

Therapeutic Response and Long-term Outcome of Differentiated Thyroid Cancer with Pulmonary Metastases Treated by Radioiodine Therapy

Jasmin Ferdous¹, Fatima Begum², Papia Akhter³, Urnas Islam³ and Zeenat Jabin⁴

¹Associate Professor & PMO, National Institute of Nuclear Medicine & Allied Sciences (NINMAS), Block-D, BSMMU Campus, Shahbag, Dhaka-1000

²Professor & Head, Thyroid division, NINMAS

³Assistant Professor & SMO, Thyroid division, NINMAS

⁴Professor, Thyroid division, NINMAS

Correspondence Address: Dr. Jasmin Ferdous. Associate Professor & PMO, National Institute of Nuclear Medicine and Allied Sciences (NINMAS), BSMMU Campus, Bangladesh Atomic Energy Commission. Dhaka. Email: jasmin.ferdous.aelee@gmail.com. Mobile: 01711941264

ABSTRACT

Objective: This retrospective study was conducted to assess the efficacy of radioactive iodine therapy (RAIT) and investigate the prognostic factors for patients with pulmonary metastasis from differentiated thyroid carcinoma (DTC).

Materials & Methods: A total of 80 patients treated with radioactive iodine (¹³¹I)-avid pulmonary metastasis from DTC treated with ¹³¹I from 2001 to 2016 at National Institute of Nuclear Medicine & Allied Sciences (NINMAS) were enrolled in this study. Treatment response was mainly measured by serum thyroglobulin (Tg) levels, diagnostic ¹³¹I whole-body scan (DxWBS) and patients clinical response. According to the treatment response patients were classified in two groups-complete response (CR) and persistent disease (PD).

Result: Among 80 patients; 53(66.25%) males and 27(33.75%) females. Six patients were lost to follow-up; this study was done on the rest 74 patients. Out of 74 patients according to histological pattern 65(87.84%) were PTC and FTC 09(12.16%). Among 74 patients 50 had LN metastases; lung metastases were in 18 cases and six patients showed both lungs and bone metastases initially. RxWBS revealed lung metastasis in all of these 74 patients. The average received a dose of ¹³¹I was 537 ± 17.6 m Ci. Average postoperative serum Tg level at the time of presentation at NINMAS was 97.3 ng/ml with a decline in serum Tg levels after RAIT to 90 ng/ml. In the case of CR 14 patients showed diffuse lung uptake and 13 showed focal uptake; among PD 40 patients showed diffuse uptake and 14 showed focal lung uptake (p-value-0.004). The average follow-up period was 06 years. We observed CR in 25 (33.78%) patients and PD in 49 (66.21%) patients. The patient with CR; their an initial Tg level average of 38.9 ng/ml and after receiving last therapy their follow-up average Tg was 1.9 ng/ml (p value-0.001). For the patient who had PD, their initial Tg level was 126.2 ng/ml, follow up average Tg was 150 ng/dl with rising Tg level.

Conclusion: From this study, it may be concluded that patients with DTC with lung metastases, most of the patients showed persistence of disease (66.21%) even after giving repeated radioiodine therapy. DxWBS and serum Tg levels at diagnosis are both important factors to

evaluate the therapeutic response. Patients presenting with high serum Tg at initial diagnosis and subsequent bony metastases are likely to show a poor outcome.

Key words: Differentiated thyroid carcinoma, lung metastases, treatment response.

Bangladesh J. Nucl. Med. Vol. 24 No. 1 & 2 year 2021

Doi: <https://doi.org/10.3329/bjnm.v24i1-2.59334>

INTRODUCTION

Differentiated thyroid carcinoma (DTC) is one of the most common types of endocrine cancer. Its clinical manifestations are relatively occult, and the early detection will obtain a better prognosis. Though distant metastases are an uncommon event in DTC, a wide range in prevalence (4–23%) has been reported (1,2). Lungs are the most common site of distant metastasis which is the cause of death in these patients (3,4). Complete surgical resection followed by radioactive iodine (¹³¹I) therapy (RAIT) is the main method for the treatment of DTC with lung metastasis (5) along with thyrotropin suppression by levothyroxine. According to iodine-concentrating capacity (6) pulmonary metastases (PM) are classified as ¹³¹I-avid and non-¹³¹I-avid. ¹³¹I therapy is only recommended for patients with ¹³¹I-avid lung metastases. The purposes of this study are: i) to assess the therapeutic response of radioiodine treatment on ¹³¹I-avid pulmonary metastases ii) to investigate the prognostic factors related to ¹³¹I-avid pulmonary metastases; iii) to evaluate the disease-free state.

