

Outcome of Well-Differentiated Thyroid Carcinoma Patients Receiving a Cumulative Doses of ≥ 600 mCi (22GBq) of I-131

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ABSTRACT

Background: There is no maximum limit for cumulative dose of I-131 for persistent disease in well-differentiated thyroid carcinoma (DTC) patients. However, most remissions are obtained with cumulative activity equal to or lower than 600 mCi (22 GBq). On the other hand a significantly increased risk of leukemia and secondary cancers has been reported with high cumulative dose of I-131 (≥ 600 mCi). Above this cumulative activity further radioiodine therapy should be taken on an individualized basis.

Objective: The aim of the study was to see the outcome of patients with well differentiated thyroid carcinoma receiving a cumulative doses (CDs) of ≥ 600 mCi I-131.

Patient and Method: A retrospective study of 72 patients with DTC receiving a CDs of ≥ 600 mCi I-131 in the National Institute of Nuclear Medicine and Allied Sciences (NINMAS), Dhaka during the period of January 1994 up to December 2007 was carried out. Initially all patients were treated by thyroidectomy followed by radioiodine therapy as adjusted by standard protocol. The mean period of follow up was 8.9 ± 6 years.

From the medical files, age, gender, histopathological variant, thyroid remnant and radio ablation doses, follow up data were recorded. Age was further categorized as <45 and ≥ 45 years. Thyroid bed remnant was designated as significant if the thyroid bed uptake was $\geq 5\%$ after surgery. Dose was categorized in ≤ 5 dose and > 5 doses to find its association with status on last follow up. Disease free (DF) was established as: undetectable or suppressed serum Tg levels <2.0 ng/mL and stimulated serum Tg level <10 ng/mL, two consecutive negative whole body scans.

Results: A total of 38 patients had papillary carcinoma, eight had follicular variant of papillary carcinoma and 26 had follicular carcinoma. Age range at diagnosis was nine to 72 years. There were 22 males and 50 females giving a M: F ratio of about 1:2. Among the 72 patients 25 patients had lymph node metastases, eight had lung metastases and 20 had bone metastases at presentation. Twenty-one patients died during the whole observation period and 20 of them were cancer related. Two patients developed second malignancy.

Conclusion: DTC patients with follicular variant, ≥ 45 years of age, having bone metastasis and significant thyroid remnant have less favourable outcome in spite of high cumulative doses of radioiodine. DTC patients with higher TNM stage and bone metastasis require higher and more radioiodine doses.

Key Words: Well differentiated thyroid carcinoma, Cumulative Dose

INTRODUCTION

Thyroid cancer is one of the commonest endocrine malignancies. Well-differentiated thyroid carcinoma (DTC) accounts for 2% of all cancers (1). Surgical resection is the mainstay of treatment for DTC. Radioactive iodine (RAI) is used as an adjuvant therapy to reduce the risk of tumour recurrence and to facilitate future cancer surveillance. The outcomes of DTC patients are excellent with long term disease survival rates approaching 90% over 20 years (2,3). It has been found that age, sex, size of the tumour, stage of disease, distant metastasis and completeness of resection are factors influencing the prognosis significantly (4). Despite the overall excellent outcome some DTC patients have a worse prognosis and are frequently unresponsive to conventional therapy requiring multiple doses of RAI. The disease persists or recurs with a considerable impact on quality of life in up to 60% of the patients (5, 6).

There is no maximum limit for cumulative dose of I-131 for persistent disease in DTC patients. However, most remissions are obtained with cumulative activity equal to or lower than 600 mCi (22GBq). Durante et al. clearly showed 96%

of patients with DTC and advanced diseases will respond with this activity (7). Many authors consider that 600 mCi of CDs would be a limit to consider RAI refractoriness. On the other hand, a significantly increased risk of leukemia and secondary cancers has been reported with high cumulative dose of I-131 ($\geq 600\text{mCi}$) (8, 9). The aim of the present study is to assess the outcome of patients with DTC receiving a cumulative dose of ≥ 600 mCi (22GBq) I-131.

PATIENT AND METHOD

A retrospective study of 72 patients with DTC receiving a CDs of ≥ 600 mCi I-131 in the National Institute of Nuclear Medicine and Allied Sciences (NINMAS), Dhaka during the period of January 1994 up to December 2007 was carried out. All patients were initially treated by thyroidectomy followed by radioiodine therapy as adjusted by standard protocol. Patients with enlarged lymph nodes both pre and intraoperatively underwent regional neck dissection.

From the medical files age, gender, histopathological variant, thyroid remnant and radio ablation doses, follow up data were recorded. Age was further categorized as <45 and ≥ 45 years. Staging was done at the time of initial treatment according to The American Joint Committee on Cancer (AJCC) (10). Thyroid bed remnant was designated as significant if the thyroid bed uptake was $\geq 5\%$ after surgery. Dose was categorized in ≤ 5 dose and >5 doses to find its association with status on last follow up.

