

# Reduction in relapse rate of radioiodine therapy in patients of toxic multinodular goiter: A quality improvement project

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## ABSTRACT

**Introduction:** Radioiodine (I-131) therapy is the definitive treatment of toxic multinodular goiter (TMNG). Treatment failure may result in relapse after I-131 therapy. The present study was undertaken to reduce treatment failure rate of I-131 therapy in TMNG patients. **Materials and Methods:** Multiple causes may have led to treatment failure of I-131 in TMNG patients making it difficult to establish a direct cause–effect relationship and take corrective action. Therefore, the JURAN methodology of quality improvement was applied. The treatment failure rate in 80 TMNG patients treated with I-131 in the period 2003–06 was 29%. The root cause analysis identified delay in decision to radioablate and concomitant antithyroid drugs (ATD) with I-131 therapy as factors leading to relapse. In 2007, a change in management was introduced with decision to radioablate all TMNG patients not remitting at 1 year of ATD and to withdraw ATD for 2 weeks prior to I-131 therapy. A total of 63 patients of TMNG followed the changed protocol between 2007 and 2009. Further analysis showed that one of the factors identified in the initial brainstorming (high iodide pool in the patient) had not been addressed in the protocol currently followed. The protocol was modified to include patient preparation and implemented after standardization. **Results:** The post-I-131 relapse rate in patients treated after implementation of the new protocol from 2007 to 2009 was 18% which further reduced to 16% in 2011 after modification of the protocol. **Conclusion:** The failure rate of I-131 therapy in TMNG reduced from 29% to 16% through standardization of the treatment procedure achieved by the use of Juran Methodology that helped to identify process-related defects.

**Keywords:** Juran methodology, radioiodine therapy, relapse, toxic multinodular goiter

## INTRODUCTION

Radioiodine (I-131) is the definitive therapy for hyperthyroidism. The reported failure rate after I-131 therapy in toxic multinodular goiter (TMNG) varies from 12% to 20%.<sup>[1,2]</sup> Antithyroid drugs (ATD), both Methimazole and Propylthiouracil, are used in the first-line treatment for hyperthyroid patients. The influence of ATD on I-131 therapy has however been a matter of controversy. In a systematic review and meta-analysis, Martin A Walter concludes that “given in the week before or after radioiodine, ATD increase the failure rates and reduce the hypothyroidism rates.”<sup>[3]</sup> Some authors describe no effect of ATD

on treatment failure rates.<sup>[4]</sup> While ATD is obviously beneficial, it may have radio protective properties on the thyroid gland and cause a high failure rate following I-131 therapy.

On retrospective data analysis, a relapse rate of 29% at 1-year post-I-131 therapy was seen in TMNG patients treated with I-131 in our hospital during the period 2003-06.

## MATERIALS AND METHODS

The study was carried out in the Thyroid Clinic of an 890-bedded industrial hospital that receives referrals from within and outside the hospital.

Since the relapse rate in TMNG could be influenced by a number of established or unknown factors, the Juran methodology of problem solving and continuous improvement was used to tackle the problem.

The Juran Methodology of Quality Improvement<sup>[5]</sup> consists of

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the Plan-Do-Check-Act (PDCA) cycle [Figure 1]. The steps in the PDCA cycle are as follows:

**PLAN**

- Diagnose the root cause of a problem
- Plan remedial measures to address the root cause

**DO**

- Implement preferred solution

**CHECK**

- Monitor results

**ACT**

- Standardize process to ensure irreversibility.

**Team formation**

A cross-functional team of doctors from Departments of Medicine and Nuclear Medicine, who were the primary physicians for hyperthyroid patients, was constituted to address the problem through a Quality Improvement Project (QIP).



Figure 1: PDCA cycle

	Proof of need	Identify problem with identification of present status
PLAN	Diagnostic journey	Study current situation Collect data on present status Determine goals to be accomplished Decide data of completion Analyze problem Identify possible causes Shortlist likely causes Isolate root cause (s)
DO	Remedial journey	Implement solution for the identified root cause List possible solutions Select preferred solution with justification Implement preferred solution
CHECK		Check and monitor results
ACT	Holding the gains	Standardize improvement If goals have been met, standardize solutions If goals have not been met, steps 2–4 are repeated Establish future plans Review the whole process Identify the next problem

The problem statement or the proof of need was “an unacceptable relapse rate following I-131 therapy in TMNG patients at Tata Main Hospital.”