MATERIALS AND METHODS

Eighty diagnosed DTC patients with pulmonary metastases on their post-therapy whole body scan (RxWBS) from January 2001 to December 2016 were enrolled in this study. All of them are treated and managed at National Institute of Nuclear Medicine & Allied Sciences (NINMAS) and analyzed retrospectively. The inclusion criteria were as follows: **i)** radioiodine uptake in lung fields in RxWBS which indicates pulmonary metastases. **ii)** the chest X-ray or CT

examination indicated the lung metastasis from DTC. The patients who had ^{131}I treatment contraindication and previously received radiotherapy or chemotherapy treatment were excluded from this study. This study was approved by the Medical Research Ethics Committee of NINMAS. Written informed consent was obtained from all participants. Statistical analyses were carried out using the Statistical Package for Social Sciences version 26.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Variables are expressed in number, mean, and

Table-I: Comparison of clinical characteristics of patients between the complete response (CR) group and persistent disease (PD).

Characteristics	Total patients no (%)	CR no (%)	PD no (%)	P-value
Gender	74	25 (33.78%)	49 (66.22%)	0.022
Male	49	12 (24.49%)	37 (75.51%)	
Female	25	13 (52%)	12 (48%)	
Age	74	33.4 \pm 7.07* (33.32 \pm 3.34)	40.5 \pm 4.9* (40 \pm 2.47)	0.117
Surgery				
Total Thyroidectomy	36	12	24	
Total thyroidectomy+ lymph node dissection:	38	13	25	
Histology				
Papillary	65	23 (35.38%)	42 (64.62%)	0.709
Follicular	9	2 (22.22%)	7 (77.78%)	
Tg level				
Initial (stimulated)		38.9	126.2	0.001
Last		2	150	
Time of lung metastases diagnosis				
Before RAI	18	1 (5.56%)	17 (94.44%)	
During RAIT	56	24 (42.86%)	32 (57.14%)	
Pattern of lung uptake in WBS				
Diffuse:	54	14 (25.93%)	40 (74.07%)	0.004
Focal:	20	13 (65%)	07 (35%)	
Cervical nodal metastases				
No	34	15 (44.18%)	19 (55.88%)	0.092
Central & lateral neck lymph nodes	50	20 (40%)	30 (60%)	
Extrapulmonary distant metastases				
Yes	0		5	0.160
No	25		44	

RAIA-radioactive iodine ablation, RAIT- radioactive iodine therapy

percentages. For age and Tg level analysis t-test; for other variables Chi square test and the Fisher exact test were applied. P value <0.05 was considered as statistically significant.

Treatment method

The total thyroidectomy was performed in all patients, followed by the ^{131}I therapy. Firstly, risk stratification was done, and the ^{131}I was orally administered, with a dose of 75-150 mCi for ablation of the residual thyroid tissue according to risk and stage. After the treatments, the patient was followed up three monthly up to six months to observe the treatment response. The therapy outcome was evaluated by diagnostic whole-body scan (DxWBS), thyroglobulin (Tg) level, and patient's clinical response (7). Routine consultation with a pulmonologist before RAIT was done in each of these patients with careful observation and care was given during the isolation period.

Prognostic factor

The following factors may have an influence on the curative effects of radioiodine therapy for lung metastases of DTC: age at diagnosis, gender, type of surgery, histological diagnosis, the pattern of lung uptake in RxWBS or DxWBS, cervical nodal metastases, absences, or presence of extra-pulmonary distant metastases, such as bone or other organ metastases, duration of lung metastases, and serum Tg level at diagnosis.

Criteria for determination of overall treatment response

After receiving radio iodine therapy, the overall treatment efficacy was determined according to criteria as follows: **i)** Complete response (CR) was considered when both the DxWBS showed that the metastatic

lesions disappeared and the serum Tg level was <2 ng/ml in the stimulated situation; **ii)** Persistent Disease (PD): the RxWBS scan showed that the metastatic lesions were static, enlarged or increased, and the serum Tg level remains static or increased in the stimulated situation.

