Original Article

A Randomized clinical Trial Comparing 50mCi and 100mCi of Iodine-131 for ablation of Differentiated Thyroid Cancers

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Abstract

Objective: To compare the efficacy of low (50 mCi) and high dose (100 mCi) Iodine-131 in ablation of differentiated thyroid cancer remnants.

Methods: Baseline serum thyroglobulin (sTg), thyroglobulin antibody (Tg Ab) and diagnostic whole body iodine scan with 2 mCi of I-131 were performed in each individual. After 6 months serum Tg, Tg Ab (of-thyroxin) and WB iodine scan with 10 mCi of I-131 were done to assess the efficacy of the low and high dose of I-131. Iodine ablative therapy (IAT) was considered successful (complete ablation) if the I-131 whole body scan was negative and sTg level was undetectable. In case of positive scan and/or sTg level detectable the patient was considered as unsuccessfully/partially ablated.

Results: In group A, (high dose) successful IAT was seen in 12/20 (60%) patients. Of these 5/7 (71%) had follicular Carcinoma on histopathology and 7/13 (54%) had papillary Ca. In group B, (low dose) successful IAT was seen in 8/20 (40%) patients, out of which 3/10 (30%) had follicular Carcinoma on histopathology and had successful IAT. 5/10 (50%) patients with papillary Carcinoma had successful IAT. As far as histopathology is concerned, in group A, response to high dose I-131 was better in follicular type than papillary type. Whereas in group B, response to low dose I-131 was better in patients with papillary type than follicular.

Conclusion: 100 mCi of radioactive Iodine-131 (I-131) is a more effective therapeutic dose than 50 mCi (I-131) in the treatment of differentiated thyroid cancer remnants. Furthermore, follicular Carcinoma respond better to 100 mCi I-131 than 50 mCi while papillary Carcinoma showed an almost equal response to both (JPMA 56:353;2006).

Introduction

The incidence of thyroid carcinoma is estimated at approximately 40 cases per million people per year in USA.[1] Differentiated thyroid cancers (DTC) occur more frequently than any other endocrine tumour, with an annual incidence of 1.2-2.6 per 100,000 males and 2.0-3.8 per 100,000 females. Prognosis depends on age, sex, tumour stage, histological type and initial treatment.[2] Papillary carcinoma of thyroid is much less aggressive than the follicular type. The overall 10-years survival after initial therapy of papillary thyroid carcinomas was found to range from 87% to 92%, whereas follicular carcinomas showed a range of 43%-94% depending on patient selection.[3] Thyroid cancers are more common in females, as is non-malignant thyroid disease, whereas these cancers are usually more aggressive in men.[4]

The indications and appropriate use of available treatment options i.e., surgery, radioactive iodine (RAI) treatment, and thyroid hormone supplementation have been subjects of controversy for many decades. Because of the protracted course of most thyroid carcinoma cases, it is extremely difficult to design a prospective randomized clinical trial evaluating the efficacy of radioactive iodine (RAI) treatment. Large retrospective series have clearly demonstrated a significant outcome benefit for both ablation and therapy with RAI. The early results of the National Thyroid Cancer Treatment Cooperative Study confirmed that postoperative RAI treatment was associated with improved cancer-specific mortality rates and disease progression in both papillary and follicular cancer.[5] However, there have been major and, as of yet, unresolved controversies in the management aspect of patients with differentiated thyroid cancers (DTC). The most important controversial issues are the extent of thyroidectomy and the indication and dose of RAI ablation therapy.[6] The objective of this study was to compare the efficacy of low and high dose I-131 therapy (50/100 mCi) in postoperative differentiated thyroid cancer with no distant or local metastasis.

Patients and Methods

Inclusion criteria for this study were differentiated thyroid carcinoma who had undergone total or near-total

thyroidectomy without any evidence of local or distant metastasis and serum thyroid stimulating hormone (TSH) above 30 iu/mL. Forty patients were included, who were randomly grouped into high dose i.e. 100 mCi (20 patients) and low dose i.e. 50 mCi (20 patients), labeled as A and B respectively.

Patients that were selected for the study were referred to the thyroid OPDs of Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN) and Atomic Energy Medical Centre (AEMC), Jinnah Postgraduate Medical Centre, Karachi. Pregnant or lactating females and patients with inadequate surgery were not included. All patients were informed about the procedure and informed consent was taken.

Thyroid scan with Technetium-99m pertechnetate and thyroid function tests were performed in all patients. A diagnostic whole body iodine scan (WBIS) with 2 mCi of radioactive Iodine-131 administered orally and after 48 hours whole body images were acquired using Sieman ECAM and Sopha DSX digital gamma cameras. A base line serum thyroglobulin level and thyroglobulin antibodies were also measured in all patients using immunoradiometric assay (IRMA) technique.

