

Role of Radio-Iodine Ablation According to Risk Stratification in Well Differentiated Thyroid Cancer

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ABSTRACT

The current study includes prospective analysis of 70 patients with well differentiated thyroid cancer to evaluate the role of I^{131} ablation therapy according to risk stratification. The latter includes age, pathological type, histopathological criteria (tumor size-Capsular and vascular invasion- lymph nodal involvement). According to these criteria patient population was divided into low risk group (30 patients) and high risk group (40 patients). The former group received 30 mCi, while high risk group received 80 mCi. I^{131} therapy was repeated every 6 months till achievement of complete ablation or for maximum of 4 doses. Fifty five patients had complete response, while 15 patients had incomplete ablation. The mean dose which produces total ablation in low dose therapy was 93.9 mCi versus 158.2 mCi in high dose therapy group. There was higher response rate in the low risk group compared to the high risk group, yet, the difference is not statistically significant. Higher incidence of incomplete ablation was found in patients with follicular carcinoma, positive capsular and vascular invasion and regional lymph nodal involvement. Also, patients who had done hemithyroidectomy had higher incidence of partial response compared to those who had near total thyroidectomy \pm block neck dissection. Tc99m MIBI scan in addition to estimation of serum thyroglobulin (Tg) level were useful in postablation group for assessment of residual, recurrent or metastatic disease.

In conclusion: In patients with well differentiated thyroid cancer, Low dose ablation therapy had better response in low risk group compared to high dose therapy in high risk group. Also, serum Tg and Tc99m MIBI whole body scan (WBS) are greatly sensitive in follow up of patients after complete ablation for early detection of local recurrence or remote metastases.

Key Words: I^{131} therapy - Risk factors - DTC.

INTRODUCTION

There is general agreement that surgery, whenever feasible, is the primary treatment of choice in differentiated thyroid carcinoma. The

spectrum of surgery is variable, yet, near-total thyroidectomy is preferred because post-surgical thyroid ablation with I^{131} is more effective with small residual [9].

The appropriate dose of I^{131} thyroid ablation is a source of continuing controversy. High fixed dose (75-150 mCi) have been advocated by some authors, obviating the need for reablation [2-3]. Low dose ablation, i.e. a fixed dose of 30 mCi has also been advocated avoiding hospitalization in isolated room with low radiation dose to the patient particularly young individuals who may wish to have children and have a longer life expectancy during which potential tumorigenic effects may be expressed [8,21].

There are multiple factors of prognostic significance on assessing treatment failure in differentiated thyroid cancer including age, tumor size, histopathologic type, extracapsular invasion, vascular or lymphatic invasion. Patients with bad prognostic criteria require more aggressive treatment following surgery [20].

The aim of this study is to assess the role of radio-iodine ablation therapy given according to risk stratification in well differentiated thyroid cancer. Also, to assess the role of Tc99m MIBI and serum Tg as alternative modalities for follow up of post ablated patients with well differentiated thyroid carcinomas.

PATIENTS AND METHODS

The current study includes post operative analysis of 70 patients (42 females-28 males) with well differentiated thyroid cancer. Follow

up was performed in all patients for 2 years. Eligibility criteria for inclusion in this study include:

- Histopathologically proven well differentiated thyroid carcinoma (both low and high risk groups were included).
- Adequate hepatic and renal function.
- Adequate bone marrow reserve.
- Karnovsky performance status > 60%.

All patients presented post operatively, with hemithyroidectomy performed in 7 patients, near total thyroidectomy in 34 patients and near total thyroidectomy associated with block neck dissection in 29 cases.

I¹³¹ therapy: Ablative I¹³¹ therapy was given to all patients according to risk stratification, patients in the low risk group received 30 mCi while those with high risk criteria received 80 mCi:

- Low risk group: 30 patients with well differentiated thyroid cancer with the following criteria:

Age < 40 years, tumor size < 3 cm, No lymphatic, capsular or vascular invasion and no lymph nodal involvement.

- High risk group: 40 patients with well differentiated thyroid cancer with the following criteria:

Age > 40 years, tumor size > 3 cm and/or one of the following pathological criteria: lymphatic, capsular or vascular invasion or multicentricity.

Repeated ablation doses were given every 6 months till either achievement of complete ablation or up to 4 doses, with stoppage of thyroxine 4-6 weeks prior to every dose.