RESULTS

A total of 80 DTC patients were enrolled in this study; 53 (66.25%) males and 27(33.75%) females, M: F- 1.9:1. The average age of the study population was 37.8 ± 17 years; with a range of 14 to 65 years. Six patients were lost to follow-up; this study was done on the rest 74 patients. Out of 74 patients according to histological pattern 65 (87.84%) were PTC and FTC 09 (12.16%). Among 74 patients 50 had LN metastases; lung metastases were in 18 cases and six patients showed both lungs and bone metastases initially. RxWBS revealed lung metastasis in all of these 74 patients. The average received a dose of ^{131}I was 537 ± 17.6 m Ci. The patients received average 04 times (1-10 times) with an interval of six months. Average postoperative serum Tg level at the time of presentation at NINMAS was 97.3 ng/ml (Range: 1.25 to 211 ng/ml) with a decline in serum Tg levels after RAIT to 90 ng/ml (Range: 0.19 to 246 ng/ml). In the case of CR 14 patients showed diffuse lung uptake and 13 showed focal uptake; among PD 40 patients showed diffuse uptake and 14 showed focal lung uptake (p-value-0.004). The average follow-up period was 06 years (Range: 1 to 16 years). We observed CR in 25 (33.78%) patients with an average received dose of 425 m Ci and PD in 49 (66.21%) patients with an average received ^{131}I dose of >650 m Ci. The patient with CR; their an initial Tg level average of 38.9 ng/ml and after receiving last therapy their follow-up average Tg was 1.9 ng/ml (p value -0.001). For the patient who had PD, their initial Tg level was 126.2 ng/ml, follow up average Tg was 150 ng/dl with rising Tg level (Table-I).

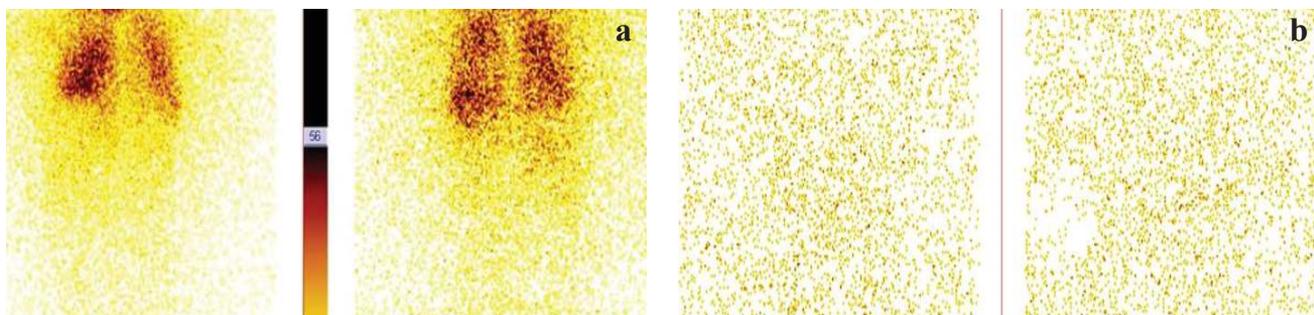


Figure-1: a) Post therapy whole body scan showing diffuse lung uptake; b) Diagnostic whole body scan showing no lung uptake at disease free condition.

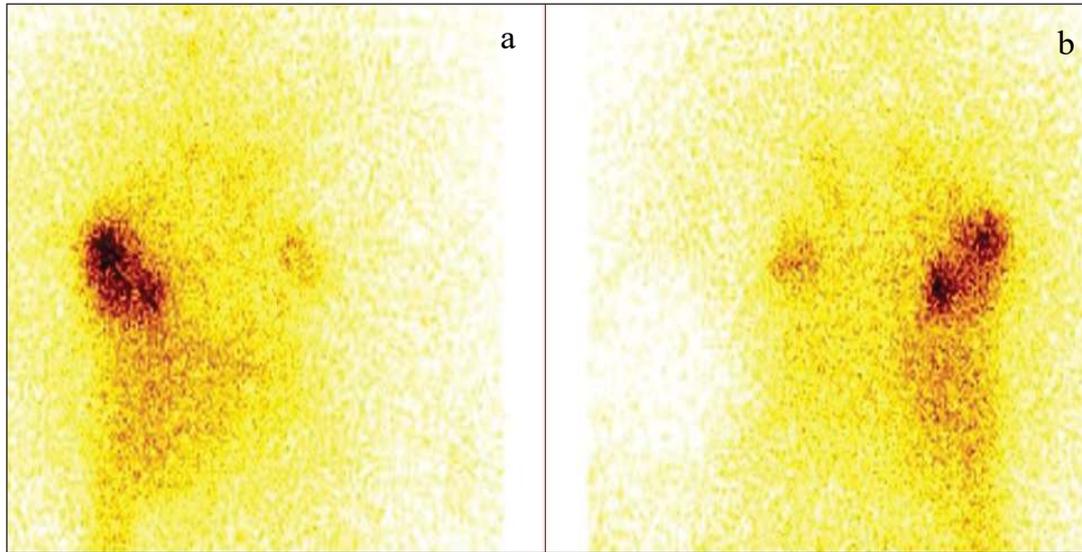


Figure 2: Multiple irregular intense uptakes of ¹³¹I in the right lungs after 1st dose of radio-iodine ablation in the a) anteroposterior and b) postero-anterior view