**PLAN phase**

The first step in the plan phase was to quantify the problem.

A retrospective data analysis of 80 patients treated with I-131 in the period 2003-2006 showed a treatment failure rate of 29%.

The relapse rate at 12 months (expressed as % of total patients of TMNG treated with I-131) was used as the performance measure for quantifying improvement.

The next step was to undertake a diagnostic journey to establish the root cause of the high relapse rate of I-131 therapy in TMNG. In the Juran methodology, this is done by considering all possible contributory causes, short-listing the most likely causes and then isolating the root cause.

Identification of possible causes was done through a brainstorming session with the team members. The listed causes were grouped under the heads of Man, Medicine, Method and Disease [Figure 2].

Analysis of past data for the factors identified in the brainstorming (age, sex, disease duration, dose of radioiodine, adjuvant ATD) was done. There was no statistical difference for these factors in the relapse and remission subgroups of the group A patients (n = 80) [Table 1]. However, the average disease duration in the relapsed patients was 55.3 months and 39.7 months in patients who did not. Also 64% of the relapsed patients had continued to receive ATD in the week preceding radioiodine therapy whereas this was only 27% in patients who did not relapse.

The probable causes of relapse identified on data analysis were as follows:

- Longer disease duration with delay in decision for radioiodine therapy
- Adjuvant ATD with I-131 therapy; ATD was either not withdrawn or withdrawn for 5 days or less before I-131 therapy.

To confirm that these were the root cause, the hypothesis was tested by evidence (Testing of Theories). Adjuvant ATD with radioiodine therapy as a factor for relapse was supported by the work of Walter, *et al.*,<sup>[3]</sup> whereas it was refuted by Braga, *et al.*<sup>[4]</sup> Data in the present study [Table 1] supported this as a valid factor.

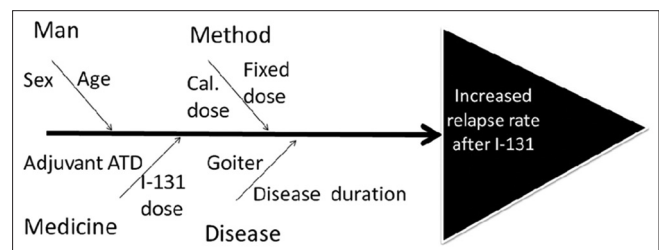


Figure 2: Cause-effect or the Fishbone diagram

The evidence supporting delay in treatment with radioiodine as a possible factor was the higher percentage of relapse in advanced disease.

Therefore, literature and objective evidence established delay in decision for radioiodine therapy and adjuvant ATD with I-131 therapy as valid root causes for relapse following I-131 therapy.

### DO phase (implementation of solution)

The root causes identified were delay in definitive therapy with I-131 and continuation of adjuvant ATD therapy in the week before I-131 was given.

The remedial steps taken to address these were the following:

1. Early decision for definitive therapy with I-131: For closer monitoring, diagnosed TMNG patients were referred to the specialty Thyroid Clinic in the Department of Nuclear Medicine. A thyroid card was developed to keep track of the total duration that the patient was on ATD and record the serial thyroid function reports. Carbimazole was given in dose varying from 30 mg to 60 mg daily and titrated to the TSH level and assayed every 3 months. Between 10 and 14 months, ATD was tapered and stopped and patient reviewed after eight weeks. If patient continued to show clinical features of toxicity, a decision to treat with radioiodine was taken.
2. Discontinuation of adjuvant ATD before I-131 therapy: ATD was withdrawn for one to three weeks before I-131 was given.  $\beta$ -blockers were continued and the patients were closely monitored in case severe toxic symptoms developed. Patients unable to tolerate ATD withdrawal were restarted on Carbimazole. Radioiodine was given as a fixed dose regime, in a dose varying between 7.0 and 8.5 mCi. The patients were prescribed  $\beta$ -blockers for a month following radioiodine. Total  $T_4$ , TSH were assayed at six weeks and twelve weeks to assess thyroid function status. Patients who showed symptoms of hypothyroidism with a TSH > 10.0  $\mu$ IU/ml were started on replacement Thyroxine in appropriate dose. A second dose of I-131 was considered if patient did not show remission post-I-131 at 12 months.