In a randomized fashion 50 mCi (low dose group) and 100 mCi (high dose group) of radioactive Iodine-131 was administered orally to 20 patients in each group. These patients were kept in isolation for sometime till the dose rate was less than 5 mR/hr at 1 meter distance. After 72 hours all patients were started on thyroxin suppression therapy (to keep TSH level <0.5 IU/ml).

After 6 months, in all patients thyroxin was stopped for 21 days and once serum TSH was more than 30 U/ml, serum thyroglobulin level with Tg antibodies and whole body iodine scan (10 mCi of I-131) were performed to assess the efficacy of high and low dose I-131 administered 6 months back. A detectable level of serum thyroglobulin level (= 2 ng/ml) and positive WBIS (iodine uptake in thyroid bed or elsewhere) were regarded as ablation failure. Similarly criteria for successful ablation were undetectable serum thyroglobulin level (=2 ng/ml) and a negative WBIS (no tracer deposition in neck or elsewhere).

Results

Forty patients were included in the study. Among them, 31 were female and 9 were male (M: F 1:2.99) with a mean age 38.3 (±11.7) years. In group A (100 mCi of I-131) out of 20 patients, 13 had papillary carcinoma (subgroup A1) while remaining 7 had follicular carcinoma (subgroup A2). Similarly in group B (50 mCi of I-131) histopathology revealed follicular carcinoma in 10 (subgroup B1) and papillary carcinoma in remaining 10 patients (subgroup B2).

Pre-ablative Technetium-99m pertechnetate and diagnostic whole body scan revealed residual functioning thyroid tissue varying from a small patch to large area over the thyroid bed. Similarly baseline serum thyroglobulin level was found in a range of 0.6 ng/ml to 60 ng/ml depending upon the mass of residual tissue. In all patients thyroglobulin anti-body was negative (with a cut of value of 30 IU/ml).

Six months follow up WBIS in group A (100 mCi of I-131) was negative in 14 and positive in 6.

In Group B (50 mCi of I-131) follow up WBIS was negative in 10 and positive in remaining 10. Their histopathological sub-grouping is given in Table.

Table. Follow up WBIS of group A and B.

	Group A		Group B	
	WBIS +ve	WBIS -ve	WBIS +ve	WBIS -ve
Papillary Ca	4	9	3	7
Follicular Ca	2	5	7	3
Total	6	14	10	10
	20		20	

Six month follow-up serum Thyroglobulin level in Group A (100 mCi of I-131) showed undetectable Tg level (i.e. < 2 ng/ml) in14/20 (70%) patients (7 with papillary ca. and 7 with follicular carcinoma) while it was in the detectable range (≥ 2 ng/ml) in remaining 6/20 (30%) patients. All 6 of them had papillary carcinoma.

Six months follow up serum thyroglobulin level in group B showed undetectable level in 11/20 (55%) patients (5 with papillary and 6 with follicular carcinoma) while it was in the detectable range in remaining 9/20 (45%) patients (5 with papillary. and 4 with follicular carcinoma).

Comparing the serum Tg and WBIS results in group A, complete concordance was noted in 12 (60%) patients with undetectable Tg and negative WBIS (successful ablation) while in 4 (20%) patients increased Tg was detectable with positive WBIS (ablation failure). Discordance was seen in rest of 4 (20%) patients with serum Tg detectable with negative WBIS in 2 (10%) and undetectable Tg with positive WBC in remaining 2.

Comparing the WBIS and serum Tg result in subgroup A1, complete concordance was noted in 5/7 (71%) patients with undetectable Tg and negative WBIS (successful ablation) while none of the patients had increased Tg with positive WBIS (ablation failure). Discordance was seen in 2 (10%) patients with serum Tg undetectable and positive WBIS.

Comparing the WBIS and serum Tg result in subgroup A2, complete concordance was noted in 7/13

(54%) patients with undetectable Tg and negative WBIS (successful ablation) and in 4 patients increase Tg was detectable with positive WBIS (ablation failure). Discordance was seen in rest of 2 patients with serum Tg detectable and negative WBIS.

Comparing the serum Tg and results in subgroup B, complete concordance was noted in 8 (40%) patients with undetectable Tg and negative WBIS (successful ablation) and in 7 (35%) patients increased Tg was detectable with positive WBIS (ablation failure). Discordance was seen in rest of 5 (25%) patients with serum Tg detectable and negative WBIS in 2 (10%) and in remaining 3 (15%), Tg was undetectable with positive WBIS.

Comparing the WBIS and serum Tg results in subgroup B1, complete concordance was noted in 3/10 (30%) patients with undetectable Tg and negative WBIS (successful ablation) and in 4 (40%) patients increased Tg was detectable with positive WBIS (failed ablation). Discordance was seen in 3/10 (30%) patients with serum Tg undetectable and positive WBIS.

