# DIFFERENTIATED THYROID CARCINOMA (DTC) PATIENTS REFFERED FOR RADIOACTIVE IODINE THERAPY AT FIRST PRESENTATION : A 10-YEAR REVIEW

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## ABSTRACT

**OBJECTIVE:** To evaluate the patient characteristics, histological subtype, presenting symptoms and metastatic evidence in thyroid cancer patients referred for radioactive iodine (RAI) therapy at first presentation.

**METHODS:** A retrospective study of patients with differentiated thyroid carcinoma (DTC) registered at Nuclear Medicine Section, Siriraj Hospital during January 1989 to December 1998 was reviewed.

**RESULTS:** Five hundreds and sixty-six DTC patients, aged 9-96 years (mean=46.8±16.7), including 440 women and 126 men were analyzed. The overall female/male ratio was 3.5:1. According to the histopathology, 370 papillary carcinomas (65.4%), 191 follicular carcinomas (33.7%), 5 Hürthle cell carcinomas (0.9%) were found. The most common age group was in the range of 31-60 years, accounting for 56% of all patients. There was at least one organ metastasis at first presentation in 235 cases (41.5%). Lymph node is the most often involved organ found in 169 cases (29.9%), followed by lung (52 cases, 9.2%) and bone (49 cases, 8.7%). Ninety-one patients (16.1%) revealed distant metastases at the time of referral. Papillary thyroid carcinomas most commonly metastasize to regional lymph node (39.7%) followed by lung (8.4%), and bone (4.3%), while follicular carcinoma more often metastasize to bone (17.3%) and lung (10.5%).

**CONCLUSION:** DTC is not uncommon in Thais and affects women rather than men. Papillary carcinoma is the most common histological subtype followed by follicular carcinoma. Since the prevalence of regional node and distant metastases is quite high at presentation, early diagnosis and appropriate treatment are essential for improving the disease outcomes.

**Key Words:** thyroid cancer, differentiated thyroid carcinoma, radioactive iodine, iodine-131

## INTRODUCTION

The thyroid gland is considered a relatively uncommon site of cancer in United States, accounting for 0.6% and 1.6% of all cancers among men and women, respectively.[1] However,

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these figures seem to be higher in Thais. According to the tumor registry at Siriraj Cancer Center from 1989-1998, thyroid cancer accounted for 2% of all new cancer patients, or 1.2% and 2.5% of male and female patient respectively. Fortunately the majority, which is about 89% of thyroid cancers in our institute were differentiated thyroid carcinomas (DTC) and can be treated postoperatively with radioactive iodine ($^{131}I$).

The objective of this study is to evaluate the patient characteristics, histological subtypes, presenting symptoms and metastatic evidence at first presentation in DTC patients referred for radioactive iodine (RAI) therapy at our institute.

## PATIENTS AND METHODS

We retrospectively reviewed the data of 590 new DTC patients referred for RAI treatment at Division of Nuclear Medicine, Siriraj Hospital during January 1989 and December 1998. However, 24 patients who had previous RAI therapy from elsewhere or had incomplete medical records were excluded.

## STATISTICAL ANALYSIS

Percentage, mean, standard deviation (SD) and student t-test were used for statistical analysis.

## RESULTS

## DEMOGRAPHIC FEATURES

Totally 566 DTC patients were included for the analysis. There were 440 women and 126 men with age range 9 - 96 years, mean = 46.8 $\pm$ 16.7 years. The overall female to male ratio was 3.5:1. From 1989 - 1998, the number of DTC patients referred for RAI treatment seemed to be increasing (Figure 1).

The patients' age distribution was displayed in Figure 2. The mean age in both sexes and that in two major types of thyroid cancer i.e. papillary and follicular carcinomas were similar (Table 1). The common age ranges were in between 31 - 60 years old, which accounted for 56% of all DTC patients (318/566). About 39% (222/566) of the patients were 40 or under, which have favorable prognosis. However, the remaining 344 cases (61%), being the majority of the patients, were older.

