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Therapy Response and Prognostic Impact of Lung Metastases in Differentiated Thyroid Carcinoma

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ABSTRACT:

The aim of this study is to assess the response of functioning lung metastases of thyroid origin to radioactive iodine-131 therapy out of one hundred fifty patients with metastatic differentiated thyroid cancer, who were assessed to evaluate the response of metastatic lung lesions to RAI-131 therapy. The peak age of onset was between 39-57 years, 64 patients (62.1%) were females compared to 39 males (37.9%). 51 patients (49.5%) had papillary type while 52 patients (50.5%) had follicular type. Among the lung metastases which were detected in 103 patients, 62 patients had only lung, 32 patients had lung and bone and 9 patients had multiple sites,

most of these metastases were at initial presentation or detected after the first therapy dose. Complete response was detected in 23 (22.4%) patients, partial response in 33 patients (32%), 36 patients (35%) were in stable state, & 11 patients (10.6%) showed evidence of disease progression. The overall survival from the detection of metastases was 95% at 5 years & 81% at 10 years. **Conclusion:** Radioiodine therapy is still the most effective systemic therapy to treat patients with metastatic lung lesions. From differentiated thyroid carcinoma (DTC) with favorable outcome and over all 5 as well as 10 year survival rate.

Keywords: DTC, RAI-131.

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INTRODUCTION:

Cancer thyroid accounts approximately for 1% of all malignancies in developed countries with an estimated annual incidence of 122,000 cases worldwide. They represented the most common malignancies of endocrine system ⁽¹⁾. The incidence of thyroid carcinoma has increased in recent years which were facilitated by the widespread use of improved imaging techniques & the popularity of fine needle aspiration biopsy ⁽²⁾. 80% of all thyroid cancer cases had papillary thyroid cancer ^(3, 4). However, during the last decades; mortality rates have steadily declined because of improved treatment including radioactive iodine therapy ⁽⁵⁾. The incidence of cancer thyroid in National Cancer Institute of Egypt was 2.3% ⁽⁶⁾. The most common thyroid neoplasm (50-80% of total) is papillary carcinoma followed by follicular carcinoma (10-40%) and medullary carcinoma (5-15%) ⁽⁵⁾.

Distant metastases are the main cause of death from papillary & follicular carcinoma, approximately one third of differentiated (follicular & papillary) thyroid cancers recur ⁽⁷⁾. I-131 treatment prolongs survival in patients with lung metastases; although the rate of cure is low

these patients tend to live longer with metastatic disease ^(8,9). The lung metastases from differentiated thyroid cancer are potentially curable, particularly in children & young adults who often live for decades with diffuse pulmonary metastases that have been appropriately treated. The prognosis depends upon the burden of disease, the intensity of radioiodine uptake by the tumor and the inherent growth characteristics of the tumor. However, long term survival is high when lung metastases are too small to be seen on the standard chest radiograph or CT.

Ten year survival rates are approaching 100% when metastases are only evident on the post-treatment whole Body scan. The 10 year survival rates steadily decline to 40% if metastases become larger with micro-nodules (≤ 1 cm) on the chest X-ray & 15% when the nodules are larger than 1cm ⁽¹⁰⁾.

MATERIALS and METHODS:

One thousand four hundred fifty one (1451) patients with differentiated thyroid carcinoma were treated at the National Cancer institute (2000-2010), 103 patients of them had lung metastases.

Clinical information was extracted from the medical records including age, sex, method of diagnosis, detailed pathology, serum Thyroglobulin, imaging findings, treatment details, response to treatment & disease status. Data were entered into a computerized data base. The study endpoints included date of last follow-up or patient death.

Diagnostic procedures: All patients were evaluated by series of investigations including TG level, diagnostic 1-131 WBS, chest X-ray or chest CT. Patients were then scheduled for 1-131 therapy after T4 withdrawal for 4 weeks to insure that TSH level ≥ 30 uIU/ml which was measured at day of therapy associated with measuring TG level. Patients were hospitalized for three days. T4 treatment was resumed on the fourth day with a post-therapy WBS performed 5-7 days after oral intake of 1-131. A Fixed dose of 150mCi of RA1-131 was given every 6 months. Close follow-up is advised with no further 1-131 therapy if the patient has a stable disease after 3 or more therapeutic doses.

Follow-up: Patients with negative studies after radioiodine therapy for lung metastases were followed up after 6 months with clinical & laboratory examinations (TSH and TG) under

hormonal suppression therapy. The absence of radioiodine uptake was supplemented by normal TG level & 1-131 WBS with a diagnostic dose after 6 months.