Follow up scanning was performed using I¹³¹ and Tc 99m MIBI WBS prior to ablation doses till complete ablation and every 6 months thereafter till the end of 2 years follow up period. Estimation of serum thyroglobulin (Tg) level was also performed every 6 months.

The results of I¹³¹ therapy using low and high doses according to risk stratification were analyzed.

The response to therapy was assessed according to the following criteria:

- Complete response (complete ablation): No clinical evidence of disease and negative I¹³¹

whole body scan (WBS).

- Partial response (incomplete ablation): 50% reduction of I¹³¹ uptake compared to initial scan.
- Progressive disease: No reduction in I¹³¹ accumulation or appearance of recurrence or metastatic disease.

The sensitivity and specificity of follow up diagnostic study using Tg level, WBS with I¹³¹ and Tc 99m MIBI were calculated using standard statistical evaluation.

RESULTS

All patients included in the current study received ablative I¹³¹ therapy. 30 patients (42.8%) in low risk group received low dose therapy (30 mCi), while 40 patients (57.2%) in high risk group received high dose therapy (80 mCi).

The majority of patients (55 patients) had achieved complete ablation (78.5%), while the remaining 15 patients (21.5%) had incomplete ablation. A higher incidence of complete ablation was found in low risk group (86.6%) (Fig. 1) compared to (72.5%) in the high risk group. The difference between both groups as regards complete response was statistically insignificant ($p > 0.05$) (Table 1).

There was no difference in the rate of complete response between low dose and high dose therapy in relation to the number of doses given. However, a higher response rate in low doses was always found after first, second, third and fourth doses, yet, the difference was statistically insignificant (Table 2).

The possible causes of partial response include:

Pathological type: follicular carcinoma had higher incidence of incomplete ablation (partial response, 55.5%) compared to (9.6%) in papillary carcinoma, with a statistically significant difference between both groups ($p < 0.0001$). The majority of follicular cancer patients (70%) were in the high risk group (Table 3).

Patients with capsular invasion and lymph nodal metastases also showed higher incidence of incomplete ablation (57.1%) (Fig. 2) compared to those without, with a statistically significant difference between both groups ($p < 0.0001$) (Table 3).

Patients who had done hemithyroidectomy had higher incidence of partial response compared to patients who had done near total thyroidectomy (11.7%) or near total thyroidectomy and block neck dissection (24.1%). All cases with incomplete response with near total thyroidectomy ± block neck dissection were seen in high risk group (Table 3).

The sensitivity of diagnosis of residual func-

tioning thyroid tissue immediately postoperatively was 100% for I¹³¹ WBS, compared to 68.5% for Tc 99m MIBI scan, while for postablative scan (After 4 doses), both had 100% sensitivity and specificity.

Concordant results between both I¹³¹, Tc99m MIBI scan and low thyroglobulin level (< 10 ng/ml) was found in 53 patients (Table 4).

Table (1): The relation between the number of doses of radioactive I¹³¹ and response rate in patients who received low dose (30 mci) and high dose of I¹³¹ (80 mci).

No. of doses	Low risk group (30 mci)					High risk group (80 mci)				
	Total No. of patients	Complete response		Partial response		Total No. of patients	Complete response		Partial response	
		No.	%	No.	%		No.	%	No.	%
Single dose	30	10/30	33.3	20/30	66.7	40	12/40	30	28/40	70
Two doses	20	9/20	45	11/20	55	28	10/28	41.6	18/28	46.2
Three doses	11	4/11	36.4	7/11	63.6	18	4/18	22.2	14/18	77.7
Four doses	7	3/7	42.8	4/7	57.2	4	3/14	21.4	11/14	78.5
Total	30	26	86.6	4	13.4	40	29	72.5	11	27.5

$p > 0.05$

Table (2): The relation between cumulative dose of radio-iodine therapy and response rate.

Low I ¹³¹ therapy doses	Complete response in low risk group		High I ¹³¹ therapy doses	Complete response in high risk group	
	No.	%		No.	%
30 mCi	10/30	33.3	80 mCi	12/40	30
60 mCi	19/30	63.3	160 mCi	22/40	55
90 mCi	23/30	76.7	240 mCi	26/40	65
120 mCi	26/30	86.6	320 mCi	29/40	72.5

Table (3): Possible factors that affect response to I¹³¹ ablation therapy.