## PATHOLOGY

According to the histopathology, 370 (65.4%) papillary carcinomas (including mixed papillary-follicular carcinomas), 191 (33.7%) follicular carcinomas, and 5 (0.9%) Hürthle cell carcinomas, a follicular variant were found. Therefore, papillary tumors were almost twice as common as follicular carcinomas. The female to male ratio of papillary cancers was 3.2:1 and that of follicular carcinomas was 4.5:1 (Table 2)

## PRESENTING SYMPTOMS

The majority of DTC patients presented with thyroid abnormalities, particularly solitary thyroid nodules with or without cervical node metastases. The others may present with metastatic lymph nodes alone, distant metastases, or symptoms related to direct tumor invasion such as hoarseness of voice due to vocal cord paralysis, and upper airway obstruction due to laryngeal or tracheal involvement. Sixty-three (11%) patients were referred for RAI treatment because of recurrent tumor after a variable period of thyroid surgery. On the other hand, the cancer was found incidentally in ten (1.8%), among which eight were operated on hyperthyroidism. The presenting conditions of DTC patients were listed in Table 3.

## ORGAN METASTASES

Overall 235 cases (41.5%) showed at least one organ metastasis at first presentation. Lymph node is the most often involved organ found in 169 cases (29.9%), followed by lung (52 cases, 9.2%) and bone (49 cases, 8.7%) (Table 4). Most of the patients (196 cases, 34.6%) had single organ metastasis and the remaining (39 cases, 6.9%) had multiple organ metastases, which the most common combination is lymph node and lung metastasis in 19 cases. When lymph node was not taken into account, ninety-one patients (16.1%) had distant visceral organ metastases at the time of referral. Of these, 45 cases (12.2%) of patients with papillary cancers and 45 cases (23.6%) of those with follicular carcinomas revealed distant metastases. Six patients had uncommon sites of metastases, including brain,[4] liver,[1] and kidney.[1]

For papillary carcinomas, lymph node was most commonly involved organ (147 cases, 39.7%), followed by lung (31 cases, 8.4%), and bone (16 cases, 4.3%). On the other hand, the metastases from follicular thyroid carcinomas were more commonly seen in bone (33 cases, 17.3%) than lymph nodes (22 cases, 11.5%) and lung (20 cases, 10.5%).