Hormonal therapy: In between therapy doses, patients were maintained on high suppression therapy with thyroid hormones to keep the TSH level around 0.01 mIU/ml. Hormonal therapy was stopped 4 weeks before starting the next therapeutic dose.

In four patients with proved lung metastases radiologically and elevated TG yet with negative whole body iodine scan were referred to the Oncology Department for trial of targeted therapy or chemotherapy.

Assessment of response to radioactive iodine therapy:

Four groups of patients were identified:

Group 1 (complete response): Patients with negative imaging studies who had no persistent uptake on post-therapy 1-131 WBS with no radiological abnormalities & markedly reduced thyroglobulin level, less than 2ng/ml.

Group 2 (partial response): patients who had significant improvement on post-therapy scans with reduced TG

(More than 25%) as compared to previous study. **Group 3 (stationary course):** Patients who show almost stationary state on serial post-therapy scans with minimal drop or increase (less than 15%) or no change in TG level.

Group 4 (disease progression): Patients who had progressive state on post-therapy scans with increased TG level (more than 25%).

RESULTS:

Out of 103 patients with functioning distant metastases, the peak age of onset was

between 39-57 years; 64 patients (62.1%) were females as compared to 39 (37.9%) males.

On histological analysis, 51 patients (49.5%) had papillary type while follicular type was evident in 52 patients (50.5%). Only lung metastases were present in 62 patients out of 103 patients (60.3%) followed by bone & lung in 32 patients (31%) and multiple sites in 9 patients (8.7%). Multiple metastatic lesions were evident at initial presentation in 57 patients (55.3%), 38 patients (36.9%) after first therapy dose & 8 patients (7.8%) within 5 years of initial presentation (*Table 1*).

Table (1): Characteristics of 103 patients with lung metastases including response rate and overall survival.

Characteristics	No.	%
Sex		
Female	64	62.1
Male	39	37.9
Age (years)		
<40	24	23.3
>40	79	76.7
Histology		
Papillary	53	51.5
Follicular	50	48.5
Site of metastases		
Lung only	62	60.3
Lung & bone	32	31
Lung & Multiple sites	9	8.7
Response to therapy		
Complete response	23	22.4
Partial response	33	32
Stable disease	36	35
Progressive disease	11	10.6
Overall survival		
At 5 years	103	95
At 10 years	103	81

Lung lesions were initially detected by chest X-ray in 8 patients (7.8%) and 23 patients (22.3%) with CT, diagnostic 1-131 WBS in 26 patients (25.2%), while post-therapy 1-131 WBS revealed lung metastases in 46 patients (44.7%) (*Table 2*). By analysis of overall sensitivity of

follow up radiological investigations, chest radiographs were positive in 22 patients (21.4%), chest CT was positive in 59 patients (57.3%). Diagnostic 1-131 WBS was positive in 77 patients (74.8%) as compared to 103 patients detected on post-therapy iodine scans (100%) (*Table 3*).

Table (2): Sites of lung metastases as detected by radiologic and whole body iodine scan.

Characteristics	No.	%
Metastases are initially by:		
Chest X-ray	8	7.8
Chest CT	23	22.3
Diagnostic 1-131 WBS	26	25.2
Post-therapy 1-131 WBS	46	44.7

Table (3): Radiological sensitivity on follow up studies.

Radiologic sensitivity of follow-up studies	No.	%
Chest X-ray	22	21.4
Chest CT	59	57.3
Diagnostic 1-131 WBS	77	74.8
Post-therapy 1-131 WBS	103	100

Response to therapy: At the end of treatment, among 103 patients who had initial 1-131 uptake in their metastases, 23 patients (22.4%) achieved complete response, 33 patients showed partial response (32%), 36 patients (35%) were in stationary state, and 11 patients (10.6%) showed evidence of disease progression (*Table 1*).

Patients who achieved complete and partial response: Among the 56 patients who achieved complete and partial

response, 37 patients had papillary thyroid carcinoma and 19 patients had follicular thyroid carcinoma. According to metastases, 38 patients had only lung metastases, 14 patients had both lung & bone metastases and 4 patients had multiple metastases.

Complete response was obtained in 12 patients at mean therapeutic dose of 16.6 GBq (450mCi) and 11 patients at mean therapeutic dose of 27.7GBq (750 mCi), (*Table 4*), (*Fig. 1*).

Serum TG level was measured in 23 patients with complete response; TG was <2ng/ml in 21 patients and 2-5ng/ml in 2

patients. After withdrawal of T4 therapy, 15 patients had serum TG < 2ng/ml, while 8 patients had serum TG>2 and < 5ng/ml.