### Check

The average disease duration before I-131 therapy and the relapse rates were monitored after the implementation of the new protocol. The average disease duration reduced to 33.2 months, but the SD remained high because a number of patients with a long history of pre-existing disease but presenting to Thyroid clinic for the first time were also included in the study.

Though the relapse rate reduced to 19% from the initial 29% after 2 years of implementation of the new protocol, it was still significantly high at 19% [Table 2].

Therefore a 2<sup>nd</sup> PDCA cycle was undertaken.

A relook at the initial Cause effect diagram [Figure 2] showed that one of the possible causes (patient preparation) had not been addressed in the remedial action [Figure 3]. Dietary iodine may increase the “cold” iodine pool in the patient which may interfere with the thyroid uptake of I-131.

The protocol for patient preparation was modified to follow the recommended practice in postthyroidectomy I-131 ablation in differentiated thyroid cancer.<sup>[6]</sup> As part of patient preparation, patients of differentiated thyroid cancer undergoing radioiodine ablation are advised to reduce dietary intake of iodine and avoid iodine containing topical preparation. The same practice was adopted as part of patient preparation before radioiodine therapy for TMNG.

### Act

The protocol was standardized by enumerating each task, fixing responsibility and reviewing the outcome at fixed intervals. A Standard Operating Procedure (TMH/PROC/COP/NMU/01) was written and controlled in the Document Control System of the hospital.

Patients were followed up clinically and with total  $T_4$ , TSH assay every 3 months to record their thyroid function tests. Patients not showing remission at one year post-I-131 therapy were given a second dose of I-131.

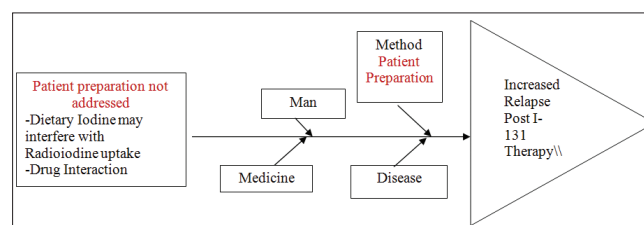


Figure 3: Relook at the cause effect diagram

Table 1: Analysis of past data (2003-2006) group A, n=80

Factor	Relapse group (29%) n=25	Remission group (69%) n=55
Mean age (years)	46.6	48.4
% Female	64	72
Average I-131 dose (fixed) in mCi	7.6	7.8
Average disease duration before I-131 given (months)	55.3	39.7
ATD not withdrawn before I-131 therapy	64%	27%

Table 2: Comparison of disease duration and relapse rates after implementing the changed protocol

Factor	Group A (2003-06) n=80	Group B (2007-09) n=63
Mean age (years)	47.9±9.8	44.9±11.2
% Female	70	63
Average I-131 dose (fixed) in mCi	7.76±1.12	8.43±2.1
Average disease duration before I-131 given (months)	44.6±25.7	33.2±23.5
Relapse rate	29%	19%

Patients who became hypothyroid were started on Thyroxine replacement in appropriate dose.

### Observation

Retrospective data analysis of patients treated with I-131 in the period 2003-06 (group A,  $n = 80$ ) [Table 3] was done to compare age and sex, duration of disease, dose of I-131 and use of adjuvant ATD in the week preceding I-131 therapy in patients who showed remission and those who relapsed post-I-131. The age and sex distribution was comparable in both groups of patients. The overall average duration of disease was  $44.6 \pm 25.7$  months. In patients who relapsed, it was 55.3 months and 39.7 months in those who showed remission. 64% of patients who relapsed had continued to receive ATD in the week preceding I-131 therapy, only 27% of patients had done so in the group that showed remission.

Group B ( $n = 63$ ) [Table 3] consisted of patients treated with I-131 from 2007 to 2009, who followed the new protocol that did not include dietary restrictions as part of patient preparation. The age and sex distribution and the dose of I-131 in groups A and B were comparable [Table 2]. The disease duration before radioiodine was given was  $44.6 \pm 25.7$  months in group A and  $33.2 \pm 23.5$  months in group B.

