

## The Effectiveness of Radioactive Iodine for Treatment of Well Differentiated Thyroid Carcinoma with Distant Metastases (10 Years Study)

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### ABSTRACT

**Background:** The most prevalent endocrine malignancy is thyroid carcinoma. It accounts for around 3% of all recently found cancer cases. More than 90% of endocrine neoplasms are accounted for by it. Thyroid cancer accounts for around 1% of all cancer deaths worldwide. **Objective:** The study's goal was to assess the effect of radioactive iodine alone or in combination with other treatment modalities, on overall survival (OS) and prognostic OS characteristics in metastatic well differentiated thyroid carcinoma (DTC) after total or near-total thyroidectomy.

**Patients and Methods:** We reviewed all the files of patients diagnosed with cancer thyroid attended to Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital from January 2012 to the end of December 2021 to get the number of well DTC with distant metastases. 70 patients with DTC with distant metastases were included in this retrospective analysis.

**Results:** The median OS from well DTC with distant metastases diagnosis was 79.06 months and it was significantly reduced in case of male sex and T4 stage. Among 70 patents diagnosed with DTC with distant metastases, 12 cases lost follow up, 5 patients (8.62%) achieved complete response following RAI treatment, either alone or in combination with radiotherapy. Age below 55 years, poor performance status and staging were predictive for complete response, **Conclusion:** Radioactive iodine therapy is an effective method in the treatment of DTC with distant metastases since it reduces the number of adverse events while maintaining a high standard of living and improves OS.

**Keywords:** Impact; Ablative low dose radioactive iodine; Thyroidectomy; Low-risk differentiated; Thyroid cancer.

### INTRODUCTION

The most frequent endocrine neoplasm, with an increasing frequency over the past few decades, is differentiated thyroid carcinoma. The increased detection of clinically irrelevant papillary microcarcinomas is mostly to blame for this rising occurrence<sup>(1)</sup>. The most frequent thyroid tumor is papillary carcinoma (PTC), which accounts for 50–80% of all cases, followed by follicular carcinoma (FTC), which accounts for 10%–40%. Well-differentiated epithelial thyroid cancer (DTC) can be made up of either PTC, FTC, or Hurthle cell thyroid cancer (HCTC)<sup>(2)</sup>. Around 4% of patients develop distant metastasis, which lowers survival rates to 24–76%. Lungs and bones are the most frequent locations for distant metastasis<sup>(3)</sup>. In most situations, the presence of distant metastases indicates a dismal prognosis. Patients who have metastatic differentiated thyroid cancer can benefit from radioactive iodine therapy, which extends their lives dramatically<sup>(4)</sup>.

The widespread use of highly effective multimodality treatments like surgery, adjuvant radioactive iodine, and radiotherapy depending on the site and type of distant metastasis is partially responsible for the encouraging survival rates for patients with distant metastatic well-differentiated thyroid carcinoma<sup>(5)</sup>.

### AIM OF WORK

A retrospective study looks to assess the effect of radioactive iodine on response rate in metastatic well differentiated thyroid carcinoma after total or near-total

thyroidectomy and survival functions including disease free survival and overall survival in patients who were treated at Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital through the period from January 2012 to the end of December 2021 inclusive.

### PATIENTS AND METHODS

This cross-sectional analysis of 70 patients treated at the Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital with well-differentiated thyroid cancer with distant metastases between January 2012 and December 2021 inclusive.

We retrospectively reviewed the data of consecutive 29950 cancer patients who attended to the outpatient clinic of Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital during the previously mentioned period then we reviewed all the files of cancer thyroid to obtain only the number of well differentiated thyroid cancer cases with distant metastasis.

All patient information data were analyzed, and data were collected using a standard form: patient characteristics, presenting symptoms, tumor characteristics, investigation (laboratory tests radiological assessment, pathological evaluation), treatment details (surgery and radioactive iodine), follow up after treatment, treatment outcome (survival details).

American thyroid association (ATA) guidelines criteria were used to assess the results. Disease-free survival (DFS) was measured in terms of the number of

months that passed between the time of surgical resection and the discovery of a disease recurrence, lost follow-up, or death.

We collected the data of adult patients with eligibility criteria which included patients aging more than 18 years old who presented with distant metastatic well differentiated thyroid cancer either from the start or during follow up.

On the contrary we excluded cases with the following criteria; other thyroid tumors rather than well differentiated thyroid carcinoma, previous neck surgery, previous neck irradiation and age below 18 or more than 70 years.

