups after 1st dose (Table 4). On low dose group shows only 33.3% ablation success but in high dose group shows about 62.3% of ablation success after first dose which is significantly higher than the low dose group (p value < 0.005). On the contrary, the success rate of ablation in second dose is higher in low-dow dose group than high-dose group (72% vs 42%). After 2nd dose, the ablation success is nearly similar in both group (81.5% Vs 78.0% in low dose and high dose group, respectively, with p value > 0.1). But the average dose given to the patient, after 2nd dose, is significantly different in two groups, 103.07 mCi in low dose group and more than 200 mCi in high dose group.

In our study we tried to give more attention on those patient treated by low dose I-131, to find out the real success and the factors related to success or failure. Like other study on low dose trial, our study also shows good success related to young age and male patients. The patients of papillary cell type treated by low-dose show relatively less success (16%) after the 1st dose but significant success (90%) after the 2nd dose. In case of follicular cell type shows 41% success after the 1st dose and about 80% after 2nd dose but the success in mixed variety is relatively higher (45%) after the 1st dose but relatively lower (72%) after the 2nd dose (table 5).

In our study we have 14 patients with local (cervical) lymph node involvement on initial diagnosis and one of the patients had suspected mediastinal metastases. Out of these 14 patients, one patient was completely ablated by single dose (50mCi), showing no recurrence and 11 patients were ablated by two dose. Two patients need more than two doses.

Table 1. Details patient's characteristics

Patient's Profile	Treated by 20-50mCi (Group-A)	Treated by 100mCi. (Group-B)
Total patients :	54	159
Age range (years) :	8-68	17-89
< 40 years	36	88
> 40 years	18	71
Sex :		
Male	13 (24%)	18 (11.6%)
Female	41 (75.9%)	141 (88.4%)
Histopathologic types :		
Papillary	19 (35.18%)	106 (66.67%)
Follicular	24 (44.44%)	29 (18.23%)
Mixed (P+F)	11 (20.37%)	24 (15.10%)

Table 2 and 3 show variation in success according to the different patient characteristics.

Table 2. Status of patients treated by low dose of I-131

	Single Dose	Two Doses	> Two Doses
Total patients :	18	26	10
Age range (years) :	13-53	19-68	8-63
< 40 years	14 (77.8%)	17 (65.4%)	5 (50.0%)
> 40 years	4 (22.2%)	9 (34.6%)	5 (50.0%)
Sex :			
Male	5 (27.7%)	7 (27.0%)	1 (10.0%)
Female	13 (72.2%)	19 (73.0%)	9 (90.0%)
Histopathologic types :			
Papillary	3 (16.7%)	14 (53.8%)	2 (20.0%)
Follicular	10 (55.5%)	9 (34.6%)	5 (50.0%)
Mixed (P+F)	5 (27.8%)	3 (11.5%)	3 (30.0%)
Average Total Dose (mCi) ±	43.63	103.07	-
SD	±10.45	±24.78	
Recurrent	3 (16.6%)	8 (30.7%)	4 (40.0%)

Table 3. Status of patients treated by high dose of I-131

	Single Dose	Two Doses	> Two Doses
Total patients :	99	25	35
Age range (years) :	17-68	21-75	20-84
< 40 years	44 (44.4%)	13 (52.0%)	18 (52.4%)
> 40 years	55 (55.6%)	12 (48.0%)	17 (48.6%)
Sex :			
Male	11 (11.1%)	3 (12.0%)	3 (8.5%)
Female	88 (88.9%)	22 (18.0%)	32 (91.5%)
Histopathologic types :			
Papillary (total 106)	69 (69.7%)	15 (60.0%)	22 (62.9%)
Follicular	10 (55.5%)	9 (34.6%)	5 (50.0%)
Mixed (P+F) (total 24)	5 (27.8%)	3 (11.5%)	3 (30.0%)
Surgery :			
NTT	99 (100.0%)	25 (100.0%)	35 (100.0%)
STT	-	-	-
Partial thyroidectomy	-	-	-
Total Dose (mCi)	100	200	300