Similarly in subgroup B2, complete concordance was noted in 5 (50%) patients with undetectable Tg and negative WBIS (successful ablation) and in 3 (30%) patients increased Tg was detectable with positive WBIS (ablation failure). Discordance was seen in rest of 2/10(10%) patients with serum Tg detectable and negative WBIS.

Discussion

Papillary and follicular thyroid cancers, together referred to as differentiated thyroid cancer (DTC), is usually curable when discovered at an early stage. The comprehensive management of DTC patients consists of surgery, radioactive Iodine-131 ablation and thyroxin suppressive therapy. There have been controversies in the management aspect of patients with DTC. The most important controversial issues are the extent of thyroidectomy and the indication and dose of radioactive Iodine-131 ablation therapy.[7]

The amount of radioiodine needed to achieve ablation of post-thyroidectomy functioning remnants is also a matter of debate, with estimates ranging from less than 30 mCi to 100-200 mCi.[8] Various therapeutic doses of I-131 have been used in treatment of DTC but which one is ideal for these patients is still debatable. Most physicians treat lesions visible on I-131 scintigraphy with a standard amount of radioiodine, usually 100 mCi.[9] Some prefer larger 131I doses to ablate thyroid tissue and to treat residual microscopic cancer. A meta-analysis found that a single administration of about 30 mCi failed to fully ablate the remnant (46%) more often than did 77-100 mCi (27%, P <0.001). There was, however, a wide range of failures among the low-dose cases due to the definition of ablation and variation in the extent to surgery.[6]

In this randomized trial, scintigraphic ablation (i.e. negative WBIS) was found in 70% patients treated with 100 mCi of ^{131}I (Group A) and 50% of patients treated with 50 mCi (Group B). Serum thyroglobulin level was undetectable in 70% population of Group A and 55% of patients of Group B. The overall vield of disease freedom (i.e. negative WBIS and undetectable thyroglobulin level) achieved in Group A was 60% and 40% in Group B. Many studies in literature detected complete ablation of the thyroid bed in 80% of patients treated with 30-50 mCi of ^{131}I, providing the surgeon had left small remnant of functioning tissue seen on a diagnostic WBIS using 2-3 mCi ^{131}I.[10,11] In a study published by Johansen K, et al., successful ablation of thyroid bed was noted in 81% of patients given 30 mCi and in 84% treated with 100 mCi of first dose of ^{131}I.[12] Another randomized study that administered fixed amounts of ^{131}I ranging from 25-200 mCi found that increasing the empirical dose to more than 50 mCi resulted in a plateau of the dose response curve, complete ablation occurred in 63% of the 30 mCi group, 78% of the 90 mCi group, and 77% of the 155 group.[10] Another study found a dose averaging 87 mCi of ^{131}I and ranging from 26-246 mCi that delivered at least 300 Gy was successful in ablating thyroid bed after a single initial ^{131}I administration in 84% of inpatients and in 79% of outpatients; administered activities low enough to permit outpatient therapy (i.e. <30 mCi) were used in 47% of the patients.[13] Importantly, the amounts of ^{131}I that deliver more than 300 Gy do not result in a higher ablation rate. Lower success rates were found when large pretreatment scanning doses were used, regardless of the therapeutic dose of ^{131}I and are attributed to thyroid stunning.[6]

The degree of radioiodine uptake depends upon the follicular element of the DTC. Follicular thyroid carcinoma can concentrate radioiodine and can be demonstrated scintigraphically. Mixed papillary-follicular carcinomas can also be demonstrated, and a high percentage of cancers classified histologically as papillary have sufficient follicular element to be visualized.[12] Comparing the histopathology and successful ablation, this randomized study shows that papillary neoplasm behaved almost similarly to 100 and 50mCi of I-^{131} i.e. 54%, 50% respectively but follicular cancers behaved much better to 100 mCi dose than 50mCi of I-^{131} i.e. 71% and 30% respectively. Review of the histopathology clearly demonstrate that follicular cancersof the thyroid are usually well differentiated and demonstrate a capability of taking up iodine, although the uptake of iodine is significantly less than that of normal thyroid follicular cells but majority of follicular cancers take up ^{131}I radioiodine at the time of presentation. It has also been shown by Mazaferri et al. that 50% of papillary carcinomas are also able to take up

and the presence of follicular elements on histology is an indicator of iodine uptake capabilities.[11] The reason for variable behaviour of follicular and papillary carcinomas to 100 mCi and 50 mCi of I-131 could be explained by the better uptake of iodine-131 by follicular Ca. resulting in optimal dose deliverance (about 300 Gy) to the residual functioning tissue.

Conclusion

We conclude that 100 mCi dose of radioactive Iodine-I-131 is more effective therapeutic dose than 50 mCi dose for the ablation of differentiated thyroid cancer remnants. Furthermore, follicular carcinoma responds better to 100 mCi I-131 than 50 mCi while papillary carcinoma shows an equal response to both.

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