**Ethical consent:**

**Approval of the study was obtained from Mansoura University Academic and Ethical Committee. Every patient signed written consent accepting the use of his(her) data in medical research. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

**Statistical analysis**

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) program for Windows (Standard version 26). Quantitative data were presented as median and standard error (SE). Qualitative data were described using number and percent. Chi square test was used to compare qualitative variables, Fisher exact test was used to compare qualitative variables when expected count was less than 5, and Kaplan–Meier test was employed for assessing the survival function. For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level.

**RESULTS**

Our analysis was conducted on 70 patients diagnosed as metastatic well differentiated thyroid carcinoma. To obtain this number of metastatic cases with well differentiated thyroid cancer, we reviewed all the files of cancer thyroid referred to the Department in ten years, which constitute 6.04% of total malignant cases referred to the Department in that period. (Table 1).

**Table (1): Collective data of malignant cases referred to Mansoura Clinical Oncology and Nuclear Medicine Department between January 2012 and December 2021**

Total malignant cases	Thyroid carcinoma cases	%	DTC	%	Metastatic cases	%
29950	1808/29950	6.04	1691/1808	93.5	70/1691	4.1

DTC is differentiated thyroid carcinoma

The majority of patients (65.7%) were over the age of 55, while the remainder (34.3%) were under the age of 55. The study's average age was 57.7 years (Table 2).

**Table (2): Patients characteristics for metastatic cases (70 cases)**

Items	Number	Percentage
<b>Gender</b>		
Male	35	50
Female	35	50
<b>Age</b>		
<55 y	24	34.3
>55 y	46	65.7
<b>ECOG</b>		
0	17	24.3
1	53	75.7
<b>Presenting symptoms</b>		
Symptoms related to metastatic disease.	42	60
Neck swelling	26	37.1
Hoarseness of voice	6	8.6
Obstructive symptom	5	7.1
<b>Risk group</b>		
High	62	88.6
Intermediate	7	10
Low	1	1.4

As regard tumor characteristics, most of cases (43 patients) presented with PTC (61.4%) (**Table 3**). Any patient may have none or more than 1 tumor characteristic.

**Table (3): Tumor characteristics for 70 pathological examinations**

Tumor characteristics	Number	Percentage
<b>Pathology</b>		
PTC	43	61.4
Follicular thyroid carcinoma	24	34.3
Hurthle cell carcinoma	3	4.3
<b>T Staging</b>		
T2	32	45.7
T1	17	24.3
T3	12	17.1
T4	9	12.9
<b>N staging</b>		
N0	41	58.6
N1	29	41.4
Capsular invasion	23	32.9
Lympho-vascular invasion	15	21.4
Extra thyroid extension	14	20
Extra nodal extension	4	5.7
Gross residual	4	5.7
Multifocality	4	5.7

Regarding the most common site of distant metastasis, 23 patients (32.9%) had lung and bone metastasis (**Table 4**).

**Table (4): Site of distant metastasis and lymph node metastasis among 70 patients**

Site of Metastasis	No	%
Lymph node metastasis	29	41.4
Lung + bone	23	32.9
Bone	21	30
Lung	18	25.7
Lung + Bone + Liver	2	2.9
Lung + Liver	2	2.9
Bone + Liver	1	1.4
Facial nerve infiltration	1	1.4
Lung + Brain	1	1.4
Lung + Gingiva	1	1.4

All the studied group cases (100%) had total thyroidectomy. Forty-six cases (65.7%) received radioactive iodine (RAI) dose more than 100 mCi with 12 cases (17.1%) did not receive RAI. Forty-two cases received palliative radiotherapy on metastatic bony sites. Only six cases received systemic therapy (**Table 5**).

**Table (5): Distribution of the studied cases according to types of treatment**

Treatment	Type of treatment	No of patients	%
Surgery	Total thyroidectomy	70	100
	Subtotal thyroidectomy	0	0
	Hemi thyroidectomy	0	0
RAI	80 mCi	7	10
	100 mCi	5	7.14
	>100 mCi	46	65.72
	No RAI	12	17.14
External beam radiotherapy	Radical on neck	2	2.9
	Palliative on bone	42	80
Systemic therapy	Chemotherapy	2	2.9
	Tyrosine kinase inhibitors	4	5.7

In **Table (6)** there is a strong statistical relation between ablation response vs. age (more or less than 55), ECOG (0 or more than 1) and bone metastasis. Five of the 58 patients had a complete response (8.6%) while 53 patients had incomplete response (91.4%).