Table 4. Comparison of success of ablation between two groups of patients treated by I-131

Dose group	1st Dose ablation	2st Dose ablation	1st + 2stDose ablation	The rest of the patients
20-50 mCi (Group-A)	18/54 (33.3%)	26/36 (72.2%)	44/54 (81.5%)	10/54 (18.5%)
100mCi (Group-B)	99/159 (62.3%)	25/60 (41.7%)	124/159 (78.0%)	35/159 (22.0%)
P value	< 0.005		> 0.1	

Table 5. Comparison of success of ablation in different cell types between low-dose (A) and high-dose (B) groups.

Cell type	Patients' group	1st Dose ablation	2nd Dose ablation	1st + 2nd Dose ablation
Papillary	A (n = 19)	15.9 %	87.5 %	89.8 %
	B (n = 106)	65.0 %	40.5 %	79.2 %
Follicular	A (n = 24)	41.7 %	64.0 %	79.0 %
	B (n = 29)	62.0 %	45.4 %	79.3 %
Mixed	A (n = 11)	45.4 %	50.0 %	72.7 %
	B (n = 24)	50.0 %	46.7 %	70.8 %

DISCUSSION

Despite many controversies, I-131 has been used for nearly 50 years to ablate POTR as fundamental steps in the management of differentiated thyroid carcinoma to prevent risk of recurrence and death. Arguments in favor of I-131 ablation includes the existent, though low, mortality from differentiated cancer and it's known response to I-131,[4] the multicentric nature of the tumour,[5] the known recurrence in remaining normal thyroid[6] and the known association between differentiated and anaplastic cancer,[7] possibility of occult cervical lymph node metastases showing up after ablation,[8,9] and facilitation of follow up assessment[4,10] and improved survival in certain subsets.[11,12] Therefore thyroid remnant ablation should lead to low recurrence rate and improved chance of survival in the majority of patients.[13]

Because of wide variation in uptake and size of residual thyroid, no amount of radioiodine can ensure complete ablation. It appears that 30 mCi of I-131 can completely destroy the thyroid remnant in some patients while 150 mCi may not be sufficient in others. The radiation dose delivered to the thyroid remnant depends not only the number of mCi administration but also depends on the size of the remnant, the thyroid uptake and the effective half-life (T1/2 eff) of I-131 of the remnant.[2]

Before I-131 administration for whole body imaging, ablation or treatment of thyroid cancer, condition should be optimized so that uptake of I-131 is as high as possible. This will increase effectiveness of treatment, since doubling the uptake is equivalent to giving twice as much I-131.[2]

Differentiated thyroid carcinoma has receptor for TSH, but much less sensitive to being stimulated than normal thyroid follicular cells. Prior to whole body imaging, ablation or therapy, thyroid hormone should be discontinued to induce temporary hypothyroidism. Serum TSH should be determined before imaging or ablation to ensure that TSH is sufficiently elevated.[2]

The second major determinant of radioiodine uptake is the serum inorganic iodine concentration as it competes with I-131 to enter thyroid follicular cells at level of iodine trapping. An increase in number of inorganic iodine in blood decreases the uptake of radioiodine.

The most appropriate and effective dose

of I-131 for successful ablation of POTR is controversial. In different literatures variable dose recommendation from different authorities, ranging from 20-250 mCi, have been reported.[13-17] It was believed for a long time that higher initial I-131 doses are more effective in achieving complete ablation with a single dose.

There are some controversies about the appropriate approach, whether patients with POTR should be treated with series of empirical dose of I-131 or whether the dose should be individualized by careful dosimetry after appropriate tracer studies.

Some groups tried to quantitate the activity of iodine necessary to ablate residual thyroid. In delivering 30,000 rads (about 30 mCi), Maxon et al[18] achieved successful ablation in 81% of 70 patients, with no increase in success rate at higher doses.