Possible cause of partial response	No. of patients	No. of patients with partial response (15)	No. of patients with low risk + partial response (4)	No. of high risk patients with partial response (11)
1- Pathologic type:				
- Papillary	52	5 (9.6%)	1 (1.9%)	4 (7.7%)
- Follicular	18	10 (55.5%)	3 (16.6%)	7 (38.8%)
- Total	70	15	4 (5.7%)	11 (15.7%)
2- Capsular invasion:				
- Positive	21 (30%)	9 (42.8%)		9 (42.8%)
- Negative	49 (70%)	6 (12.2%)	4 (8.1%)	2 (4.1%)
3- Lymphnodal involvement:				
- Negative	41 (58.6%)	5 (12.1%)	4 (9.7%)	1 (2.7%)
- Positive	29 (41.4%)	10 (34.4%)		10 (34.4%)
4- Extent of surgery:				
- Hemithyroidectomy	7 (10%)	4 (57.1%)	4 (57.1%)	4 (11.7%)
- Near total thyroidectomy	34 (58.5%)	4 (11.7%)		2 (24.1%)
- Near total + BND	29 (41.5%)	7 (24.1%)		

Table (4): Correlation of thyroglobulin level and radionuclide I¹³¹ and Tc99m MIBI WBS in the follow up of 55 patients of differentiated thyroid cancer.

		Thyroglobulin		
		True negative	False negative	False positive
I131 WBS	True negative	53	-	2
	False negative	-	-	-
Tc-MIBI WBS	True negative	53	-	2
	False negative	-	-	-

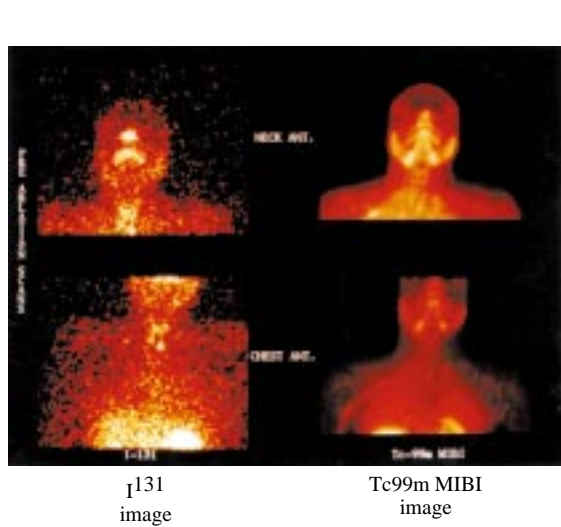


Fig. (1,A) residual thyroid tissue in the neck

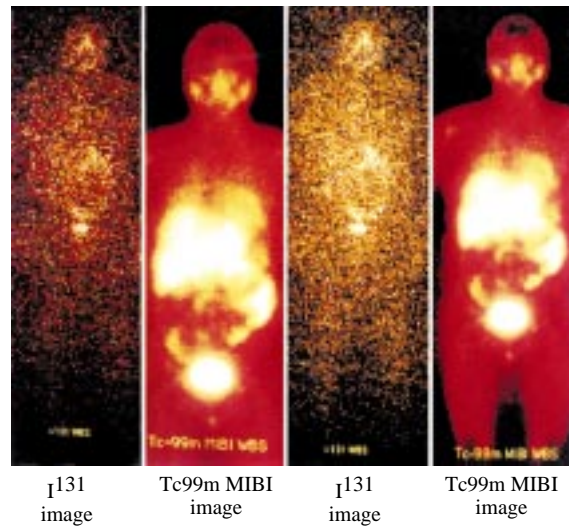


Fig. (1,B) Complete ablation of thyroid tissue

Fig. (1): Low risk patient with complete ablation after single low dose of I¹³¹.

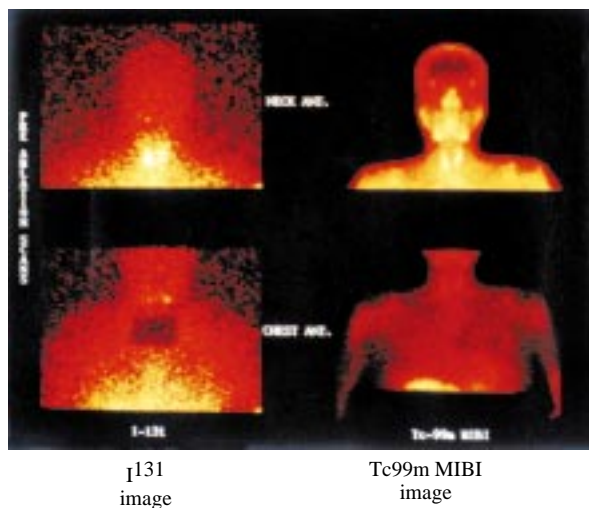


Fig. (2,A): Preablation neck and chest images residual Functioning thyroid tissue in the neck