**Table (6): Response after radioactive iodine therapy according to patients' characteristics. (Univariate analysis)**

Patients' characteristics			Complete response (n=5)		Incomplete response (n=53)		P-value
	Total number of cases	Number of cases received RAI	No	%	No	%	
<b>Age</b>							<b>0.018*</b>
18-55	24	19	4	80.0	15	28.3	
>55	46	39	1	20.0	38	71.7	
<b>Sex</b>							0.528
Male	35	31	2	40.0	29	54.7	
Female	35	27	3	60.0	24	45.3	
<b>Site of Mets</b>							
Lung	47	41	4	80.0	37	69.8	0.632
Liver	5	5	0	0	5	9.4	0.472
Bone	47	40	1	20.0	39	73.6	<b>0.013*</b>
Brain	1	1	0	0	1	1.9	1.0
Pleura	1	1	0	0	1	1.9	1.0
Gingiva	1	1	0	0	1	1.9	1.0
Facial nerve	1	1	0	0	1	1.9	1.0
<b>ECOG</b>							<b>0.004*</b>
0	17	15	4	80.0	11	20.7	
>1	53	43	1	20.0	42	79.3	
<b>Total</b>	70	58	5	8.6	53	91.4	

In **Table (7)** four cases out of total 5 cases achieved complete response, 4 of them were high risk, while 53 cases achieved incomplete response, 46 of them were high risk group. show 46 cases received RAI doses more than 120 mCi, 4 cases achieved complete response (8.7 %) while 42 cases achieved incomplete response (91.3%). Five cases received RAI 100 mCi all achieved incomplete response. Seven cases received RAI 80 mCi, one patient had complete response while 6 cases achieved incomplete response.

**Table (7): Response after radioactive iodine therapy according to risk and radioactive iodine dose**

Risk stratification			Complete response (n=5)		Incomplete response (n=53)		P-value
	Total number of cases	Number of cases received RAI	No	%	No	%	
<b>Risk stratification</b>							0.817
<b>Low</b>							
Inter-mediate	1	1	0	0	1	1.9	
High	7	7	1	20.0	6	11.3	
	62	50	4	80.0	46	86.8	
<b>Radioactive iodine dose</b>							0.685
80 mci		7	1	20.0	6	11.3	
100 mci		5	0	0	5	9.4	
>120 mci		46	4	80.0	42	79.2	

In **table (8)** there was a weak statistical link between ablation response and surgery, thyroglobulin (Tg) and presenting symptoms apart from neck swelling, which shows a significant statistical association.

**Table (8) Response after radioactive iodine therapy according to type of surgery, thyroglobulin level and presenting symptoms (Univariate analysis)**

Factors	Complete response (n=5)		Incomplete response (n=53)		P-Value
	No	%	No	%	
<b>Surgery</b>					
Total thyroidectomy	5	100	53	100	1.0
Subtotal thyroidectomy	0	0	0	0	
<b>Thyroglobulin</b>					0.458
<1 ng/ml	1	20.0	5	9.4	
1 ng/ml	4	80.0	48	90.6	
<b>Presenting symptoms</b>					
Neck swelling	4	80.0	2	3.8	≤0.001*
Hoarseness of voice	0	0	4	6.9	0.524
Symptoms related to metastatic disease	3	60.0	30	56.6	0.883

While in **table (9)** there is a low correlation between ablation response and T stage, LN stage, capsule infiltration, multifocality, LVI, gross residual, tumor size and ENE. However, only T3 and Stage III are highly statistically significant.

**Table (9) Response after radioactive iodine therapy according to tumor characteristics (univariate analysis)**

Factors	Complete response (n=5)		Incomplete response (n=53)		P-value		
	Total number of cases	Number of cases received RAI	No	%		No	%
<b>T</b>							
T1	17	13	0	0	13	24.5	0.208
T2	32	24	2	40.0	22	41.5	0.947
T3	12	12	3	60.0	9	17.0	<b>0.023*</b>
T4	9	9	0	0	9	17.0	0.316
<b>Lymph node</b>							0.081
N 0	41	33	1	20.0	32	60.4	
N 1	29	25	4	80.0	21	39.6	
<b>Stages</b>							
I	4	2	0	0	2	3.8	0.658
II	23	19	0	0	19	35.8	0.102
III	10	5	3	60.0	2	3.8	≤0.001*
IV	33	32	2	40.0	30	56.6	0.475
<b>Multi-Focality</b>	4	4	0	0	4	7.6	0.524
<b>LVI</b>	15	12	2	40.0	10	18.9	0.246
<b>Gross residual</b>	4	3	0	0	3	5.2	0.584
<b>Capsular infiltration</b>	23	17	0	0	17	32.1	0.132
<b>Extra-nodal extension</b>	4	1	0	0	1	1.9	1.0
<b>Tumor size</b>							
<2.5 cm	17	14	0	0	14	26.4	0.187
>2.5 cm	53	44	5	100	39	73.6	

**Table (10)** shows association of low strength between DFS and age, site of metastasis and lymph node metastasis. However, RAI dose shows statistically significant association of high strength.