McCowen et al[19] reported that doses of 80-100 mCi were not more effective than 30 mCi. Other retrospective studies confirmed similar findings.[13,20] In addition, various prospective studies have also shown that low dose I-131 ablation is as effective as high dose in achieving successful ablation by single dose.[16,17,21,22]

In 1995, Chandrsekhar et al reported the ablation rate of 63% at 19,800 cGy and increased to 77.8% at 31,372 cGy with no further increase ablation even at 130,200 cGy. Since thyroid malignancy is heterogenous in nature, it may harbour variable populations of relatively radio-sensitive and radio-resistant cells which may explain the observation. Most probable the radio-sensitive cells are killed first and leave the relatively radio-resistant cells in situ with sub-lethal damage. These sub-lethally damaged cells may behave in two ways: part of them becomes more susceptible to subsequent destruction due to a higher radiation absorbed dose and the remaining cells evolve in a true radio-resistant population. So even we increase the administered dose to the thyroid gland while the radio-sensitive cell population is constant, the radiation absorbed dose beyond 30,000 cGy is only going to increase the undue whole body radiation to the individual.

In our study we found lower success rate of ablation (33%) in low-dose group and relatively high success rate (62%) in high-dose group after the first dose. Interestingly after the second dose, the success ablation in both groups are similar (81% vs. 78%). The likely explanation for slightly lower success ablation after second dose in high-dose group as compared to low-dose group is that higher administered activity of I-131 yields a grater radiation dose which may produce changes in thyrocyte that can grossly shorten effective half-life and reduced the actual radiation dose to thyroid in subsequent therapy.

Our results show that by using low dose regimen we can reduce the average total I-131 dose to nearly half of high dose, therefore radiation exposure to the patient can be significantly reduced. Our results show that repeated low dose administration for thyroid remnant ablation is very useful and effective, where success rate is nearly similar to higher dose. It is believed that repeated low dose exposures allow the tissue repair mechanism to proceed in the interim period and it may cause less biological damage than the same total dose delivered to the patient as a single dose.[2]

Different studies discussed here showed some patients whose scan were borderlines at 6 months interval, become negative after observation for 12-18 months. Therefore it is suggested that a minimal or borderline positive scan at 6 months after first therapy dose is an indication of further observation rather than immediate further ablation dose. But patient with persistently positive scan after two successive low-dose, the subsequent dose should be increased.

Serum thyroglobin (Tg) is currently the most accurate way to detect recurrent thyroid cancer whether or not the patient is taking thyroid hormone. Most well-differentiated thyroid cancers but not the medullary or anaplastic cancers secrete Tg even if they do not concentrate radio-iodine. Under appropriate circumstances, serum Tg can be used as a tumour marker for persistent or recurrent well differentiated thyroid cancers.[24-30] Though in most of the patients of our study Tg correlated but few cases show raised Tg, without any detectable residual or metastatic focus in TBS. In those cases also Tl-201, MIBI or CT-scan were done and shows no detectable tissue or metastases. Interestingly most of the patient in this group shows decreased Tg value in subsequent follow-up in 12-18 Months without any treatment.

According to our study both papillary and follicular cell types show lower successful thyroid ablation in low-dose group as compared to high-dose group.

The advantages of low dose include avoidance of undue high radiation dose to some patients, decrease incidence of both early and late complications of I-131 therapy. Moreover low dose ablation is convenient and more economy since some patients can be treated as outpatients of which it is helpful for hospitals with limited beds.

In spite of all benefits of low dose, it's disadvantages should be considered as more than half of the patients required repeated dose, need longer time to achieve ablation and unrecognized metastases may be inadequately irradiated.

CONCLUSION

Considering all merits and demerits of low dose ablation it would be concluded that with empirical selection of suitable low-dose, patient selection, adequate patient's preparation and elimination of some factors to optimize the uptake of radioiodine will increase the effectiveness of low-dose ablation. We can therefore advocate the low dose as an alternative way for conservative and economic approach to thyroid remnant ablation in differentiated thyroid cancer. High dose should be reserved for cases with higher risk of recurrence and for treatment of metastases.

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