Endokrynologia Polska
DOI: 10.5603/EP.a2017.0037
Tom/Volume 68; Numer/Number 5/2017
ISSN 0423–104X

Thyroid cancer post radioactive iodine treatment for hyperthyroidism — case series and review of the literature

Rak tarczycy po terapii jodem radioaktywnym z powodu nadczynności tarczycy — opis serii przypadków i przegląd piśmiennictwa

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Abstract

Introduction: To assess the rate of thyroid cancer and mortality rate in a cohort of patients who received RAI^{131} treatment for hyperthyroidism and to report the index cases' characteristics and management

Material and methods: A cohort of 264 patients who received RAI^{131} treatment for different causes of thyrotoxicosis were followed up over a period of 18 years (1996–2014) by physical exam, radiological evaluation and serial thyroid function tests.

Results: During the follow up period, three cases of thyroid cancer were identified. The prevalence of thyroid cancer was 1.136% of cases who received RAI^{131}. The relative risk was 378.79 (95% CI: 76.8 < RR < 1868.23). The P value was < 0.0000004 and the SMR is 1.99/1000.

Conclusions: The prevalence of thyroid cancer was 1.136% in the cohort of patients treated with RAI^{131}. Despite the fact that no direct cause-effect relationship between RAI and thyroid cancer could be established, these cases highlights the importance of life-long surveillance of patients who receive RAI^{131}. **(Endokrynol Pol 2017; 68 (5): 561–566)**

Key words: *toxic multinodular goitre, thyroid cancer, radioactive iodine*

Streszczenie

Wstęp: Badanie przeprowadzono w celu oceny częstości występowania raka tarczycy i odsetka zgonów w kohorcie chorych poddanych terapii RAI^{131} z powodu nadczynności tarczycy oraz przedstawienia charakterystyki tych chorych i stosowanego u nich leczenia.

Materiał i metody: U kohorty 264 chorych poddanych terapii RAI^{131} z uwagi na tyreotoksykozę o różnej etiologii przez ponad 18 lat (1996–2014) prowadzono obserwację obejmującą badanie przedmiotowe, ocenę radiologiczną i serię badań czynności tarczycy.

Wyniki: W okresie obserwacji wykryto 3 przypadki raka tarczycy. Częstość występowania raka tarczycy w grupie chorych poddanych terapii RAI131 wynosiła 1,136%. Ryzyko względne wynosiło 378,79 (95% CI: 76,8 < RR < 1868,23). Wartości p i SMR wynosiły odpowiednio < 0,0000004 i 1,99/1000.

Wnioski: Częstość występowania raka tarczycy w kohorcie chorych poddanych terapii RAI^{131} wynosiła 1,136%. Mimo że nie wykazano bezpośredniego związku przyczynowo-skutkowego między RAI a rakiem tarczycy, opisane przypadki zwracają uwagę na znaczenie bezterminowej obserwacji chorych poddanych terapii RAI^{131}. **(Endokrynol Pol 2017; 68 (5): 561–566)**

Słowa kluczowe: *wole guzkowe toksyczne, rak tarczycy, jod radioaktywny*

Introduction

Thyroid cancer is showing an increase in its detection rate globally, which is mainly explained by the detection of histopathological micropapillary subtype [1]. Thyroid cancer is the commonest endocrine malignancy with 1–1.5% of newly diagnosed cases each year in the USA [2]. The worldwide relative frequency of occurrence of thyroid cancer is between 0.5 and 10 per 100,000 population [3] with a 2–3 fold increase in female preponderance [4]. The incidence of thyroid cancer in females is 3.3% versus 1.3% in males [5].

The prognosis for thyroid cancer is good, and the mortality rate remains stable over 30 years at 0.5 cases per 100,000 persons, despite increased incidence of new cases annually [6].

The incidence of thyroid cancer in thyrotoxic patients treated with radioactive iodine is higher than in the general population, with an increased relative risk of cancer that is proportional to the doses of radioactive iodine administered [7]. This incidence of thyroid cancer peaks at the age of 50–59 years and in those older than 70 years of age [7].