**Table (10): Multivariate logistic regression analysis for DFS**

	Chi-square	df	P value
Age	0.003	1	0.953
Site of metastasis	2.549	2	0.280
LN	2.185	1	0.139
RAI dose	33.261	1	<0.001*

Table (11) show that the median overall survival (OS) was worst in the male sex than female sex and this was of statistically significant. OS was worst in T4 stage and was the best in T1 stage and this was statistically significant.

**Table (11): Kaplan-Meier overall survival**

Variables	Overall Survival				
	Median Survival time	Std. Error	95% CI	Log Rank test	P - value
Age/ years				1.87	0.171
<55 y	90.339	10.23	70.3-110		
≥55 y	65.455	8.64	44.5-82.4		
Gender				4.64	0.031*
Male	57.846	10.012	38.22-77.5		
Female	88.695	9.119	70.82-106		
Pathology				0.842	0.657
Hurthle cell	42.667	15.786	11.72-73.6		
Follicular carcinoma	82.849	10.492	62.2-103.4		
PTC	69.239	9.794	50.04-88.4		
LN				0.088	0.767
Positive	71.609	11.660	48.75-94.5		
Negative	77.008	8.878	59.60-94.4		
T staging				8.2	0.042*
T1	103.429	10.84	82.16-124		
T2	73.978	9.81	54.7-93.2		
T3	77.925	12.28	53.85-101		
T4	41.270	6.61	28.31-54.2		
Course of disease				4.84	0.089
Progressive	45.079	6.157	33.0-57.15		
Stationary	79.738	9.494	61.1-98.34		
Regressive	67.294	3.712	60.01-74.5		
Overall OS	79.06	7.25	64.84-93.28	-	-

Log Rank (Mantel-Cox) was used, CI: confidence interval.

## DISCUSSION

The most prevalent endocrine malignancy is thyroid carcinoma. It accounts for around 3% of all recently found cancer cases. More than 90% of endocrine neoplasms are accounted for by it. Thyroid cancer accounts for around 1% of all cancer deaths worldwide in terms of fatality rates. In fact, DTC accounts for roughly 90% of all thyroid cancer cases (6,7). In our analysis, the percentage of all malignant cases referred to the department throughout the study period that were thyroid carcinomas was 6.04%. The fact that more papillary thyroid carcinoma is being found by neck ultrasound in recent years may be to blame for the increase in well-differentiated thyroid carcinoma cases, which account for 93.5% of all malignant thyroid cancer cases.

The precise strategy for managing DTC is still up for debate. The cornerstone treatment for DTC is thyroidectomy. Moreover, the majority of cases will undergo ablative/adjunctive RAI based on their recurrence risk. I131 is the treatment of choice for papillary and follicular thyroid carcinomas with distant metastases, unlike other cancers, unless they lose the capacity to bind iodine (8).

Well-differentiated thyroid cancer can spread to distant sites during treatment, which may be detected when thyroid cancer first manifests, during follow-up, or as a result of a patient receiving a low dose of RAI that is not concentrated in distant metastatic sites or not being properly evaluated prior to starting treatment (4). DTC with distant metastases was diagnosed in 70 patients in our study, representing 4.1% of all well-DTC

cases during the study period. This is higher than the percentage of well-differentiated thyroid cancer with distant metastases in the USA (SEER: 2.1%), which may be a result of patients delaying seeking medical attention. 58 instances got radioactive iodine out of a total of 70 cases classified as DTC with distant metastases, whereas 12 cases were lost to follow-up.

In this analysis, the majority of patients (65.7%) were over the age of 55, while the remainder (34.3%) were under the age of 55. The study's average age was 57.7 years. According to SEER 22, this age is still older than the median age in the United States, which is 51 years<sup>(9,10)</sup>. This may be due to delay in seeking medical advice thus delay in diagnosis.

The study included 35 female patients who represented approximately 50% of the cases, with a male to female ratio of about 1:1. This finding is similar to that of another study done by *Li et al.*, which discovered a male to female ratio of 1:1.2 in DTC with distant metastasis<sup>(11)</sup>.