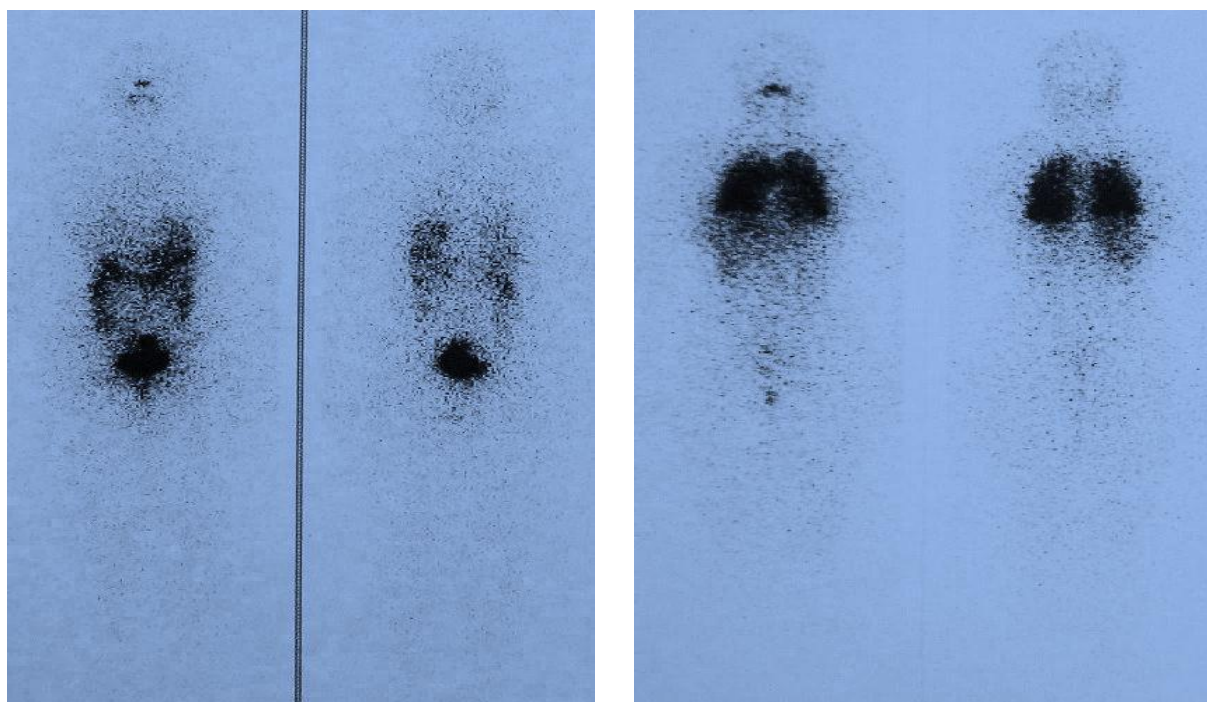


Fig (1): 26 years old female patient with post therapy scans showing complete response of lung metastases after 750mCi of RAI-131 therapy doses.

Table (4): Characteristics of patients in different groups of response.

Characteristics	Complete & partial response		Progressive & stationary disease	
	No(56)	%	No(47)	%
Age (years)				
Below 40	24	42.8	22	46.8%
Above 40	32	57.2	25	53.2%
Pathology				
Papillary	37	67.8	14	29.8%
follicular	19	33.2	33	70.2%

Twenty one patients achieved partial response at mean therapy dose of 19.2 GBq (520 mCi) and 12 patients at mean therapy dose of 43.8 GBq (1185 mCi). Serum TG was measured in the 33 patients; 28 patients showed decreased levels, 4 patients had increased levels and only one patient had almost stationary level.

Patients who had stationary and progressive disease: Fourteen patients had papillary thyroid carcinoma and 33 patients had follicular thyroid carcinoma. 21 patients of them had only lung metastases, 17 patients had both lung & bone metastases & 9 patients had metastases at multiple sites. Twenty five patients received mean therapy dose of 14.8 GBq (400 mCi) and 8 patients received mean therapy dose of 36.5GBq (986mCi). Serum TG was measured in 36 patients: - 23 versus multiple sites of metastases, however there is no significant difference related to sex, age, histology and response to therapy.

patients showed mild decreased levels within 10%, 3 patients had mild increased levels within 10% and 9 patients had almost stationary levels. Among this group, 5 patients died, three patients became dedifferentiated with no response to iodine therapy and referred for chemotherapy, cytotoxic drugs (Paclitaxel 175mg/m², Carboplatin AUC=5 every 3 weeks) were given to the three patients with no response, neurotoxicity and further progression occurred.

