

# Treatment Response following Radioactive Iodine Therapy in Miliary versus Macronodular Pulmonary Metastases in Papillary Thyroid Carcinoma

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## Abstract

**Background** Pulmonary metastases in papillary thyroid carcinoma have two common presentations—micro/miliary (MM) and macronodular metastases (MN). The mainstay of treatment, posttotal thyroidectomy, is multiple radioactive iodine ablations (RAIA) every 6 to 12 months. Response assessment is determined by decline in stimulated serum thyroglobulin levels (sTg), disease regression on chest x-ray (CXR), computed tomography thorax, or whole body iodine scintigraphy (TWBS).

**Aim** This study aims to assess the difference in response to RAIA based on the pattern of presentation.

**Methodology** Retrospective analysis of patients from January 2008 to July 2017 was done. Patients with pulmonary metastases treated with RAIA (3700MBq per therapy as opposed to the American Thyroid Association recommendation of 7400MBq per therapy) and a minimum follow-up of 8 months were included. The initial and the final sTg, TWBS, and CXR were analyzed for both groups. Final outcome in terms of complete response, disease regression, static disease, and disease progression was determined.

**Results** Of the total of 1,793 patients, 71 were included. There were 43 females and 28 males. The median age was 39 years and the range was 14 to 79 years. Forty-five (63.3%) patients had MM and 26 (36.6%) patients had MN disease. The average number of therapies was three and maximum follow-up period was 15 years. Of the 45 MM patients, 1 had progression, 7 were static, 23 had regression, and 14 had complete response. Of the 26 MN patients, 22 had progression, 2 were static, 1 had regression, and 1 had complete response.

**Conclusion** MM metastases, when compared with MN disease, respond to RAIA with a better outcome. In addition to achieving comparable response with a lower dose per therapy, there were no radiation-related long-term complications reported.

## Keywords

- ▶ lung metastases
- ▶ papillary thyroid carcinoma
- ▶ micronodular
- ▶ macronodular

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## Key Message

Response to radioactive iodine ablation (RAIA) in lung metastases of papillary thyroid carcinoma (PTC) depends on the pattern of presentation. Those with micro/miliary (MM) metastases show significant disease regression and have a favorable outcome due to increased ability to concentrate the radioactive iodine, compared with those with macronodular (MN) lung metastases. Lower dose regime will suffice in achieving the desired therapeutic response.

## Introduction

### Distant Metastases in DTC

The age- and gender-adjusted incidence of differentiated thyroid cancer (DTC) is noted to be increasing in all ethnicities.<sup>1</sup> The disease is often confined to the thyroid gland due to its slow growth. Involvement of the regional lymph nodes is the most common presentation of local metastases.

The incidence of distant metastases at presentation is infrequent and ranges between 3 and 15%.<sup>2</sup> The occurrence during subsequent follow-up visits is 6 to 20%.<sup>3</sup> Common sites of distant metastases are the lungs, followed by bones and rarely in the brain, spine, and kidneys. Although the cure rates are high in DTC, the presence of these distant metastatic diseases is the primary cause of thyroid cancer-specific mortality.<sup>4</sup>

### Pulmonary Metastases—Diagnosis and Management

Lung metastases are the most common site of distant metastases with an incidence of 2 to 20%.<sup>5</sup> Most patients are asymptomatic at presentation, while few present with dyspnea and hemoptysis. Often they are incidentally picked up on diagnostic imaging and are misdiagnosed as primary lung cancer.<sup>6</sup>

Patients are infrequently diagnosed with lung metastases on chest x-ray or diagnostic computed tomography (CT) during preoperative workup for total thyroidectomy with or without neck dissection. Postoperatively, they are referred for follow-up to the nuclear medicine physician. Adequate thyroid stimulating hormone (TSH) stimulation (TSH > 30 uIU/mL) by either withdrawal of LT4 supplements for 4 weeks or by recombinant TSH injection is ensured. Diagnostic workup in terms of serum thyroglobulin (sTg), chest x-ray (CXR), and diagnostic whole body iodine scintigraphy (TWBS) is done.<sup>5</sup>

Lung metastases are noted to have two types of patterns—miliary or MN.

A) Miliary/micronodular metastases (MM) are detected most frequently on TWBS appearing to have diffuse uptake bilaterally and may have normal CXR in half the cases, as lesions less than 1 cm are below their spatial resolution. CT thorax is utilized to increase the diagnostic accuracy and may reveal multiple miliary nodules ranging from 1 to 4 mm.<sup>6</sup> It may be a close mimicker of pulmonary tuberculosis in our scenario (see ►Fig. 1).