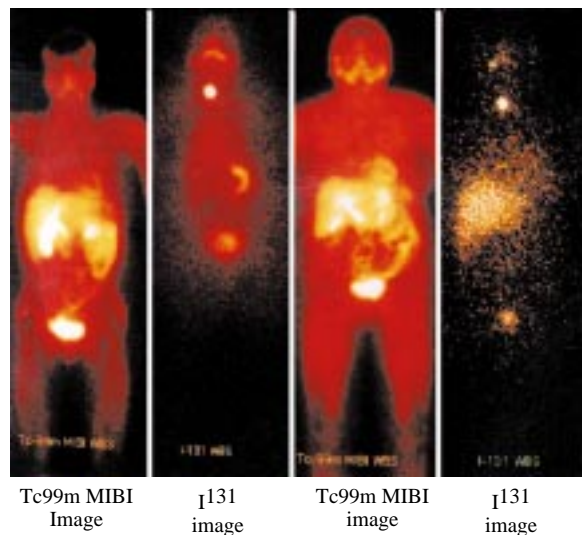


Fig. (2,B): Post ablation therapy follow-up scanning Incomplete ablation after multiple doses of I¹³¹

Fig. (2): High risk patient with incomplete ablation after multiple high doses of I¹³¹.

DISCUSSION

Maxon et al. [12] reported that total thyroid ablation by a combination of surgery and I^{131} ablation therapy is essential to avoid local recurrence and increase survival in patients over 40 years and in patients with metastatic or extrathyroidal cervical disease. Also, El-Haddad et al. [7] stated that the highest survival rate seen was in the group with radical surgery followed by radio-iodine therapy, while the survival rate was significantly decreased in the group with local residual bulky disease after incomplete surgery.

Post-operative I^{131} treatment is strongly advocated in differentiated thyroid cancer because it decreases both recurrent and death rates [13].

As regards I^{131} ablation therapy, El-Haddad et al. [8] demonstrated that low dose ablative therapy of 30 mCi is as effective as high dose ablative therapy of 80 mCi and they recommended to use low dose therapy for at least the first 2 doses, especially in younger age to avoid the risk of complications. Also, Johansen et al. [10] found that there is no difference between 100 mCi and 30 mCi of I^{131} as regards the number of doses needed for complete ablation in residual functioning thyroid tissue.

The prognostic factors of well differentiated thyroid cancer include age, sex, histopathological types, histopathological features (extent of capsular involvement, blood vessels invasion, anaplastic changes, histologic grade of tumor, multifocality of tumor), tumor burden (primary tumor size, tumor extent, lymph node involvement, distant metastases), staging at time of treatment and type of treatment (Extent of surgery) [20].

In the present work, 70 patients with well differentiated thyroid cancer were given I^{131} ablation therapy after their classification according to risk criteria into low and high risk groups. They had received small (30 mCi) and big (80 mCi) ablative doses, respectively. They were followed up for assessment of complete ablation.

Patients in the low risk group had their age below 40 years, whereas 33 patients of high risk group were in second age group (> 40 years). Only 7 patients with high risk had their age below 40 years. Strong [20] concluded that

survival was better in those less than 40 years of age. Tennvall et al. [22] reported that age at diagnosis is an important predictor for prognosis in both papillary and follicular carcinoma.

As regards pathology, the majority of our patients had papillary carcinoma (74.2%), while follicular carcinoma was only encountered in 18 patients (25.8%). This is in agreement with the findings of Clarke [5] who reported higher incidence of papillary carcinoma. Incomplete ablation was found in follicular carcinoma in (55.5%) of our cases compared to only 9.9% in papillary carcinoma, the difference between both groups was statistically significant ($p < 0.00001$). The majority of cases of follicular carcinoma were in the high risk group (70%). Similar higher incidence of partial response to iodine therapy in follicular carcinoma was reported by Bacourt et al. [1], Simpson et al. [19] and Strong [20] who reported that papillary type had higher incidence of response than follicular type as the latter is more common in old age, associated with vascular invasion and anaplastic changes.