Survival in metastatic lung patients: At the end of the study, the overall survival rate of lung metastases was 95% at 5 years and 81% at 10 years. After analysis of individual characteristics the study showed the data presented in table 5. There is significant difference in survival related to the presence of lung metastases The difference in survival rate was significant between patients with only lung metastases and those with multiple sites (p=0.027) (*Table 5*).

Table (5): The overall 10 years survival rate.

	10 years survival	Significance (p-value)
Sex Female Male	83% 76%	0.08
Age (years) Below 40 Above 40	92% 79%	0.09
Histology Papillary Follicular	74% 61%	0.6
Response to therapy Complete or partial Stationary progressive	87% 71% 23%	0.06
Site of metastases Lung only Lung &bone Lung &multiple sites.	81% 77% 63%	0.027

DISCUSSION:

The molecular profile of tumors is different for different sites of distant metastases. Thus the outcome is dependent on the site of distant metastases in different types of cancer, it has been recently reported that the molecular profile for patients with bone metastases is very different to that for lung metastases ⁽¹¹⁾.

Radioiodine is the only available effective systemic therapy to treat patients with metastases DTC. The present study was designed to categorize the response to

radioiodine treatment and select patients who might benefit from serial therapy doses in case of lung metastases of DTC whether only lung or associated with other sites of metastases. The study was carried out on 103 patients with functioning distant metastases of differentiated thyroid carcinomas to lung.

The present study showed that among the 103 patients who had lung metastases, lung lesions were first detected by post-therapy I-131 WBS in 46 patients (44.7%),

Diagnostic I-131 WBS in 26 patients (25.2%), chest CT in 23 patients (22.3%) and chest radiographs in 8 patients (7.8%), these data suggest the superiority of post-therapy I-131 scan over diagnostic pre-therapy scan in detecting distant metastases modifying disease stage and / or therapeutic approach. This is supported by the reported data that 35 patients with post-operative thyroid carcinoma who received diagnostic total body I-131scans & demonstrated that additional uptake on the post-treatment scan occurred in 7 of 35 patients (20%)^(12,13). In the present study 12 out of the 23 patients who achieved complete response, after receiving 16.6 GBq (450 mCi), they achieve 10 years survival rate 92%, as these patients had diffuse microscopic lung metastases with normal chest radiology.

Similar data was reported by Schlumberger et al,⁽⁸⁾ in a series of 124 patients with metastatic thyroid cancer achieved complete response and reported that 82% of 84 patients had micro-metastases with normal chest X-ray. On the other hand the 10-year survival rate for patients with distant metastatic thyroid cancer ranges from 26 to 60%^(14,15).

Durante et al,⁽¹⁶⁾ concluded that six variables proved significant for survival including female patients, younger age at

the time of detection of metastases, those with papillary and follicular well differentiated carcinoma, those with a limited extent of disease, and those with I-131 uptake in their metastases had a lower risk of death. Our results showed that pulmonary metastases had better outcome and prognosis than extra pulmonary metastases with higher survival rate. Although Iain et al,⁽¹⁷⁾ reported that approximately half of patients with WDTC presenting with distant metastases die of disease within 5 years of initial diagnosis despite thyroid surgery and RAI.

Avidity to RAI is directly related to the degree of differentiation of thyroid cancer, with better results in young age. Complete response in children with widespread pulmonary metastases is not unusual with excellent outcomes. Loss of RAI avidity occurs when dedifferentiation occurs in thyroid cancer and that has been associated with a poor outcome⁽¹⁸⁾.

In our study, better outcome was evident in patients with radioiodine-avid metastatic disease compared to patient's disease progression and failure of treatment in non-iodine avid patients.

Three patients with no response to radioiodine therapy and received chemotherapy showed further disease progression.

Similar data was reported by **Naifa and Maria**,⁽¹⁹⁾ using cytotoxic chemotherapy (Paclitaxel 175mg/m², Carboplatin AUC=5) with limited response rate and significant toxicity. Therefore such management reserved for symptomatic progressive disease in a patient that cannot get on a clinical trial or tolerate anti-angiogenic therapy. Survival analysis in the present study revealed that the main

prognostic factor with statistical significance was found to be the site of metastases. The survival rate at 10 years was 81% in the 62 patients with only lung metastases and 77% in 32 patients with both lung and bone metastases (p=0.027). The other factors such as age, gender, pathology and response to therapy showed higher survival rates with non-significant results.

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