The incidence of relapse at 12 months post-I-131 was 29% in group A and 19% in group B.

Group C ( $n = 64$ ) consisted of patients treated in 2010-11 in whom the newly established standard operating protocol was followed [Table 4]. Six patients could not tolerate ATD withdrawal and the protocol was not followed in them.

The average disease duration before I-131 therapy in group C was 14.4 months and the relapse rate was 16%.

## DISCUSSION

The meta-analysis of Walter, *et al.*,<sup>[3]</sup> included 14 randomized control trials on the effect of ATD on radioiodine therapy in hyperthyroidism. The trials included were conducted over a period of 54 years. Five of these were conducted on patients of TMNG; the rest were on patients with Grave's disease. All trials except one included both men and women and the mean age of the patients ranged from 37 to 60 years. The median

**Table 3: Comparison of outcome after implementation of modified protocol**

Parameter	Past data 2003-06 group A $n=80$	Remedial journey 2007-09 group B $n=63$	Holding the gains 2010-11 group C $n=64$
Disease duration in months before I-131 given	44.6	33.2	14.4
Relapse rate	29%	19%	16%

range of radioiodine ranged from 188 to 585 MBq (5.0-15.0 mCi). Some trials used Methimazole, others PTU or both, together with beta-blockers. Five trials gave ATD before I-131, seven with I-131 and two, after. When used before I-131, it was withdrawn in the control group for a maximum period of 7 days before I-131 administration. There was no difference in treatment effects for different discontinuation intervals of ATD. Trials using fixed dose regime showed a higher risk of failure compared to those in which uptake based calculated dose was used.

The summary risk ratio of treatment failure of I-131 with the use of adjunctive ATD compared to control was 1.28.<sup>[3]</sup>

The present study included patients of TMN goiter only. Failure of treatment was defined at 12 months follow-up. The study included both males and females and the mean age of patients was 44.9 years. Methimazole was the only ATD used and fixed dose regime was used in all patients. ATD was withdrawn for a period ranging from 7 days to 21 days. In 82% of patients, ATD was withdrawn for 21 days. None of the trials quoted in Walter's study had followed the patient preparation protocol of radioablation in Ca thyroid patients. Also, duration of disease as a factor contributing to treatment failure had not been considered in any study.

The treatment failure rate due to radioiodine in TMN goiter reduced from 30% to 19% by withdrawing ATD for a longer period (7-21 days) before radioablation. It further reduced to 12% by reducing the "cold" iodine pool in the patient through restricting intake of iodine-rich food and medicines.

Standardization of the treatment regime was done through application of basic quality improvement tools.

### Limitations of the study

The effect of ATD withdrawal on rate of hypothyroidism

**Table 4: Defining the standard operating protocol for treatment of TMNG with I-131**

Step	Responsibility	Record	Review
Diagnosis of hyperthyroidism	All clinical departments	TSH, thyroid scan	
Referral to thyroid clinic	All clinical departments		
Registration in thyroid clinic and start ATD	Specialist, NM	Patient details in thyroid card	Monthly
Withdrawal of ATD at 1 year	Specialist, NM	Instructions in thyroid card	Monthly
TSH after 2 months	Specialist, NM	TSH in thyroid card	
Appointment for I-131 therapy if relapse	NM Technologist	Time to I-131 therapy	Monthly
Instructions for patient preparation	NM Technologist	Patient instruction leaflet	
Radioiodine given in fixed dose	NM Technologist	Dose in thyroid card	
Follow-up in thyroid clinic	Specialist, NM	Thyroid card	

following radioiodine has not been studied. Also, the study has not considered the effect of ATD in the week following radioiodine therapy on subsequent treatment failure.

The measurement of urinary iodide is required to provide objective evidence of reduction in “cold” iodide pool by dietary restriction.

## CONCLUSION

The relapse rate of radioiodine therapy in TMN goiter reduced from 29% to 16% through standardization of the treatment protocol.

The use of PDCA cycles helped to identify delay in decision to treat with radioiodine and adjuvant ATD as possible factors leading to increased treatment failure of radioiodine. Correction of these process-related factors through a standard operating procedure helped to reduce radioiodine treatment failure in TMN goiter.

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