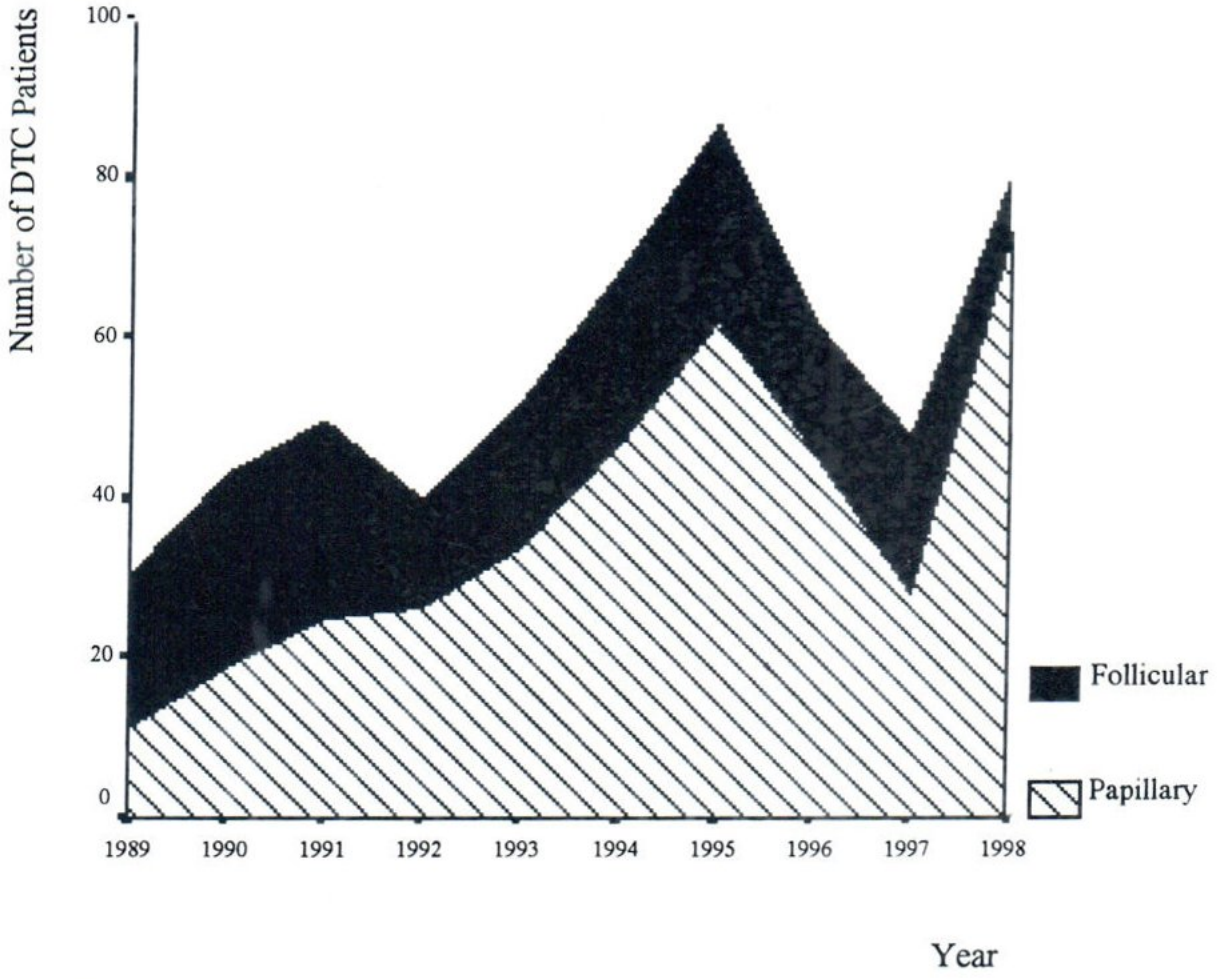


**Fig. 1.** DTC patients referred for RAI treatment during 1989-1998

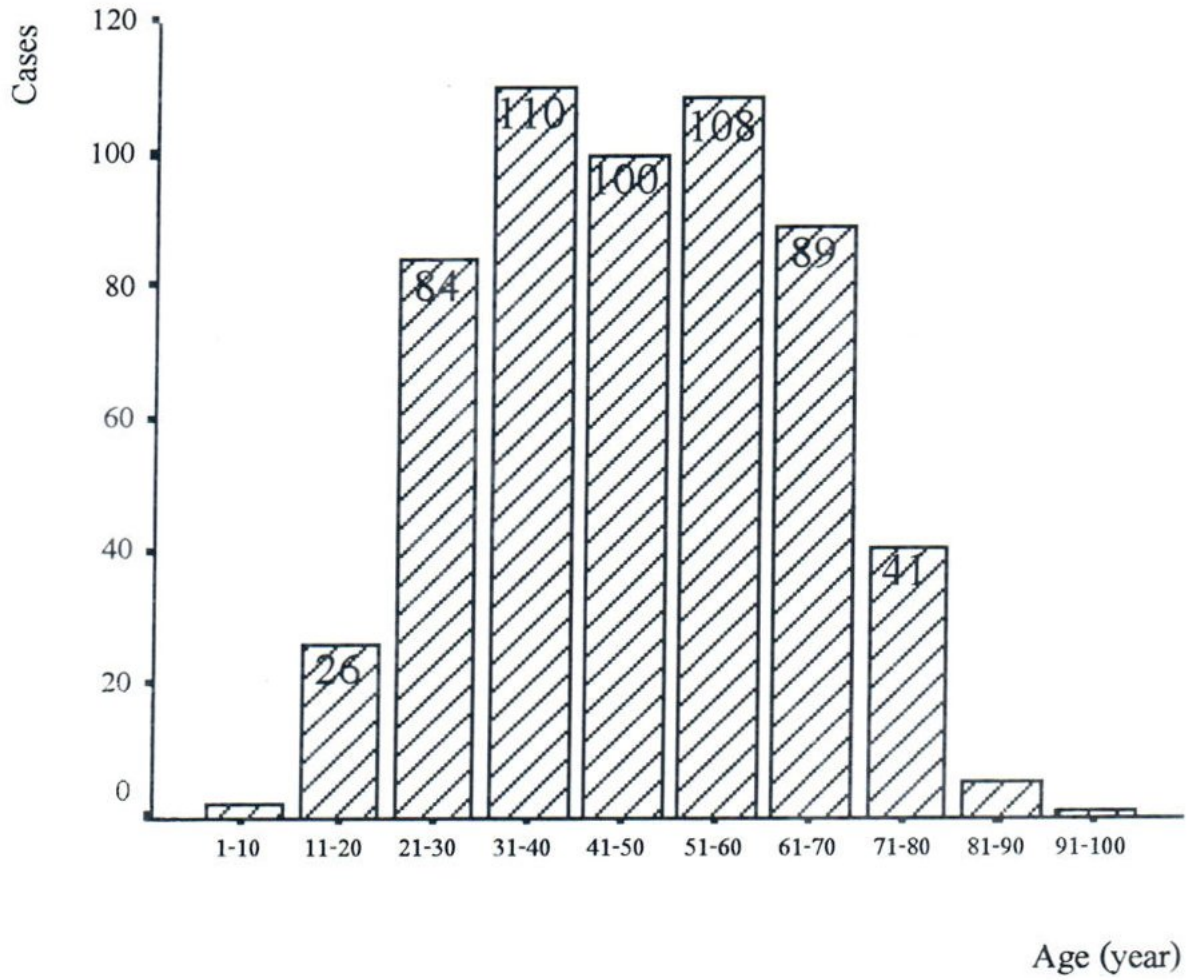


**Fig. 2.** Age distribution of DTC patients referred for RAI treatment

**Table 1.** Age ranges of DTC patients referred for RAI treatment

| Sex -Type | Cases | Age Range (year) | Mean Age (SD) (year) | p value |
|---|---|---|---|---|
| Female | 440 | 12-96 | 46.2 (16.5) | 0.1 |
| Male | 126 | 9-81 | 49.0 (17.3) | |
| Papillary | 370 | 9-84 | 46.6 (16.8) | 0.7 |
| Follicular | 191 | 12-96 | 47.2 (16.7) | |
| All | 566 | 9-96 | 46.8 (16.7) | |

**Table 2.** Sex distribution of DTC patients according to histological subtypes.

| | Papillary | | Follicular | | Follicular | | Hürthle cell | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cases | Percent | Cases | Percent | Cases | Percent | Cases | Percent | Cases | Percent |
| Female | 281 | 63.9 | 156 | 35.5 | 156 | 35.5 | 3 | 0.7 | 440 | 77.7 |
| Male | 89 | 70.6 | 35 | 27.8 | 35 | 27.8 | 2 | 1.6 | 126 | 22.3 |
| Total | 370 | 65.4 | 191 | 33.7 | 191 | 33.7 | 5 | 0.9 | 566 | 100 |

Female : male ratio for all DTC patients = 3.5:1,
Female : male ratio for papillary carcinoma patients = 3.2:1
Female : male ratio for follicular carcinoma patients = 4.5:1

**Table 3.** Presenting Symptoms of DTC Patients Referred for RAI Treatment

| Presenting Symptoms | All | | Papillary | | Follicular | |
|---|---|---|---|---|---|---|
| | Cases | Percent | Cases | Percent | Cases | Percent |
| Thyroid nodule | 384 | 67.8 | 255 | 68.9 | 126 | 66.0 |
| Lymph node enlargement | 25 | 4.4 | 19 | 5.1 | 6 | 3.1 |