B) MN metastases appear as foci of uptake on the TWBS. They are larger in size, may be single or multiple on CXR and CT thorax. The radiological size of the nodule is more



**Fig. 1** Miliary lung metastases (x-ray).

than one cm.<sup>7</sup> However, detection of central micronodules on CT thorax is challenging as it is undistinguishable from adjacent vessel structures compared with peripheral nodules<sup>8</sup>(see ►Fig. 2).

RAIA with I-131 is the mainstay of treatment.<sup>9</sup> However, some lung lesions may be dedifferentiated and non-I-131 avid on TWBS but may be picked up on CT thorax or 18F-fluorodeoxyglucose positron emission tomography (F18 FDG PET) CT.<sup>10</sup> FDG PET and <sup>131</sup>I scintigraphy provide complementary information for the metastatic lung lesions.<sup>11</sup>

Several studies have proposed multiple prognostic factors. Few of them include older age at diagnosis, elevated sTg, multiple sites of metastases, and <sup>131</sup>I nonavidity in the lesions on TWBS.<sup>12</sup>

To analyze the difference in treatment response to RAIA in patients based on the pattern of lung metastases, this retrospective study was done in our population.

## Methodology

Retrospective analysis of patients who visited the nuclear medicine outpatient department from Jan 2008 to July 2017



**Fig. 2** Macronodular lung metastases (x-ray).

**Table 1** Age and gender distribution

Age distribution (y)	Men	Women
< 30	5	15
30–50	14	21
> 50	9	7

was done. All of them were diagnosed with PTC and had undergone total thyroidectomy with or without neck dissection.

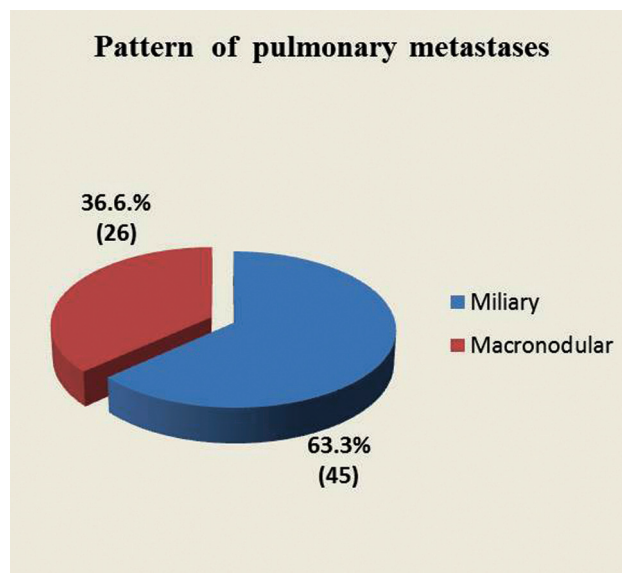
Of these, patients with pulmonary metastases (diagnosed on CXR/TWBS or CT thorax) who were treated with RAI (3700MBq in our setting) and having a minimum follow-up of 8 months were included in the study. Adequate TSH stimulation (TSH > 30 uIU/mL) was achieved by either withdrawal of LT4 supplements for 4 weeks or by recombinant TSH injection. F-18 FDG PET/CT was not done as a part of the routine workup.

They were divided into two groups based on the nodular pattern of pulmonary metastases—miliary and MN. Nodules were classified as “Miliary” when the metastases demonstrated a diffuse uptake on TWBS, which were or were not evident on CXR. “Macronodular” nodules showed discrete foci of uptake of approximately more than 1 cm in size and single or multiple in presentation as noted in the CXR and TWBS. As CT thorax was not performed in all patients, exact size and number of the nodules were not assessed in all patients. The dosimetry and uptake of the metastases on the TWBS were not quantified in all the patients. The sTg, TWBS, and CXR at initial presentation and at the final visit for both groups were analyzed. Based on the biochemical, scintigraphic, and radiological response, they were categorized as complete response (CR), partial response (PR), static disease (SD), and disease progression (DP). The response was termed CR, when the TWBS showed no evidence of functioning lung metastases and sTg was negligible (i.e., < 2 ng/dL) and CXR and/or CT thorax was normal. The response was defined as PR when there was decrease in sTg from the initial value with decrease in disease burden on the TWBS. When there was no significant change in the disease burden biochemically (sTg) and scintigraphically (on TWBS), it was SD. Disease was classified as PD if there was a biochemical elevation in Tg or an increase in disease burden clinically, radiologically, or scintigraphically. Even an isolated elevation in any of the above factors was termed PD.