The overall cancer mortality was not increased in two large American and British studies that followed large cohorts of thyrotoxic patients receiving RAI^{131}, except for thyroid cancer [8] and small bowel cancer [9]. Both studies showed that the increase in thyroid cancer

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incidence and deaths were small but that close and continuous attention should be paid to such patients. These observations, however, were not supported by the group of 35,000 patients followed up by Holm L-E et al. who did not find a proof that RAI^{131} is carcinogenic in humans [10].

According to the Middle East Cancer Consortium (MECC), which includes Jordan, Israel, Egypt, Cyprus, Palestinian Authority and Turkey, thyroid cancer patients revealed age standardised incidence rates (ASR) of 3/100,000 in Jordan in 2005 [11] (4.5/100,000 for females and 2.7/100,000 for males [5]). The expected death rate for the general population in Jordan is 3.69/100,000 [12].

In this study we identified and will discuss cases of thyroid cancer among a cohort of Jordanian patients with hyperthyroidism, who received radioactive iodine between 1996 and 2014, we calculate the rate of thyroid cancer and SMR, and discuss the association of thyroid cancer with RAI^{131}.

Material and methods

Longitudinal study of 264 hyperthyroid consecutive patients who received RAI^{131} since 1996 and were followed-up till 2014.

Graves' disease was diagnosed in 198 patients, toxic multinodular goitre in 47 and toxic nodule in 19 patients.

Inclusion criteria included all patients who received RAI^{131} for different causes of thyrotoxicosis because of failure of medical treatment, patients unfit or refused surgery , if rapid restoration of thyroid function was needed, or due to the patient's own preference.

Exclusion criteria included previous personal history of thyroid cancer, family history of thyroid cancer, and/or history of multiple endocrine neoplasia (MEN).

The cohort was followed-up by physical examination and serial blood testing for thyroid function test (TFT) every 3–6 months until full restoration of their clinical status to a euthyroid state and normalisation of TFT and/or they became clinically biochemically hypothyroid. TFT was then performed twice yearly for life. TSH was adjusted accordingly to be kept in the lower quartile of the reference range. FNA biopsy was performed in patients who noticed an increase in nodular size, the appearance of new nodules and/or lymph nodes, or the appearance of new goitres.

Statistics

Descriptive statistics for prevalence and rates, mean and standard deviation (SD) for dosage, odd ratio (OR), relative risk (RR), and 95% confidence interval (CI) were calculated using Epi Info version 6 and Fisher's exact test. Standard Mortality Rate per 1000 was measured by calculating observed mortality over expected mortality in the general population [12].

Results

A total of 264 (91 males) with a mean age(± SD) of 43.3 ± 14.05 years received 278 doses of RAI^{131} with a mean dose of 15.98 ± 2.5 mCi and were followed-up for a period of 18 years (1996 to 2014) at the Endocrine Clinic at King Hussein Medical Centre, Amman-Jordan.

During the follow-up period, three cases of thyroid cancer were observed. The mean duration from RAI^{131} treatment until diagnosis of cancer was 8.3 ± 5.1 years. The prevalence of thyroid cancer in this cohort was 1.136%. The Relative risk was 378.79 (95% CI: 76.80 < RR < 1868.23). P value < 0.0000004 and odds ratio: 383.13 (95% CI: 61.7–2379.1).

The standard mortality rate (SMR) using the expected mortality rate in Jordan of 3.8/1000 is 1.99/1000 patients receiving radioiodine treatment.

Case 1

A 75-year-old female patient, non-smoker, hypertensive, on α-methyldopa 250 mg twice daily, was admitted in November 1992 to King Hussein Medical Centre with rapid atrial fibrillation and was found to have hyperthyroidism due to toxic multinodular goitre. FT3 was 5.2 ng/dL (normal range: 1.2–3.6), FT4 was 2.9 ng/dL (0.8–1.9), and TSH was 0.006 uiU/mL (0.4–4.0). She denied family history for thyroid cancer or other malignancies (Table I).