| Thyroid and lymph node | 10 | 1.8 | 8 | 2.2 | 2 | 1.0 |
| Distant metastasis | 44 | 7.8 | 12 | 3.2 | 32 | 16.8 |
| Recurrent tumor | 63 | 11.1 | 50 | 13.5 | 12 | 6.3 |
| Invasive property | 30 | 5.3 | 19 | 5.1 | 10 | 5.2 |
| Incidental | 10 | 1.8 | 7 | 1.9 | 3 | 1.6 |
| Total | 566 | 100.0 | 370 | 100.0 | 191 | 100.0 |

**Table 4.** Summary of organ metastasis in DTC patients at first presentation

| Metastasis/ | Papillary | | All | Follicular | | All | Hürthle Cell | | All | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pathology | Cases | % | % | Cases | % | % | Cases | % | % | Cases | % |
| Presence of metastasis | 173 | 46.8 | 30.6 | 61 | 31.9 | 10.8 | 1 | 20 | 0.2 | 235 | 41.5 |
| Lymph node metastasis | 147 | 39.7 | 26.0 | 22 | 11.5 | 3.9 | 0 | 0 | 0 | 169 | 29.9 |
| Bone metastasis | 16 | 4.3 | 2.8 | 33 | 17.3 | 5.8 | 0 | 2 | 0 | 49 | 8.7 |
| Lung metastasis | 31 | 8.4 | 5.5 | 20 | 10.5 | 3.5 | 1 | 20 | 0.2 | 52 | 9.2 |
| Other metastasis | 2 | 0.5 | 0.4 | 3 | 1.6 | 0.5 | 1 | 20 | 0.2 | 6 | 1.1 |

## DISCUSSION

From the tumor registry, we found that thyroid cancer in Thailand is somewhat more common than that occurring in USA.[1,2] However, the majority of these tumors is similar, i.e. DTC. As compared to the United States, papillary carcinoma is still the most common histological subtype, but papillary: follicular ratio is lower (2:1 vs 3:1). Thus, follicular tumors are relatively more common among Thais. In addition, DTC is predominant in females with female:male ratio of 3.5:1, which is higher than that observed in US population (2.3:1).[3] Race may be an important factor for these differences.

