Article published online: 2022-03-30

Original Article

Outcomes following I-131 treatment with cumulative dose exceeding or equal to 600 mCi in differentiated thyroid carcinoma patients

ABSTRACT

To evaluate treatment outcomes following radioactive iodine (RAI) treatment with a cumulative dose of ≥600 mCi in differentiated thyroid carcinoma (DTC) patients, a retrospective review of medical records was done in 176 DTC patients with a cumulative dose of 600 mCi from January 1993 to December 2013. All patients were followed up for at least 2 years after receiving 600 mCi of I-131 treatment. Remission criteria were no clinical and imaging evidence of disease and low serum thyroglobulin levels during thyroid-stimulating hormone suppression of <0.2 ng/ml or of <1 ng/ml after stimulation in the absence of interfering antibodies. A total of 176 patients were included in the study: 137 – papillary thyroid cancer, 29 – follicular thyroid cancer, 9 – mixed papillary and follicular thyroid cancer, and 1 – Hurthle cell carcinoma. Most of the patients (118, 67%) had locoregional metastasis, whereas 48 patients (27%) had distant metastases at presentation. The median cumulative dose was 900 mCi (range: 600–2200 mCi). The mean follow-up period was 82.84 ± 42.41 months. Only 16 patients (9.1%) met remission criteria at the end of treatment. The rest of patients (160, 90.9%) were not remitted: stable disease in 94 (53.4%), at least 1 metastasis without I-131 uptake in 34 (19.3%), progressive disease in 21 (11.9%), and death during the whole follow-up period in 11 (6.3%). Two patients (1.1%) developed second primary malignancy. Eighteen cases were suspected of bone marrow suppression (14 cases [7.9%] had anemia and 5 cases [2.8%] had neutropenia). Seven patients (3.9%) developed permanent salivary gland dysfunction. Although the complications after receiving RAI treatment with a cumulative dose of ≥600 mCi were low and not severe, the patients with remission were in <10%. Our study suggests that the decision to administer further treatments should be made on an individual basis because beneficial effects may be controversial.

Keywords: 600 mCi, cumulative dose, differentiated thyroid cancer, radioiodine therapy

INTRODUCTION

Distant metastases occur in <10% of patients with papillary and follicular carcinoma but represent the most frequent cause of thyroid cancer-related death. Treatment of distant metastasis (DM) patients is based on radioiodine and locoregional therapies. One-third of DM patients have no I-131 uptake and die because of radioiodine refractory (RR).[1] According to the American Thyroid Association (ATA) 2015, radioiodine refractory is classified in four ways: (i) the malignant/metastatic tissue does not ever concentrate RAI, (ii) the tumor tissue loses the ability to concentrate RAI after previous evidence of RAI-avid disease, (iii) RAI is concentrated in some lesions but not in the others, and (iv) metastatic disease progresses despite significant concentration of RAI.[2] These conditions have led to the development of targeted therapy and tyrosine kinase inhibitors, which have shown clinical activity in Phase III trials.[3,4] However, these drugs have significant

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Submitted: 16-Apr-2020, **Revised:** 18-Jun-2020, **Accepted:** 26-Jun-2020, **Published:** 22-Aug-2020

Access this article online	
Website: www.wjnm.org	Quick Response Code
DOI: 10.4103/wjnm.WJNM_49_20	

How to cite this article: Kaewput C, Pusuwan P. Outcomes following I-131 treatment with cumulative dose exceeding or equal to 600 mCi in differentiated thyroid carcinoma patients. World J Nucl Med 2021;20:54-60.

toxicities. The previous study of Durante *et al*.[5] revealed that most remission is obtained with cumulative activity equal to or lower than 600 mCi (22 GBq). The cumulative activities of I-131 larger than 600 mCi are associated with an increased risk of cancer and leukemia. The aim of our study was to study the outcomes and complications in differentiated thyroid carcinoma (DTC) patients who received RAI treatment with a cumulative dose exceeding or equal to 600 mCi.