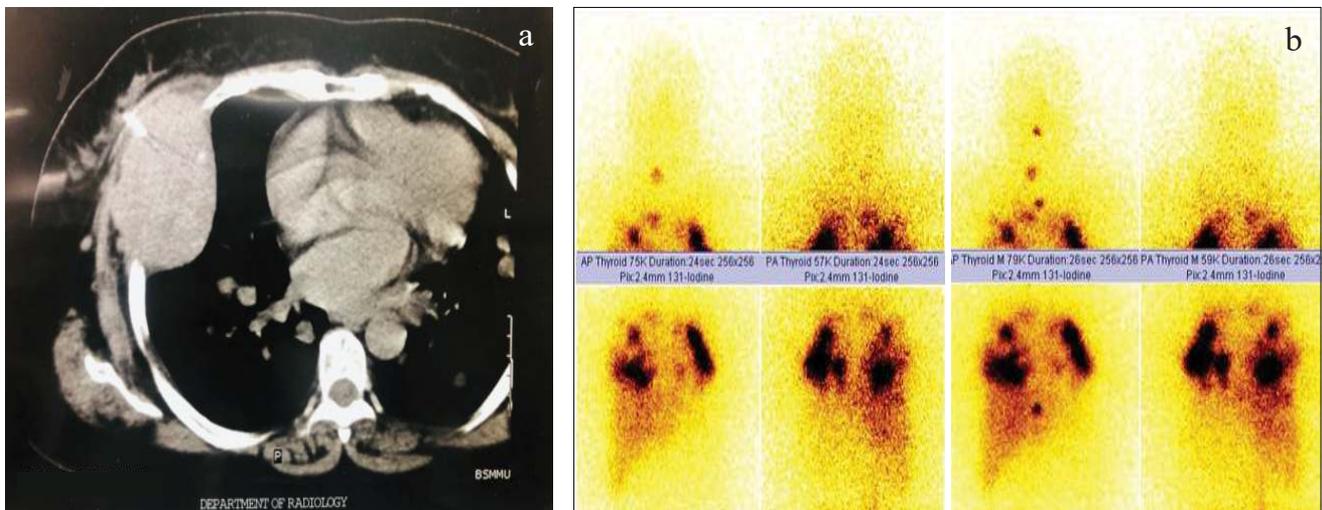


Figure 3: a) Axial CT scan of a 56 years old female DTC patient showing multiple nodules of variable sizes in both lungs, the biggest mass located in the right lung invading the chest wall b) Persistent irregular bilateral lung uptake of ¹³¹I in post-therapy whole-body scan after 1st and 2nd radioiodine therapy

DISCUSSION

According to European statistics, thyroid cancer is three times more common in women than men (8). The male to female ratio is not reflected in this study group as the ratio of male to female is 1.9:1. The discrepancy in the M:F ratio may be due to male patients showing more pulmonary metastases.

In this study, the efficacy of ¹³¹I therapy and the prognostic factors of patients with ¹³¹I-avid thyroid cancer with lung metastases were assessed. The variables which were predictors of the efficacy of ¹³¹I therapy were

age, serum Tg level at diagnosis, and the absence or presence of extrapulmonary distant metastases. Tg level and DxWBS were used to measure the treatment response of RAIT in this study along with RxWBS as these played important role in evaluating the outcome of RAIT for DTC with lung metastases (8).

The Mean age of the patients who showed PD was 40.5±4.9 years, CR was 33.4±7.07 years. In recent years, DTC has shown a rising trend in elderly patients and has a high rate of distant metastasis e.g. lung, bone, etc. (9). Due to the age factor, the physical conditions of the

elderly are very different from the young. Elderly patients showed more nodular pulmonary lesions, with a high incidence of distant metastases. Cho et al (10) reported that older patients with lung metastasis had poor prognosis. Poor prognosis in older patients can be explained as a relatively longer disease duration, more advanced stage in the older group, lower radiation sensitivity, and decreased immunity (11). Non-elderly or young patients have relatively good health, with evidence of more diffuse pulmonary lesions and low incidence of distant metastases (12). For these reasons, younger patients had better responses than older patients. But this study demonstrated no significant impact of age difference. However, relatively younger patients showed better response; the mean age of CR group was 33.4 years and PD was 40.4 years.