Since these thyroid tumors arise from thyroid follicular cells, they usually have the ability to concentrate radioactive iodine, and thus, benefit from the RAI treatment. However, in the early years of the study, a few DTC patients were referred for additional RAI therapy following complete surgery. These included in particular follicular carcinomas rather than papillary tumors. Nevertheless, the number of the patients referred for RAI treatment has been recently increasing, exclusively papillary thyroid cancers, which in the past was used to be treated with surgery alone or just combined with thyroid hormone following surgery. This might because more and more clinicians have accepted the role of RAI therapy to treat DTC patients. The benefit of postoperative RAI therapy in papillary tumors was shown by Mazzaferri et al.[4] who found that the recurrence rate had been reduced from 32% in patients treated with surgery alone, to 11% in those given thyroid hormone postoperatively, and to 2.7% in those who received RAI therapy followed by hormonal treatment after surgery. In the patients with follicular carcinoma, there is also significant reduction of recurrence following postoperative I-131 ablation.[5] The reason for this is believed to be due to a direct effect on the micrometastases rather than destruction of residual cancer in the small thyroid remnant.[6] Therefore, it is now generally accepted, that DTC should be treated by near-total thyroidectomy and followed by RAI treatment with long-term follow-up program. As recurrence is twice more commonly found in the patients with nodal metastases than those without node involvement (32% vs 14%), RAI treatment in patients with node involvement is very reasonable.[7] Although combined RAI therapy has important role in most well-differentiated thyroid carcinomas, it may be not necessary in patients with occult primary tumors (less than 1.5 cm in diameter) since they have relatively benign clinical behavior and excellent prognosis.[8,9]

Age at the time of diagnosis and treatment is considered the single most important prognostic factor of patients with DTC.[9] The mean age at initial diagnosis of follicular carcinomas is previously reported to be about 9 years older than that of papillary cancers.[8] In our series, however, there is no any significant difference between age in papillary and follicular carcinomas, and also in both sexes. Nevertheless, the duration of the developing tumors in each patient is quite varied prior to the presentation. Papillary carcinomas may arise for a long time before the patients come to see the doctors because the course of the disease is quite indolent. In contrast, the patients with follicular cancers may be diagnosed earlier due to more common occurrence of distant metastasis. As observed in this study that several patients presented with distant metastases, in particular skeletal metastases.

Another interesting aspect includes the concurrence of thyroid cancer and hyperthyroidism, which has been recently reported to occur in 0.6% to 5.9% of thyrotoxic patients.[10-12] This occurrence raises the importance of studying and excluding the possibility of the neoplastic formation in a more systemic approach.

In contrast to papillary and follicular carcinomas, a follicular variant called Hürthle cell carcinoma rarely collects radioiodine.[13] However, we observed RAI uptake in a case of Hürthle cell carcinoma with bilateral pulmonary metastases. Thus, whole-body I-131 diagnostic scan may guide for the decision of following RAI treatment in this type of tumor.

In terms of tumor spreading, papillary and follicular carcinomas have quite different modes of metastasis. Papillary cancers tend to spread initially via the lymphatic system while follicular carcinomas more often produce hematogenous metastases to bone and lung.[3,6] In our series, lymph node metastases are found in about 40% of patients with papillary cancer and approximately 12 % of those with follicular carcinoma, which is similar to the figures reported by Maxon and Smith[14] (35% and 13% respectively). On the other hand, distant metastases in our study seems to be higher, which are 12.2% in patients with papillary carcinoma and 23.6% in those with follicular cancer, as compared to 3.8% and 16.4% respectively as previously reported.[14] A reason for this may be associated with delayed consultation, which leads to delayed diagnosis and treatment of the patients. Thus, the patients who have thyroid-related symptoms should go to see their doctors sooner and clinicians or surgeons should also be alert for malignant condition and not delay the diagnosis. Furthermore, many patients have inadequate previous thyroid surgery and/or lack of combined RAI treatment for their tumors, which results in recurrent or metastatic disease. Therefore, early diagnosis with prompt and appropriate treatments after the diagnosis including surgery followed by radioiodine, and hormonal therapies in each patient should be attempted.

## CONCLUSION

DTC is not uncommon in Thais. Although it has quite favorable prognosis, they can metastasize to lymph node, bone, lung, etc. Presence of these metastatic evidences at first presentation of course, results in increase in morbidity and mortality. To improve the disease outcomes, early diagnosis with appropriate treatments should be warranted.

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