MATERIALS AND METHODS

Patients

A retrospective study of DTC patients who received RAI treatment with a cumulative dose exceeding or equal to 600 mCi in the Division of Nuclear Medicine, Faculty of Medicine Siriraj Hospital, from January 1993 to December 2013 was performed. Each patient was reclassified in accordance with the seventh edition (AJCC 2009) of the TNM staging system for DTC. The 2009 ATA initial risk stratification system was used in evaluation of the risk of recurrence at initiation in each patient (low-risk patients were defined as having intrathyroidal DTC with no evidence of extrathyroidal extension, vascular invasion, or metastases; intermediate-risk patients demonstrated either microscopic extrathyroidal extension, cervical node metastases, RAI-avid disease in the neck outside the thyroid bed, vascular invasion, or aggressive tumor histology; high-risk patients had gross extrathyroidal extension, incomplete tumor resection, distant metastases, or inappropriate post-operative serum thyroglobulin (Tg) values). From the medical folder, age at diagnosis, gender, histopathological type, tumor invasion, radioiodine uptake of postoperative thyroid remnant, radioiodine doses, follow-up period, and outcome of treatment after receiving RAI treatment with a cumulative dose exceeding or equal to 600 mCi were recorded. Patients who were lost to follow-up or died within the first 2 years were excluded. The study was approved by Siriraj Ethics Committee for Human Experiment for retrospective reviews of patient medical records, and the need for informed consent was waived (COA no. Si 106/2015). The patient characteristics are described in Table 1.

Outcome of treatment

All patients were followed up for at least 2 years (mean follow-up period was 82.84 ± 42.41 months). Follow-up included whole-body scan (WBS) after RAI treatment and other imaging modalities such as ultrasound (US), computed tomography (CT), or magnetic resonance imaging, and subsequent thyroid-stimulating hormone (TSH), Tg, and Tg antibody (TgAb) measurements were used for detection of metastatic site. Using these, parameter status on follow-up was classified as remission and nonremission.

Table 1: Baseline demographic and clinical characteristics (*n*=176)

Characteristics	*n* (%)
Gender (female)	116 (65.9)
Age at diagnosis (years), mean±SD	43.22±17.68
24-h I-131 uptake, median (range) (%)	3.3 (0.2-35.1)
Histologic cell type	
PTC	137 (77.8)
FTC	29 (16.5)
Mixed papillary and follicular cell carcinoma	9 (5.1)
Hurthle cell carcinoma	1 (0.6)
Metastasis	
No	10 (5.7)
Locoregional metastasis	118 (67.0)
Distant metastasis (mediastinal node, lung, and bone metastasis)	48 (27.3)
Total I-131 dose, median (range) (mCi)	900 (600-2200)
Follow-up period (months), mean±SD	82.84±42.41

PTC: Papillary thyroid carcinoma, FTC: Follicular cell carcinoma, SD: Standard deviation

Remission was defined according to:

1. No clinical evidence of disease
2. No imaging evidence of tumor by RAI imaging (no uptake at thyroid bed and no uptake outside the thyroid bed on posttreatment WBS and no imaging evidence of tumor on a recent diagnostic or posttreatment WBS) and/or neck US. The images were interpreted by an experienced nuclear medicine physician and a diagnostic radiologist
3. Low serum Tg levels during TSH suppression (<0.2 ng/ml) or after stimulation (<1 ng/ml) without interfering TgAb (<40 IU/mL).

Nonremission was defined as three groups:

a. Stable disease (SD) was classified as unaltered Tg levels, persistent uptake in the previous foci without progression or new metastatic foci
b. Progressive disease (PD) was established as increasing consecutive Tg levels and/or detection of new metastatic foci
c. At least 1 metastasis without I-131 uptake.