Tg level and RxWBS were used to measure the treatment response of RAIT in this study. In this study DTC patients with lung metastases after RAIT showed CR and PD in 33.7 % and 66.28% respectively. The mean postoperative serum Tg level at the time of presentation at NINMAS was 97.3 ng/ml (Range: 1.25 to 211 ng/ml) with a decline in serum Tg levels after RAIT to 90 ng/ml (Range: 0.19 to 246 ng/ml). The initial Tg level at the time of presentation of the patients who showed CR was 38.9 ng/ml which declined to 3.09 after RAIT and the initial Tg was 126.2 ng/ml; raised to 150ng/ml in patients with persistent disease. Several studies have shown that the serum Tg level at diagnosis is an independent prognostic indicator for ¹³¹I therapy efficacy (13,14). In agreement with the previous studies, the results of this study also showed that patients with higher Tg levels at diagnosis were more likely to show a poor prognosis. Patients with high levels of Tg might have fewer ¹³¹I avid lesions which explain the efficacy of ¹³¹I therapy that was worse in some patients with high Tg levels. Other studies performed on the basis of diagnostic value of serum Tg measurement, found that it is a highly sensitive means of detecting metastases (15). Moreover, Tg level was an independent prognostic indicator for disease-free remission and death (16). It was thought that the serum Tg level under TSH elevation (30mU/l) was the most reliable indicator for persistent or recurrent disease. However, serum Tg was

only reliable if Tg Ab was undetectable, otherwise serum Tg level could have been falsely lowered (16). This study revealed a significant decrease in serum Tg in 33.7% patients with CR but no significant change in Tg level in 66.28% patients with PD.

Present study showed the presence of extra-pulmonary distant metastases could predict a poor prognosis for RAIT, as six patients with persistent disease had extra pulmonary metastases. In a cohort study of Nixon et al., 52 patients with DTC and distant metastases showed presence of extra-pulmonary metastases which was a significant predictor of the poor outcome, despite good thyroid surgery and RAIT.

In this study, 53 patients showed diffuse pulmonary uptake; among them 13 had CR and 40 had PD. Eight patients with focal pulmonary uptake showed CR and nine showed PD. The size of pulmonary metastases was usually 1cm, which was below the spatial resolution of chest X-ray. Chest CT could enhance the diagnostic accuracy in most patients with normal chest X-ray and had an additive effect to ¹³¹I-WBS and Tg level (11). The micronodular pattern of lung metastases was invariably related to good ¹³¹I uptake, while macronodular metastases frequently showed poor ¹³¹I uptake.

CR (remission, no evidence of disease) can be considered when there is absence of structural or functional evidence of disease, undetectable Tg and negative DxWBS scan. When Tg and ¹³¹I scan were both positive, DTC metastases could be treated with ¹³¹I. ¹³¹I refractory status should be considered for those DTC patients with persistent disease (¹³¹I non avid or few avid and few non-avid) without obvious fading of lesions, or tumor progression. In ¹³¹I refractory cases due to dedifferentiation may be treated with molecular targeted therapy or external beam radiotherapy (17).

There are some limitations of this study like it was a retrospective study, small sample size, and loss of some clinical data.

CONCLUSION

DTC patients with lung metastases showed male predominance; most of the study subjects showed persistence of disease (66.21%) even after repeated

radioiodine therapy. Both DxWBS and serum Tg levels at diagnosis are important factors to evaluate the therapeutic response. Relatively younger patients of DTC had good prognosis. Patients presenting with high serum Tg at initial diagnosis and subsequent bony metastases are likely to show a poor outcome.