**Ethics:** This study was approved by the Institutional Review Board and Ethics Committee.

## Results

A total of 1,793 patients visited the outpatient department during the study period from January 2008 to July 2017. Of these, 71 patients (3.95%) fulfilled the inclusion criteria. There were 43 females and 28 males. The median age was 39 years and the range was 14 to 79 years. There were 20 patients under the age of 30 years, 35 between the ages of 30

**Fig. 3** Distribution of lung metastases.

and 50 years, and 16 patients above 50 years (→ **Table 1**). Metastases to other sites such as the bone and brain were noted in 14 patients.

The number of RAI therapies ranged from 1 to 7 with an average of three therapies. The dose per RAI was 100mCi (3700MBq), as per our institutional protocol. Repeat therapies were offered every 6 to 12 months for patients with significant disease burden in terms of elevated sTg and I-131 avid lung lesions on TWBS. The follow-up period ranged between 8 months and 15 years.

Forty-five (63.4%) patients had MM and 26 (36.6%) had MN disease (→ **Fig. 3**; → **Tables 4** and **5**). Of the 45 MM patients, 1 had progression, 7 were static, 23 had partial regression, and 14 had CR (→ **Table 2**; → **Fig. 4**). Of the 26 MN patients, 22 had progression, 2 were static, 1 had partial regression, and 1 had CR (→ **Table 3**; → **Fig. 5**). Among those 14 patients with other distant metastases, 1 had partial response, 2 had SD, and all the rest had DP.

From our study, it is evident that the pattern of the pulmonary metastases determines the treatment outcome and the prognosis (→ **Fig. 6**). Miliary or micronodular metastases have a better response to iodine therapy. In the post-ablative follow-up period, CR was observed in 14/45 (31.1%) patients with miliary metastases and in only 1 patient with MN metastases. Partial response was noted in 23/45 (51.1%) patients with miliary and only in 1 patient with MN metastases (0.03%). Biochemical, scintigraphic, and radiologic evidence of DP was observed in only 1 patient with miliary metastases but 22/26 patients (84.6%) with MN metastases.

## Discussion

The current study was aimed to assess the determinants that influence treatment response following iodine therapy in lung metastases from PTC.

In our study, it was noted miliary/micronodular pulmonary metastases (63%) had a higher incidence than the MN

**Table 2** Clinical characteristics of patients with miliary lung metastases

S. no.	Gender	Age	Biopsy	Other distant metastases
1	F	27	FVPTC	Nil
2	M	49	PTC	Nil
3	M	16	PTC	Nil
4	M	16	PTC	Nil
5	M	23	PTC	Nil
6	F	41	PTC	Nil
7	F	24	PTC	Nil
8	F	24	PTC	Nil
9	M	60	FVPTC	Nil
10	M	39	FVPTC	Nil
11	F	26	PTC	Nil
12	M	47	PTC	Nil
13	F	25	PTC	Nil
14	F	22	PTC	Nil
15	F	67	FV	Bone
16	F	48	PTC	Nil
17	F	28	PTC	Nil
18	F	43	PTC	Nil
19	F	14	PTC	Nil
20	M	30	FVPTC	Nil
21	F	38	PTC	Bone
22	M	35	PTC	Nil
23	F	34	PTC	Nil
24	F	31	PTC	Nil
25	F	28	PTC	Nil
26	M	32	PTC	Nil
27	M	44	PTC	Nil
28	F	19	PTC	Nil
29	M	16	PTC	Nil
30	M	46	PTC	Nil
31	M	46	PTC	Nil
32	M	47	PTC	Nil
33	M	58	FVPTC	Nil
34	F	37	PTC	Bone
35	M	31	PTC	Nil
36	F	35	PTC	Nil
37	F	30	PTC	Nil
38	F	26	PTC	Nil
39	M	54	PTC	Nil
40	F	27	PTC	Nil
41	M	28	PTC	Nil
42	F	34	PTC	Nil

(Continued)

**Table 2** (Continued)

S. no.	Gender	Age	Biopsy	Other distant metastases
43	F	46	PTC	Nil
44	F	25	FVPTC	Nil
45	F	26	PTC	Nil

Abbreviation: FVPTC, follicular variant of papillary thyroid carcinoma.

pattern (37%). This was also noted in a study by Song et al in 372 patients with lung metastases, in which CT thorax was negative in 7.53%, micronodular in 84.14%, and MN (> 1 cm) in 8.33% of the patients.<sup>7</sup> This may be attributed to the fact that lymphatic spread from PTC causing micronodular metastases is more commonly seen than hematogenous spread that causes MN metastases.