Complications from radioiodine treatment were described as:

1. Second primary malignancy (SPM) was clarified as solid or hematologic malignancies that occurred after receiving a cumulative dose exceeding or equal to 600 mCi of I-131. Histological results were obtained for all SPMs to exclude the possibility of metastases
2. Bone marrow suppression was clarified as abnormal of any series of complete blood count on the follow-up period after receiving a cumulative dose exceeding or equal to 600 mCi of I-131. The bone marrow suppression

was classified according to the WHO classification as described below:

- Neutropenia is diagnosed if absolute neutrophil count (ANC) <1,500 cell/mm^3
  - Mild neutropenia ANC 1000–1500 cell/mm^3
  - Moderate neutropenia ANC 500–1000 cell/mm^3
  - Severe neutropenia ANC <500 cell/mm^3
- Anemia is diagnosed if hemoglobin (Hb) <11 g/ml
  - Grade 1 (mild) Hb 9.5–10.9 g/ml
  - Grade 2 (moderate) Hb 8.0–9.4 g/ml
  - Grade 3 (serious) Hb 6.5–7.9 g/ml
  - Grade 4 (life-threatening) Hb <6.5 g/ml
- Thrombocytopenia is diagnosed if platelet count <100,000/μl

3. Salivary gland dysfunction was clarified as dry mouth, lack of taste, or sialadenitis that patient complained as shown in the medical record on the follow-up after radioiodine treatment. Sialadenitis was clinically diagnosed by swelling in the region of major salivary glands with or without pain with spontaneous resolution and without clinical signs of bacterial or viral infection.

Statistical analysis

Continuous variables were presented as mean and standard deviation. Categorical variables were presented as counts with percentage. $P < 0.05$ was considered statistically significant. Remission outcomes were analyzed using multiple logistic regression for univariate and multivariate analyses. All analyses were conducted using the SPSS software (version 22.0, IBM Corporation, Armonk, NY, USA).

RESULTS

Total number of DTC patients referred to the Division of Nuclear Medicine, Faculty of Medicine Siriraj Hospital, during period January 1993 up to December 2013. Among the 227 DTC patients who received a cumulative dose of ≥600 mCi of I-131, 51 patients were excluded due to lost to follow-up within the first 2 years. Then, 176 patients were enrolled in the study (116 women, mean age: 43.22 ± 17.68 years, range: 9–85 years). The total therapeutic dose ranged from 600 to 2200 mCi. The most common primary tumor histology type was papillary thyroid carcinoma in 137 cases (77.8%). The mean follow-up period was 82.84 ± 42.41 months. Patients and outcomes following I-131 treatment with a cumulative dose exceeding or equal to 600 mCi on the last follow-up are described in Figure 1.

Remission

Sixteen patients (9.1%) were diagnosed as being disease free at the end of the follow-up period (12 females with mean age at diagnosis of remission cases of 41.1 ± 16.5 years, mean total therapeutic dose of 795.6 ± 136.4 mCi, mean 24-h I-131 uptake of 3.5% ± 2.4%). Low, intermediate, and high risks of recurrent disease were observed in 5, 10, and 1 case, respectively. The mean period of follow-up was 92.8 ± 35.7 months, as described in Table 2. The univariate and multivariate analyses of significant prognostic factor comparison between the remission and nonremission groups are described in Table 3.

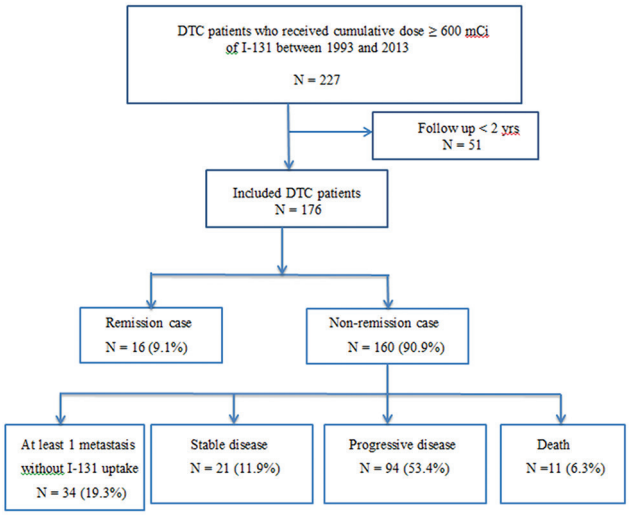

Figure 1: Flowchart of the population and outcomes following I-131 treatment with a cumulative dose exceeding or equal to 600 mCi