The presence of vascular invasion was seen in 16 patients of the high risk group, with 87% of them were in follicular carcinoma. This is in agreement with Tubiana [18] and Schlumberger et al. [23]. Also, the presence of positive capsular invasion had higher incidence of partial response (42.8%) compared to patients without capsular invasion (12.2%) with high statistically significant difference between both groups. Tennvall et al. [22] and Simpson et al. [19] reported that the presence of marked cellular atypia and tumor invasion beyond capsule are important prognostic factors that significantly affect therapeutic outcome.

A statistically significant difference was reported between incidence of incomplete ablation in patients with lymph nodal involvement and those without nodal involvement. This is in agreement with Mc Gregor et al. [14] and Rossi et al. [17]. Whereas El-Haddad et al. [7] stated that lymph nodal involvement had no influence on survival rate.

Patients with papillary carcinoma had higher incidence of lymph nodal involvement (86.2%) than follicular type (13.8%) with a statistically significant difference between both groups. This is in agreement with Brooks et al. and Clarke [4,5].

As regards extent of initial surgical treatment, higher incidence of incomplete response was reported in patients who had done hemithyroidectomy (57.1%) compared to those who had done total thyroidectomy (11.7%) or near total thyroidectomy and block neck dissection (24.1%). All patients with partial response with near total thyroidectomy and/or BND, were seen in the high risk group. This is in agreement with Leung et al. [11], who found that hemithyroidectomy was associated with higher incidence of partial response.

As regards I¹³¹ therapy, all our patient population received radio-iodine therapy. Thirty patients (42.8%) in low risk group received low dose therapy (30 mCi) while 40 patients received high dose therapy (80 mCi). The majority of evaluated patients had complete response (78.5%). Only 15 patients (21.5%) had incomplete ablation. Higher response rate was reported with low risk group (86.6%) compared to (72.5%) in high risk group, with no statistically significant difference between both groups. Also, no difference in the rate of complete response between low and high dose therapy in relation to the number of doses given. This is in agreement with the findings of Creutzig, El-Haddad, Johansen et al. and Maxon et al. [6,8,10, 12].

As regards correlation between cumulative dose of I¹³¹ therapy and response rate, there was higher response rate in low risk group after the whole 4 ablative doses, yet, the difference was statistically insignificant. The mean dose which produced total ablation in low dose therapy was 93.9 mCi versus 158.2 mCi in high dose therapy. This is in agreement with the findings of El-Haddad et al. [8], who reported that the mean dose which produce total ablation in low and high dose therapy, was 90.2 and 149.1 mCi, respectively.

3- Follow up following radio-iodine ablation:

The sensitivity of pre-ablation I¹³¹ WBS for detection of residual functioning thyroid tissue in our study was 100% compared to 68.5% using Tc 99m MIBI so, radio-iodine is the standard diagnostic test in assessment of residual functioning thyroid tissue. Whereas, the specificity of I¹³¹ and Tc 99m MIBI in the post-ablation group was equal to 100%. Similar findings were reported by Ng et al. [15], who reported that Tc 99m MIBI scanning was less sensi-

tive in detection of thyroid remnants, yet, it may reveal both functioning and non-functioning metastases which might be helpful in the follow-up of high risk differentiated thyroid cancer patients. Concordant true negative results between I¹³¹ and Tc 99m MIBI WBS and low serum thyroglobulin were found in 53 patients in our study. Two patients had false elevation of Tg level which returns to < 10 ng/ml after 1 month. This is attributed to slow decline of Tg level over a period of months to reach undetectable levels after I¹³¹ therapy [16]. Similarly, El-Haddad et al. [8] reported that there is a decrease in Tg level to its normal level within 1-3 months after I¹³¹ ablation therapy.

In conclusion, classification of patients according to their risk criteria is very useful in planning doses of I¹³¹ ablation therapy. Low dose ablation therapy had better response in low risk group compared to high dose therapy in high risk group. The former is useful in young age group with low risk criteria to reduce radiation dose to whole body and gonads. Age, pathologic type, histopathologic criteria (capsular, vascular invasion, lymph-nodal involvement and staging) as well as extent of surgery are the main risk factors influencing response to ablation therapy. Finally, Tc 99m MIBI scan in addition to serum Tg level assessment are highly beneficial for diagnosis of early recurrence and metastatic lesions in patients with thyroid cancer after complete ablation of the thyroid gland with no need to interrupt hormonal replacement therapy.

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