Similar results were published by Song et al. In 372 patients with lung metastases, the median cumulative radioiodine dose was 18.315 GBq (495 mCi) with a range of 3.7 to 86.95 GBq (100–2350 mCi). He observed that significant decrease in Tg was observed in those with “miliary” pattern. In addition, CR was noted in 24 patients with a negative chest CT examination at discovery of pulmonary metastases, 36 with micronodular, and 2 with MN metastases. The 10-year survival rate was 90.9% and only 30.6% in miliary and MN metastases, respectively.<sup>7</sup>

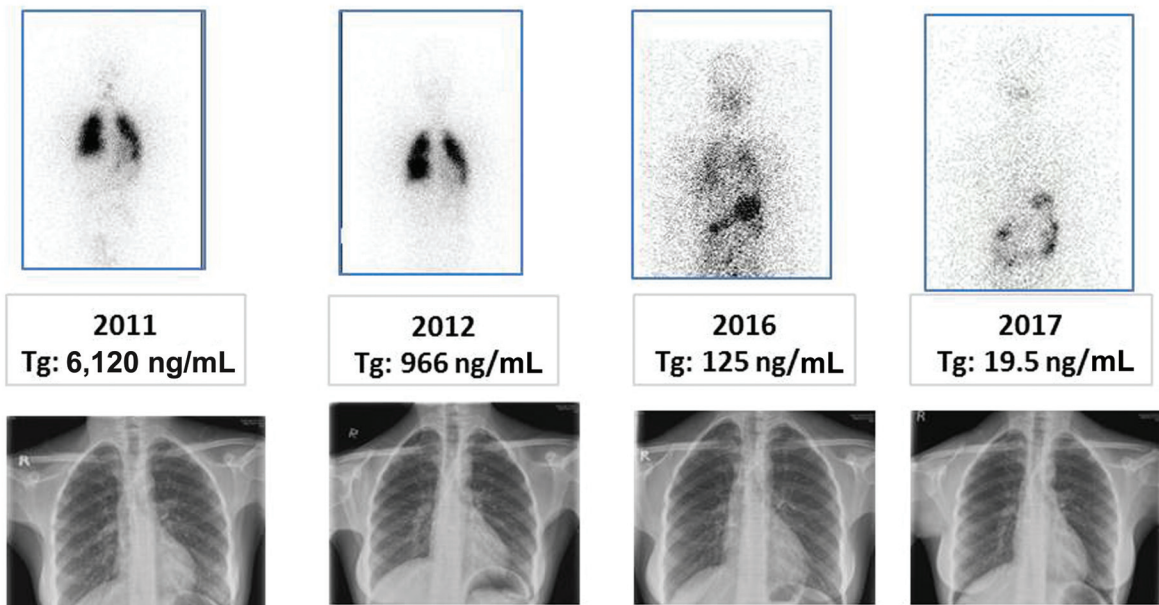
Similar outcome was noted in a study in 107 patients with lung metastases by Chen et al; results confirmed that those with pulmonary nodules  $\geq 1$  cm had a reduced likelihood of achieving remission.<sup>13</sup>

The iodine avidity of the lesions was also found to influence the treatment outcome in our study. The degree of I-131 uptake was found to be higher in miliary metastases. Similarly, Casara et al highlighted that following I-131 therapy, micronodular metastasis had a good prognosis.<sup>14</sup> The highest therapeutic efficacy of I-131 therapy in small sized lesions can be attributed to the short range of  $\beta$ -radiation (0.08–2.3 mm).<sup>15</sup> He attributed it to higher radioiodine uptake than MN lesions.