Nonremission

There were 160 nonremission cases (105 females with mean age at diagnosis of 43.4 ± 17.9 ng/ml, mean total therapeutic dose of 944.01 ± 236.9 mCi, mean 24-h I-131 uptake of 5.2% ± 5.6%). Low, intermediate, and high risks of recurrent disease were observed in 6, 107, and 47 cases, respectively. The mean period of follow-up was 83.7 ± 43.6 months. Ninety-four cases (53.4%) had SD, 34 (19.3%) had at least 1 metastasis without I-131 uptake, and 21 (11.9%) had PD. Death was found in 11 cases (6.3%), 1 died from pneumonia sepsis, 1 case was secondary malignancy related (non-Hodgkin lymphoma [NHL]), and the rest 9 cases died from an unknown cause. There was no significant difference in the mean survival time of death group (73.5 ± 39.7 months) and alive group (84.9 ± 42.7 months), $P = 0.39$.

Among the 160 cases of nonremission cases, DM was found in 117 patients (73.1%), including 34 cases of bone, 32 cases within lungs, and 51 cases within mediastinum. Locoregional metastasis was found in 23 cases.

Complications

There were 2 patients (1.1%) of SPM, 18 patients (10.2%) of

Table 2: Remission cases following radioactive iodine treatment with cumulative dose ≥600 mCi

Patient number	Age at diagnosis	Gender	24-h I-131 uptake before RAI Rx	Diagnosis (site of metastasis)	Risk of recurrence (at initiation)	Total dose (mCi)	F/U period (months)	Comments
1	67	Male	1.06	PTC	Low	600	77	Persistent uptake at thyroid bed since the second dose
2	22	Female	2.3	PTC	Low	810	(113)	Persistent uptake at thyroid bed since the first dose
3	41	Female	7.9	Mixed PTC and FTC	Low	710	(199)	
4	15	Male	2.37	FTC	Low	930	(37)	
5	37	Female	3.5	FTC	Low	980	(114)	
6	26	Female	6.5	PTC (CLN)	Intermediate	900	102	
7	30	Male	2.9	PTC (CLN)	Intermediate	930	158	
8	33	Female	1	PTC (CLN)	Intermediate	600	89	
9	37	Female	2.37	PTC (CLN)	Intermediate	800	47	
10	60	Female	2.5	PTC (CLN)	Intermediate	800	75	
11	70	Female	7.11	PTC with vascular and capsular invasion	Intermediate	750	99	
12	63	Female	1.66	PTC (CLN)	Intermediate	600	97	
13	37	Female	6.5	PTC (CLN)	Intermediate	1100	102	
14	36	Female	1.57	PTC (CLN)	Intermediate	900	41	
15	32	Male	7.14	PTC (CLN)	Intermediate	750	82	
16	53	Male	4.6	FTC (bone)	High	800	151	

PTC: Papillary thyroid carcinoma, FTC: Follicular cell carcinoma, RAI: Radioactive iodine, CLN: Cervical lymph node

Table 3: Univariate and multivariate analyses of significant prognostic factors for remission cases (*n*=16)

Characteristics	Remission, *n* (%)	Nonremission, *n* (%)	*P*	Crude		Adjusted	
				ORs (95% CI)	*P*	ORs (95% CI)	*P*
Age (years), mean±SD	41.1±16.5	43.4±17.9	0.62				
<55	12 (9.4)	116 (90.6)	0.55	Reference		Reference	
≥55	4 (8.3)	44 (91.7)		0.88 (0.27-2.87)	0.83	0.96 (0.25-3.67)	0.96
Gender							
Female	11 (9.5)	105 (90.5)	0.80	Reference		Reference	
Male	5 (8.3)	55 (91.7)		0.87 (0.29-2.62)	0.80	1.07 (0.30-3.83)	0.92
RAIU (%), mean±SD	3.5±2.4	5.2±5.6	0.24				
≤1.9	5 (9.6)	47 (90.4)	0.31	Reference		Reference	
2-3.9	6 (18.2)	27 (81.8)		2.09 (0.58-7.50)	0.26	2.33 (0.55-9.77)	0.25
≥4	5 (8.2)	56 (91.8)		0.84 (0.23-3.08)	0.79	0.77 (0.19-3.16)	0.71
Cell type							
PTC	12 (8.8)	125 (91.2)	0.96	Reference		Reference	
FTC	3 (10.3)	26 (89.7)		1.20 (0.32-4.56)	0.79	2.59 (0.33-20.51)	0.37
Others	1 (10.0)	9 (90.0)		1.16 (0.14-9.93)	0.89	0.91 (0.07-11.06)	0.94
Risk of recurrence							
Low	5 (45.5)	6 (54.5)	<0.001	Reference		Reference	
Intermediate	10 (8.5)	107 (91.5)		0.11 (0.03-0.43)	0.002	0.05 (0.01-0.49)	0.01
High	1 (2.1)	47 (97.9)		0.03 (0.00-0.26)	0.002	0.01 (0.00-0.17)	0.003
Metastasis							
No	5 (14.3)	30 (85.7)	0.24	Reference		Reference	
Yes	11 (7.8)	5 (92.2)		0.51 (0.16-1.57)	0.24	4.45 (0.50-39.66)	0.18