Radioactive iodine therapy (RIT): RITs were performed in fixed dose method. 100 mCi (3700MBq) was given for thyroid remnants, 150 mCi (5550MBq) for lymph node and pulmonary metastasis, 200-250 mCi (7400-9250 MBq) for bone metastases. However, dose was adjusted according to the age and volume of remnant in the thyroid bed. Dose was reduced when there was significant thyroid remnant determined by thyroid bed uptake $\geq 5\%$ after surgery correlated with the

ultrasonography of neck. After first therapy the decision on further therapy and dose adjustment was based on the location of metastasis, the previous dose, persistently elevated Tg level (with or without positive whole body scan) and ultrasonographic findings of the neck. Excision of recurrent enlarged lymph nodes was done prior to RIT.

Follow Up: The mean period of follow up was 8.9 ± 6 years. Follow up included whole body scan after one year of each RIT therapy and periodic whole body scan, TSH and Tg measurement, cervical ultrasound. Computerized Tomography scan, MRI was used when required for detection of metastases. Using these parameters status on last follow up was classified as disease free (DF) and not disease free (NDF).

DF was defined as: undetectable Tg levels (with or without levothyroxine suppression), two consecutive negative whole body scans. Suppressed Tg level <2.0 ng/mL and stimulated Tg level <10.0 ng/mL were used as cut off values.

NDF was designated either as stable disease (SD) or progressive disease (PD). SD was established as unaltered Tg levels, persistent uptake in the previous foci but without progression or new metastatic foci. PD was established as increasing consecutive Tg levels despite RIT and/or detection of new metastatic foci.

Death was classified into death due to cancer (DTC), death due to other cause and death due to second malignancy.

Statistical Analysis: Chi-square test was performed in order to verify association considering status on last follow up as dependent. Independent sampling by one-way ANOVA and t test were conducted for continuous variable where response variable was cumulative dose. Survival curve was estimated by the Kaplan-Meier product limit method. Significance was defined at $p < 0.05$ level. The SPSS (16.0) statistical package was used for

RESULTS

Total number of DTC patients referred to NINMAS during the period 1994 up to 2007 was 1186. Among the DTC patients 72 received a cumulative dose of ≥ 600 mCi I-131 giving a proportion of 6% of the total referred DTC patients. There were 22 male patients and 50 female patients. The age ranged from nine to 72 years with a mean of 39 ± 15 years. 61% patients were < 45 years and 39% patients were ≥ 45 years. Papillary carcinoma was found in 38 cases, follicular carcinoma in 26 cases and follicular variant of papillary carcinoma in 8 cases. 32 cases (45%) were considered TNM stage I, 14 were stage II (19%), 10 were stage III (10%) and 16 were stage IV (16%). Table -1 provides characteristics of the 72 patients in our series.

Table 1: Characteristics of the study group

	No	%
Total number of patients	72	
Sex		
Male	22	30
Female	50	70
Age		
<45 years	44	61
≥ 45 years	28	39
Range	9 -72 years	
Mean	39 ± 15 years	
Tumour Histology		
Papillary	38	53
Follicular variant of papillary carcinoma (FVPCT)	8	11
Follicular	26	36
TNM stage		
I	32	45
II	14	19
III	10	14
IV	16	22

On initial presentation 25 patients had lymph node metastasis, 20 patients had bone metastasis and eight patients had lung metastasis. Twenty one

patients died during the whole observation period and 20 of them were cancer related yielding a cancer specific mortality ratio of 27.8% (95% CI 17.2 to 38.4%) for the whole cohort. Table-2 shows the outcome and status on last follow up. Twenty six patients became DF on last follow up while 25 patients were NDF on last follow up. 18 patients died from cancer (DTC), 2 died from second malignancy and 1 died from other cause. Cancer specific survival by Kaplan-Meier Curve was 86.7% at five years, 71.9% at 10 years and 60.4% at 15 years (Figure1).

Table 2: Outcome and status on last follow up

Status	Number	Percentage
Disease free(DF)	26	36
Not disease free (NDF)	25	35
Death due to cancer (DTC)	18	25
Death due to other cause	1	1
Death due to second malignancy	2	3

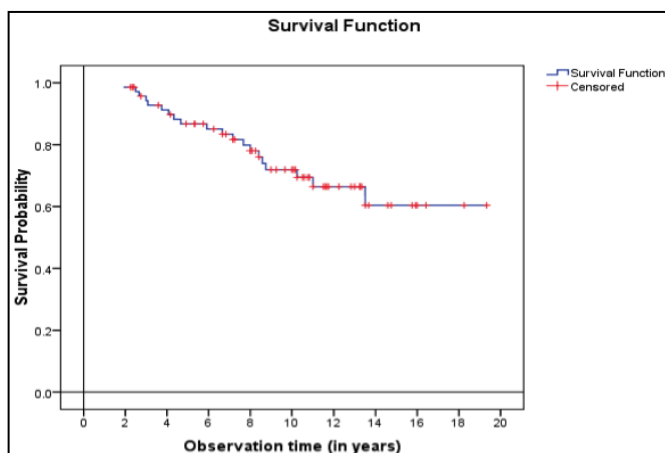


Figure 1: Kaplan-Meier Curve

The amount of CDs varied from 600 to 2400 mCi with a median of 765 mCi of I-131. Maximum CDs was 2400 mCi (88 GBq).