From our study, it was noted that few of the MN lesions did not accumulate I-131, leading to poor treatment response. According to Ronga et al, I-131 avidity of the lesions is the most important factor that positively influences the survival time. He also concluded that RAI with high cumulative dose of I-131 leads to complete recovery and higher survival time.<sup>16</sup> Kim et al also suggested that complete remission was achieved in 5.7% of cases that had nonvisualizing or micronodular lesions on chest CT and demonstrated radioiodine avidity on TWBS.<sup>17</sup> In I-131 nonavid pulmonary lesions, the efficacy of RAI is limited and the outcome is poor.<sup>12</sup>

It was also evident that individuals in the younger age group had a better outcome. On the contrary, the poor prognosis was noted in older patients. Chen et al made a similar conclusion that age over 45 years had an increased risk of DP, while Ronga et al suggested that age under 45 years positively influences survival time.<sup>13,16</sup>

**23/F, PTC, pT3N1bM1, post thyroidectomy with Miliary pulmonary metastases, total RAI: 3, follow-up period: 6 years**



**Fig. 4** Example of response in micronodular lung metastases. PTC, papillary thyroid carcinoma; RAI, radioactive iodine ablation; Tg, thyroglobulin.

**Table 3** Clinical characteristics of patients with macronodular lung metastases

S. no.	Gender	Age	Biopsy	Other distant metastases
1	F	49	Hürthle cell variant of PTC	Bone
2	F	43	FVPTC	Bone
3	F	36	PTC	Nil
4	F	53	PTC	Nil
5	F	45	FVPTC	Nil
6	F	57	PTC	Nil
7	M	70	PTC	Nil
8	F	47	PTC	Nil
9	F	50	PDTC	Bone
10	F	54	PDTC	Bone
11	M	59	PTC	Bone
12	F	42	PDTC	Brain
13	F	46	PTC	Bone
14	M	63	FVPTC	Nil
15	F	39	PTC	Nil
16	M	62	PTC	Nil
17	F	37	PTC	Nil

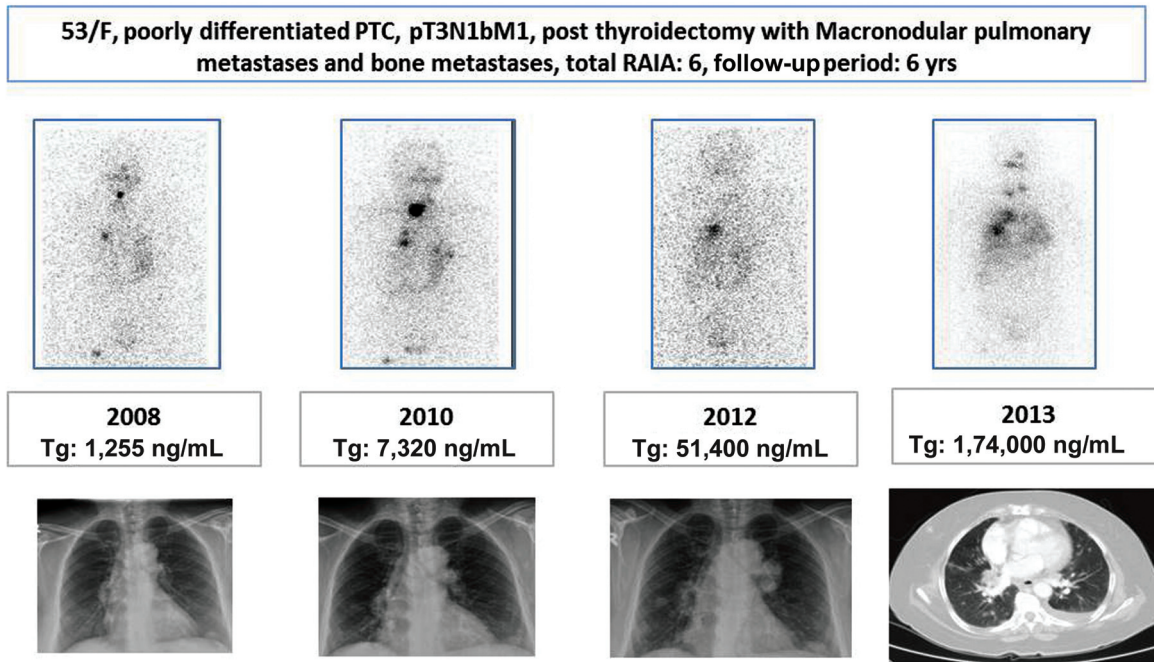
**Table 3** (Continued)

S. no.	Gender	Age	Biopsy	Other distant metastases
18	M	57	PDTC	Spinal cord
19	F	23	FVPTC	Nil
20	F	79	Columnar variant PTC	Nil
21	F	57	FVPTC	Bone
22	M	41	FVPTC	Nil
23	M	42	PTC	Nil
24	M	50	FVPTC	Bone
25	M	49	PTC	Nil
26	F	63	PTC	Nil