OR: Odds ratio, CI: Confidence interval, SD: Standard deviation, RAIU: Radioactive iodine uptake, PTC: Papillary thyroid carcinoma, FTC: Follicular cell carcinoma

suspected bone marrow suppression, and 7 patients (3.9%) of salivary gland dysfunction.

Second primary malignancy

Two of 176 patients developed SPM following I-131 treatment with a cumulative dose exceeding or equal to 600 mCi. These included 1 case of NHL and 1 case of invasive ductal carcinoma of the breast. The first case was a 65-year-old man with PTC and cervical lymph node (LN) metastasis who was diagnosed with NHL 20 months after the cumulative activity of I-131 of 600 mCi. He presented with abdominal pain and gastric ulcer, as seen on the gastroscopy. His pathological report from

gastric biopsy revealed NHL. Finally, he died from NHL. The second case was a 63-year-old woman with PTC and cervical LN metastasis who was found invasive ductal carcinoma of the right breast 2 years after the cumulative activity of I-131 of 600 mCi. She underwent right total mastectomy with sentinel LN biopsy and completed a session of chemotherapy. Then, she was in a complete remission of breast cancer.

Bone marrow suppression

At least 6 months after RAI treatment with a cumulative dose of 600 mCi, 18 cases (10.2%) were suspected of bone marrow suppression. Thirteen cases (7.4%) developed anemia, four patients (2.3%) had neutropenia, and the remaining one case (0.5%) had anemia with neutropenia.

Anemia

Fourteen cases had anemia after RAI treatment with a cumulative dose of 600 mCi (10 female [78.5%], mean age at diagnosis: 47.07 ± 16.99 years, mean Hb: 10.11 ± 0.83 g/ml). Eight cases were recovery after 6-month follow-up and the rest six cases had persistent anemia (mean follow-up period of 20.14 ± 9.13 months). Six cases with persistent anemia were 3 cases of grade I and 3 cases of Grade II anemia. Two cases of Grade II anemia, one was found lower gastrointestinal bleeding and one was proven of iron-deficiency anemia. The remaining four cases were not found the definite cause of persistent anemia.

Neutropenia

Five cases had mild neutropenia after RAI treatment with a cumulative dose of 600 mCi (4 females, mean age at diagnosis: 27 ± 4.42 years, mean ANC: 1,233.4 ± 207.63 cell/mm3). Four cases were recovery and 1 case had persistent mild neutropenia (mean follow-up period of 13.2 ± 4.96 months). The case with persistent mild neutropenia was a 27-year-old female PTC patient with cervical node, bilateral lungs, and bone metastases. She was found mild neutropenia (ANC: 1,070 cell/mm3) after receiving the fourth session of I-131 therapy (cumulative dose of 600 mCi). After 15-month follow-up, ANC was slightly increased with the level of 1400 cell/mm^3 without clinical symptom. This case also had persistent Grade I anemia without a definite cause.

Salivary gland dysfunction

Seven cases were classified as salivary gland dysfunction. Three of seven cases had dry mouth with diagnosed as xerostomia and the rest four cases had sialadenitis. From these seven patients, three cases complained about salivary gland dysfunction before the cumulative activity of I-131 of 600 mCi (1 case after 150 mCi, 1 case after 210 mCi, and 1 case after 300 mCi). All of the seven cases had persistent symptoms.