LN metastasis in our study represented (41.4%), which corresponds to a Mayo Clinic cross sectional study of 859 patients with DTC. Approximately 37% of cases had LN metastasis during treatment, according to this study. Furthermore, PTC has LN spread ranging from 35% to 50%<sup>(12)</sup>. Another study by *Shah et al.*, discovered that LN spreads was (48%)<sup>(13)</sup>.

The most common histological type in our patients was papillary thyroid carcinoma (61.4%). This agrees with *Boone et al.*<sup>(14)</sup>, who reported that the papillary carcinoma is the most common histologic type of well differentiated thyroid carcinoma, accounting for nearly 80% to 90% of all newly diagnosed thyroid cancers.

The commonest distant metastatic sites in our patients were lung and bone (32.9%), followed by bone (30%), lung (25.7%). This agrees with several previous studies: **Borschitz and his colleagues** reported that the lung and bone to be the preferential sites for thyroid cancer metastasis. Same results were reported by *Ding et al.*, study which found that the most frequent site of remote metastasis in DTC is the lungs, which account for 47.7% of the population, followed by bone metastasis. (24.9%)<sup>(15,16)</sup>.

The RAI ablation success rate (complete response) in our study after different RAI doses at our department, was (8.62%). This coincides with *Iizuka et al.* study that showed successful ablation<sup>(17)</sup>. Another study<sup>(18)</sup> showed that RAI greatly improves survival, particularly in patients over the age of 45, and in patients with well-differentiated grade subgroups in patients with distant metastases, particularly lung metastases.

Despite the fact that the relation between the dose of RAI and ablation response was weak (it was not statistically significant). However, it showed statistical significance (0.001%) in multivariate analysis. This significant failure might be caused by the relation between RAI dose and underlying aggressive disease with more complicated behavior and risk features, and

this disease setting requires further research to fully get the disease's negative and positive predictors.

We discovered that age was a statistically significant negative prognostic factor throughout the study, with a high statistical relation and an elevated failure rate with age more than 55 years old (P=0.018%). This observation was also made by another study<sup>(19)</sup>, which discovered that age is a strong prognostic indicator of well differentiated thyroid cancer carcinoma outcome.

There was a statistically significant association between bone metastasis and RAI ablation success rate (P=0.001). This agrees with *Jannin et al.* study, which reported that nearly one-third of DTC patients with RAI avid bone marrow achieved complete bone marrow response with RAI treatment alone or in combination with external beam irradiation treatment<sup>(20)</sup>.

Our study showed that cases with lung metastasis were the most cases achieved complete response after RAI remnant. However, it did not reach statistical significance (0.632%), it coincides with another study done by *Durante et al.* who showed that lung metastasis is the most common site of remission with RAI treatment<sup>(21)</sup>.

The median overall survival in our study was 79.06 months with confidence intervals (CIs) (64.84-93.28). Age represents one of the most common factors that could alter the overall survival in any cancer study<sup>(19)</sup>. Here in thyroid cancer, age represented a cornerstone factor specially in elders above 55 years at diagnosis. In the current study, increasing age more than 55 years old was associated with lower median OS (65.45 m) compared to median OS for patients with age less than 55 years old (90.339 m). Although it is not statistically significant, it coincides with *Chenyuan et al.* study, which reported that RAI could significantly improve survival in younger patients with well differentiated thyroid cancer with distant metastases<sup>(11)</sup>. This is attributed to that the younger patients showed stronger RAI avidity due to more expression of the sodium iodide symporter, as well as the decrease of the immune system and the more aggressive histological type also explain the poor response to RAI in the older patients.

The male sex had a lower median OS (57.846 m) than the female sex (88.695 m), which was statistically significant (P = 0.031). This may be explained as men take longer to seek medical help than women, resulting in more male cases with higher stages of presentation and, as a result, a higher failure rate<sup>(22)</sup>. According to a study conducted at King Faisal Hospital, they found that both the male gender and being  $\geq 45$  years of age were associated with poor disease survival and outcomes. Another study was executed by *Jonklaas et al.*, who found that prognosis was better among females less than 45 years of age compared to their age-matched male counterparts<sup>(23,24)</sup>.

In our study poor OS was significantly associated with T4 stage (P = 0.042). This coincides

with *Jannin et al.*, who noticed that poor OS is significantly associated with T4 stage <sup>(20)</sup>.

## CONCLUSION

The results of the current study suggested that postoperative radioiodine ablation may be a useful choice for the treatment of well DTC with distant metastases because it lowers the likelihood of side effects, improving OS and preserves a high quality of life.

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**Author contribution:** Authors contributed equally in the study.

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