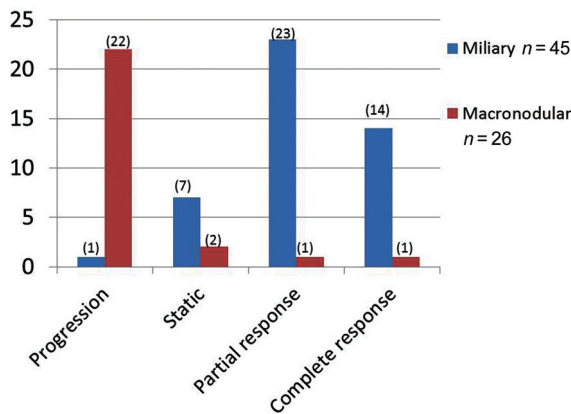
Abbreviations: FVPTC, follicular variant of papillary thyroid carcinoma; PDTC, poorly differentiated papillary thyroid carcinoma.

Overall prognosis was not affected by the timing of the presentation in our study. Lin et al made a similar observation that there was no difference between the prognosis of patients who were diagnosed with lung metastases at initial presentation and those diagnosed at a subsequent follow-up visits.<sup>18</sup>

In addition to this, presence of additional distant metastases in other sites had poor treatment response as opposed



**Fig. 5** Example of response in macronodular pulmonary metastases. PTC, papillary thyroid carcinoma; RAI, radioactive iodine ablation; Tg, thyroglobulin.



**Fig. 6** Comparison of treatment response in both groups.

to those with only lung metastases. In our study, of the 14 patients who had other distant metastases, 12 of them had DP and only 2 had SD. All the 12 patients had either poorly differentiated or follicular variant in the histology of the tumor. While identifying the prognostic factors influencing remission and disease-free survival in PTC patients over 21 years, presenting with pulmonary metastases at initial diagnosis, Chopra et al concluded that larger pulmonary nodules (visible on CXR) and additional skeletal metastases had reduced chances of remission.<sup>19</sup>

Thus, the cumulative evidence from all these studies highlights that the size and pattern of lung metastases strongly influence response to I-131 therapy.

The following observations in the current study need special mention. The ATA 2015 guidelines recommend a

**Table 4** Response in miliarypulmonary metastases

Response	No of patients n = 45	Average no of RAI
DP	1	3
SD	7	3.42
PR	23	3.39
CR	14	1.4

Abbreviations: CR, complete response; DP, disease progression; PR, partial response; RAI, radioactive iodine ablation; SD, static disease.

**Table 5** Response in macronodular pulmonary metastases

Response	No of patients n = 26	Average no of RAI
DP	22	3.4
SD	2	3
PR	1	3
CR	1	3

Abbreviations: CR, complete response; DP, disease progression; PR, partial response; RAI, radioactive iodine ablation; SD, static disease.

therapeutic dose of 200mCi (7400MBq) per therapy for lung metastases.<sup>10</sup> In our study, all patients received a maximum of 100 mCi (3700MBq) per therapy. With such lower doses, a comparable response could be achieved in 82% of patients with miliary metastases showing either CR or PR. Moreover, multiple doses, if required, could be administered without exceeding the maximum cumulative dose of 600 mCi. The ATA taskforce also recommends pulmonary function test to detect

pulmonary fibrosis, a likely sequel of radioiodine therapy in the dose range recommended.<sup>10</sup> None of our patients required pulmonary function tests with the dose range administered. In addition, it needs no emphasis to the fact that radiation exposure to the personnel involved would be lower.

The limitations of our study include its small study sample size from a single institution and its retrospective design. Due to the retrospective design, exact size of the nodules on CT thorax or quantification of uptake on TWBS was not performed in all the patients.

## Conclusion

Those with pulmonary micrometastases in PTC respond to RAI with a better outcome and prognosis when compared with those with MN metastases. The best treatment response is found in those patients with younger age group, absence of other sites of distant metastases, and I-131 avidity. Contrary to the ATA guidelines, a “lower dose regime” would be sufficient to treat these patients.

### Note

This paper was presented at the 49th SNMI (Society of Nuclear Medicine) Conference on December 16, 2017, in Delhi, India.

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None.

### Conflict of Interest

None declared.

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