DISCUSSION

The outcomes of DTC patients are excellent, with long-term disease survival rates approaching 90% over 20 years following appropriate treatment. Despite the overall excellent outcome, some DTC patients have DM with worse prognosis and are frequently unresponsive to conventional therapy requiring multiple doses of RAI therapy.[6] One-third of the DM patients have no I-131 uptake and die because of RR. The previous study of Wassermann *et al.* found that patients were classified as progressive RR had a worse prognosis which could justify molecular targeted therapy. In contrast, cases of nonprogressive RR found prolonged survival times which should be managed with "wait and see."[7] Our study found high incidences of nonremission cases (91.9%) after RAI treatment with a cumulative dose of ≥600 mCi, and most of the cases had SD (53.4%). The previous study of Nasreen *et al*.[8] revealed a higher incidence of disease-free patients (36%) and rather low incidence of nondisease-free group (35%) after receiving a cumulative dose of ≥600 mCi I-131 as compared to our study. It is possible due to different remission criteria in their study and shorter period of follow-up in our study. Another reason was that most of the patients in their study had TNM Stage I (45%) which has high chance to be in remission. Martins-Filho *et al*. found that disease status was positively associated with TNM stage by multiple logistic regression analysis. Patients with higher staging (III and IV), above 45 years of age, and aggressive variants have a worse prognosis, greater chances of local recurrence, and distant metastases and require higher and more RAI doses.[9] Our study shows similar results that the mean cumulative dose in the nonremission group was significantly higher than that in the remission group.

Nonremission cases in our study reveal multiple metastatic sites including bone, lung, mediastinal, and some of locoregional metastasis. DM is associated with mortality having five times greater probability of death than patients having no metastasis or local metastasis.[8] Although there were 73.1% of nonremission patients who have DM in our study, we were not able to evaluate the impact on overall survival since the mean follow-up time was below 10 years. A longer follow-up time is necessary in order to evaluate the impact of this information on patient management.

In the remission group, we found that the risk of recurrence at initiation was inversely associated with remission in both univariate and multivariate analyses. Between the remission and nonremission groups, mean age at diagnosis and mean 24-h I-131 uptake before RAI treatment had no statistical differences. The previous study of Liu *et al.* revealed

similar results that intermediate and high risks, as well as tumor Stage T3 or T4 and LN metastasis, were significantly associated with unsuccessful outcomes.[10]

In our study, remission cases with low risk of recurrence at initiation, the total body scan of all patients revealed persistent 1–2 uptake lesions at anterior neck region on planar images which were suspected of persistent thyroid remnant. Then, they received RAI treatment until a cumulative dose of ≥600 mCi. All of these lesions might be possible due to paratracheal node metastasis rather than residual thyroid remnant because most of the thyroid remnant should be destroyed by RAI ablation.[11] However, we cannot conclude this hypothesis because we did not perform single-photon emission CT/CT in all cases as routine protocol, and then, we did not have complete data. We also found that remission DTC patients with cervical node metastasis had metastatic foci of ≤2 lesions. One remission case with high risk of recurrence had only 1 metastatic focus at the left proximal femur since the first WBS. All of our findings suggested an important observation that I-131 treatment is possible effective in patients with few metastatic sites (≤2 foci) which have high chance to be in remission.

Second primary malignancy

The use of radioiodine therapy has raised concern about the potential for the development of SPM, especially in patients with a cumulative dose exceeding 600 mCi. Rubino *et al*. found a correlation between RAI dose and SPM (mean follow-up: 13 years).[12] In our study, we found only 2 cases (1.1%) of SPM which included 1 case of IDC of the breast and 1 case of NHL after receiving I-131 treatment with a cumulative dose exceeding 600 mCi. In the previous study of Lin *et al.* revealed higher results in which there were 6.1% of secondary malignancy who was treated with I-131 cumulative dose ≥600 mCi.[13] In the previous study of Nasreen *et al*., they also showed similar results. They reported two patients (2.78%) with SPM after receiving a cumulative dose of ≥600 mCi: one of leukemia and the other of carcinoid tumor.[8] The lower incidence of SPM in our study than that in other populations is possible from different ethnicities and different malignancy types.