REFERENCES

1. Jonklaas, J., Sarlis, N.J., Litofsky, D., Ain, K.B., Bigos, S.T., Brierley, J.D., Cooper, D.S., Haugen, B.R., Ladenson, P.W., Magner, J. and Robbins, J., 2006. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. *Thyroid*, 16(12), pp.1229-1242.
2. Lang, B.H.H., Wong, K.P., Cheung, C.Y., Wan, K.Y. and Lo, C.Y., 2013. Evaluating the prognostic factors associated with cancer-specific survival of differentiated thyroid carcinoma presenting with distant metastasis. *Annals of surgical oncology*, 20(4), pp.1329-1335.
3. Goffredo, P., Sosa, J.A. and Roman, S.A., 2013. Differentiated thyroid cancer presenting with distant metastases: a population analysis over two decades. *World journal of surgery*, 37(7), pp.1599-1605.
4. Lang, B.H.H., Wong, K.P., Cheung, C.Y., Wan, K.Y. and Lo, C.Y., 2013. Evaluating the prognostic factors associated with cancer-specific survival of differentiated thyroid carcinoma presenting with distant metastasis. *Annals of surgical oncology*, 20(4), pp.1329-1335.
5. Xu, L., Liu, Q., Liu, Y. and Pang, H., 2016. Parameters influencing curative effect of 131I therapy on pediatric differentiated thyroid carcinoma: a retrospective study. *Medical Science Monitor*, 22, pp.3079-3085.
6. Durante, C., Haddy, N., Baudin, E., Leboulleux, S., Hartl, D., Travagli, J.P., Caillou, B., Ricard, M., Lumbroso, J.D., De Vathaire, F. and Schlumberger, M., 2006. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *The Journal of Clinical Endocrinology & Metabolism*, 91(8), pp.2892-2899.
7. Sultana, S., Nahar, N., Begum, F., Alam, F., Hasan, M., Hussain, R., Haque, M., Nasreen, F., Khan, M.H., Nisa, L. and Moslem, F., 2015. Management of patients with differentiated thyroid carcinoma-SNMB guidelines. *Bangladesh Journal of Nuclear Medicine*, 18(1), pp.73-84.
8. Lortet-Tieulent, J., Franceschi, S., Dal Maso, L. and Vaccarella, S., 2019. Thyroid cancer “epidemic” also occurs in low-and middle-income countries. *International journal of cancer*, 144(9), pp.2082-2087.
9. Del Rio, P., Sommaruga, L., Bezer, L., Arcuri, M.F., Cataldo, S., Robuschi, G. and Sianesi, M., 2009. Thyroidectomy for differentiated carcinoma in older patients on a short stay basis. *Acta Bio-medica: Atenei Parmensis*, 80(1), pp.65-68.
10. Cho, S.W., Choi, H.S., Yeom, G.J., Lim, J.A., Moon, J.H., Park, D.J., Chung, J.K., Cho, B.Y., Yi, K.H. and Park, Y.J., 2014. Long-term prognosis of differentiated thyroid cancer with lung metastasis in Korea and its prognostic factors. *Thyroid*, 24(2), pp.277-286.
11. Schneider DF, Chen H. New developments in the diagnosis and treatment of thyroid cancer. *CA Cancer J Clin* 2013; 63 :374-94.
12. Cui, X. and Han, J., 2017. Comparative study on radioiodine therapy for lung metastasis of differentiated thyroid cancer in elderly and non-elderly patients. *Biomedical Research*, 28(16), pp.7088-7092.
13. Brassard M, Borget I, Edet-Sanson A, et al. Long-term follow-up of patients with papillary and follicular thyroid cancer: a prospective study on 715 patients. *J Clin Endocrinol Metab* 2011;96:1352-9.
14. Heemstra KA, Liu YY, Stokkel M, et al. Serum thyroglobulin concentrations predict disease-free remission and death in differentiated thyroid carcinoma. *Clin Endocrinol* 2007;66:58-64.
15. Lind P & Kohlfurst S. Respective roles of thyroglobulin, radioiodine imaging, and positron emission tomography in the assessment of thyroid cancer. *Seminars in Nuclear Medicine* 2006 36 194-205.
16. Brassard M, Borget I, Edet-Sanson A, Giraudet AL, Mundler O, Toubeau M, Bonichon F, Borson-Chazot F, Leenhardt L, Schvartz C et al. Long-term follow-up of patients with papillary and follicular thyroid cancer: a prospective study on 715 patients. *Journal of Clinical Endocrinology and Metabolism* 2011 96 1352-1359.
17. Nixon, I.J., Whitcher, M.M., Palmer, F.L., Tuttle, R.M., Shaha, A.R., Shah, J.P., Patel, S.G. and Ganly, I., 2012. The impact of distant metastases at presentation on prognosis in patients with differentiated carcinoma of the thyroid gland. *Thyroid*, 22(9), pp.884-889. [jc.2010-2708](#).