DISCUSSION

The aim of this study was to obtain the outcome of DTC patients receiving a CDs of ≥ 600 mCi of I-131. There is actually no maximum limit for cumulative I-131 dose in case of persistent disease in DTC patients. Previous studies showed that most remissions are obtained with cumulative activity equal or lower than 600 mCi (2, 11).

There are several studies regarding the prognostic factors of DTC patients. However there are few studies focusing on the impact of cumulative dose of RIT. This study encompassed a relatively longer follow up period up to 19 years enabling the evaluation of tumour behavior to multiple doses of radio iodine and their effect on survival.

Increasing age significantly correlates with mortality in DTC patients as a whole (12, 13). In this subset of patients age is associated with death ($p < 0.005$) where patients aged ≥ 45 years have worse prognosis as compared to patients aged < 45 years (OR 5, 95% CI 1.65-15). There is a controversial consensus regarding the effect of gender on outcome of DTC where some of the authors speculate poor outcomes in men (14-17) while others found no effect of gender on mortality (18,19). In this study group there was no association between gender and death ($p=0.39$).

In accordance to others, this study showed that patients with follicular and follicular variant of papillary carcinoma had worse prognosis (20). Death and histopathological variant are associated ($p < 0.02$) where follicular variant has 4.5 (OR 4.5, 95% CI 1.5-13) times greater probability of death as compared to other variants. As follicular variant has the hematogenic spread they have the propensity for metastases at diagnosis. This is also the reason for having progressive disease requiring higher cumulative dose.

The association between TNM stage and cumulative dose is concordant with previous studies (21, 22). Higher CDs were used in higher TNM stage tumours ($p < 0.001$), which was expected considering stage III and IV have a worse prognosis. Distant metastasis is associated with mortality ($p < 0.06$) having five (OR 5, 95% CI 1.67-15.21) times greater probability of death than patients having no metastasis or local metastasis. The mean CDs varied significantly according to the site of metastasis and further tests revealed local

metastasis and bone metastasis significantly differs in terms of CDs ($p < 0.001$). Death was associated with thyroid bed remnant at 10% level of significance ($p < 0.06$). This can be explained as presence of large amount of remnant has a negative impact on dose calculation necessitating less dose to avoid post ablation complication. On the other hand, improper surgery and dosage both leads to persistent disease requiring further doses. Significant association was observed between disease status at last follow up and number of doses where significance level was < 0.1 . Among the DF group, 93% received ≤ 5 doses of I-131 whereas 7% received > 5 doses of I-131. 65% of the patients who died of cancer received ≤ 5 doses and 35% received > 5 doses of I-131. The maximum CDs received by a patient who became DF on last follow up were 900 mCi.

High cumulative doses of I-131 may be associated with significant increase in second primary malignancy (SPM). There are controversial reports regarding this issue. Some studies (23, 24) support the fact whether other studies (25, 26) showed an increased incidence of neoplasms unrelated to I-131 therapy. Although I-131 is preferentially taken up by normal and malignant follicular cell it is also taken up and accumulated in the salivary glands, stomach, colon, urinary bladder and lactating breast. So theoretically the risk of cancer in these organs is more in DTC patients treated with I-131. Usually these second malignancy occur between two and 10 years after therapy with a prevalence of about 0.5% (27). A significant risk of leukemia has been also reported in patients with high CDs that is > 600 mCi (12). In this study two patients died of second malignancy, one from leukemia and the other from carcinoid tumour. Leukemia occurred 7 years after the initial RIT and that particular patient received four doses of RIT with a CDs of 600 mCi. Carcinoid tumour developed in the uterus of the second patient 4 years after the initial therapy and she received CDs of 850 mCi of I-131.

Another study revealed that DTC patients may have a common etiology and or genetic mechanism rather than causal relationship in developing second malignancy disregarding the fact related to I-131 therapy (28).

In this study the mean follow up was less than 10 years. A longer follow up with a large number of patients is required for establishing information, which may have an impact on patient management.

CONCLUSION

DTC patients with follicular variant, ≥ 45 years of age, having bone metastases and significant thyroid remnant have less favourable outcome in spite of high cumulative dose. DTC patients with higher TNM stage and bone metastases require higher and more radioiodine doses. Although there is no cut off point for stopping radioiodine therapy it should be decided case-by-case basis ensuring the quality of life and disease progression rate.

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