The cancer, found in our study, was not commonly found in the previous study. Second primary cancers associated with RAI treatment included bone and soft-tissue, colorectal, salivary gland cancer and leukemia.[12] In the previous study, cancer of salivary glands and leukemia are close in terms of incidence risk estimates because salivary glands receive a much higher absorbed dose and greater sensitivity of bone marrow to the stochastic effects of radiation.[13] However, some studies revealed an association between thyroid cancer and breast cancer, as seen in our study.[14]

Bone marrow suppression

Bone marrow suppression may occur within 1 month of radioiodine therapy and is usually transient. Severe bone marrow suppression seldom occurs when the radiation dose to blood is <200 cGy.[15] Bone marrow suppression occurs most often in patients who have the following risks: receive a large cumulative amount of radioiodine, receive external beam therapy in addition to I-131, have large functioning tumors that produce a high concentration of I-131, and have extensive bone metastasis.[16] In our study, we found 18 patients with suspected bone marrow suppression after receiving 600 mCi of RAI treatment, of which most of them (14 cases) had anemia. Six of 14 cases had persistent anemia for at least 6-month follow-up. Many medical conditions cause anemia such as active bleeding, iron-deficiency anemia, chronic disease, or poor nutrition. Most of the anemic patients were women who have more prevalence of anemia as compared to men. Causes of anemia in women are multiple. In majority, the cause of anemia in women is the iron-deficiency type, which occurs due to deficiency of iron, resulting in impaired formation of Hb. Women suffer from chronic blood loss due to monthly menstrual cycles, which always leads to chronic anemia. In addition, it is possible due to thalassemia or chronic disease.[17] About 1% of Thai population are affected with thalassemic disease and about 30%–40% of population are carriers of at least one of abnormal gene.[18] As there is no detail, we cannot conclude the definite cause of anemia in our study. However, the anemic patients in our study did not require blood transfusion. Otherwise, several studies have demonstrated that high-dose RAI treatment associated with leukopenia and thrombocytopenia rather than anemia.[19-21]

Salivary gland dysfunction

Iodine is greatly concentrated in the thyroid gland by carrier-mediated mechanism, but similar uptake is found in other organs, including the salivary and lacrimal glands. The concentration of secreted iodide in saliva has been reported to vary from 20 to 100 times of that in a serum. Therefore, the salivary glands can receive a substantial radiation-absorbed dose from I-131 treatment.[22] Sialadenitis and xerostomia have been considered as transient side effects of radioiodine therapy. The previous study of Ko *et al.* demonstrated that the risk of salivary gland secretion impairment significantly increased with increasing administered doses.[23] Alexander *et al*. reported that 42.9% of patients undergoing radioiodine therapy suffered from reduced salivary gland function more than 1 year after the last radioiodine application and persistent xerostomia occurred in 4.4%.[21] The previous study

of Solans revealed that 32.9% of patients reported subjective xerostomia which persisted to the second year of follow-up in 20.3% of cases and was still present more than 3 years after the last dose of RAI treatment in 15.2% of cases.[24] Our study found only 7 cases of permanent salivary gland dysfunction (1.7% of xerostomia and 2.2% of sialadenitis), in which the incidence is relatively low as compared to the previous studies. It is possible due to preventive protocol in our institution such as encourage patients to suck sour/lemon candies 24 h after RAI therapy and drink plenty of water during admission.

There are some limitations to our study. First, there is a relatively short follow-up period which limits the ability for overall survival analysis and because of the long latency of radiation-induced cytogenetic change to malignancy. Second, a retrospective cohort study is typically lower in statistical quality. A multicenter, international origin dataset is needed to validate our results. Third, the identification of salivary glands dysfunction using the patient's record instead of image measurements. The information regarding whether or not patients received protection for salivary glands was not available from the database, although such protection is routinely offered during treatment in our center.

CONCLUSION

Although the complications after I-131 treatment with a cumulative dose exceeding or equal to 600 mCi in DTC patients were low and not severe, the patients with remission were in < 10%. Our study suggests that the decision to administer further treatments should be made on an individual basis because beneficial effects may be controversial.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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