Thyroid ultrasound was in keeping with multinodular goitre with no lymph node enlargement. Thyroid isotope scan revealed enlargement of the gland (left > right) with multiple areas of decreased tracer uptake. Two-dimensional echocardiography showed GII-III mitral regurgitation with biatrial enlargement.

She was started on carbimazole 30 mg/day, propranolol 40 mg t.i.d., digoxin 0.25 mg/day, and warfarin 5 mg/day. Her thyroid status remained active despite carbimazole dose adjustment according to thyroid function test. On 15th June 1998 she was given a dose of 25 mCi radioactive iodine. After which she became clinically and biochemically euthyroid but remained in atrial fibrillation.

She was lost from follow up for eight years. In May 2006 she presented with increasing neck swelling, hoarseness of voice, shortness of breath at rest, and dysphagia for liquids and solid food. Physical examination revealed controlled AF and a large multinodular goitre, hard in consistency with enlarged cervical lymph nodes (Fig. 1A). She had dilated upper chest and neck veins and Pemberton's sign was positive. Neurological

Table I. *Laboratory features of the three cases*

Tabela I. *Parametry laboratoryjne w trzech przypadkach raka tarczycy*

	Case 1	Case 2	Case 3
WBC (4.5–10.5 × 10^3)	107 × 10^3	9.500 × 10^3	8.900 × 10^3
PCV	42.3%	46.7%	44.1%
Platelets (150–450 × 10^3)	301 × 10^3	265 × 10^3	257 × 10^3
BUN (10–28 mg/dL)	15	18	22
Serum creatinine (0.5–1.5 mg/dL)	1.30	1.10	1.25
Serum calcium (7.8–10.2 mg/dL)	7.8	8.9	9.3
Serum Phosphorous (3–4.5 mg/dL)	2.9	3.4	3.5
Serum ALP (50–160 U/L	886	155	133
Serum albumin (35–45 g/dL)	46	41	37
Serum uric acid (4–6.5 mg/dL)	12.3	5.5	6.0
PTH (15–64 pg/mL)	58	39	32
TSH [μu/mL]	4.47	3.34	2.9
Serum calcitonin pg/mL	11.3		
24-hr urine collection for metanephrines (< 1 mg)	0.6		
Duration from RAI^{131} until development of cancer [years]	7	4	14

examination revealed left lower motor neuron VII nerve palsy. Laboratory investigations are summarised in Table I.

Indirect laryngoscopy demonstrated vocal cords that were slightly mobile. There was pooling of saliva and swelling of retrocricoid area causing obstruction to the inlet of the oesophagus. Neck, chest, abdomen and pelvic CT-scan showed a large heterogeneous partially enhanced ill-defined mass lesion with central necrosis in the left side of the neck extendeing from the level of hyoid bone down the retrosternal area and medially reaching the right side of the cricoid cartilage (Fig. 1B). The mass lesion showed calcified areas encasing the trachea and the carotid artery with infiltration of the trapezius muscle and causing a mass effect pushing the midline structures to the right side. Multiple variable sized lung nodules were seen in both lungs with right-sided pleural effusion (Fig. 1C).

Thyroid fine needle aspiration revealed a malignant process (medullary versus anaplastic carcinoma) (Figure 2A). Hematoxylin and eosin stain confirms the presence of nests of spindle-shaped to polygonal cells of medullary carcinoma (Figure 2B). She was treated conservatively with correction of hypocalcaemia but her obstructive symptoms were more pronounced, so an emergency surgery attempting to relieve obstruction was done. Intra-operative findings included a large thyroid tumour with areas of necrosis with skin and subcutaneous metastatic deposits. Debulking surgery was attempted, but unfortunately her post-operative course was eventful and she succumbed postoperatively. Family refused postmortem autopsy. The histopathological

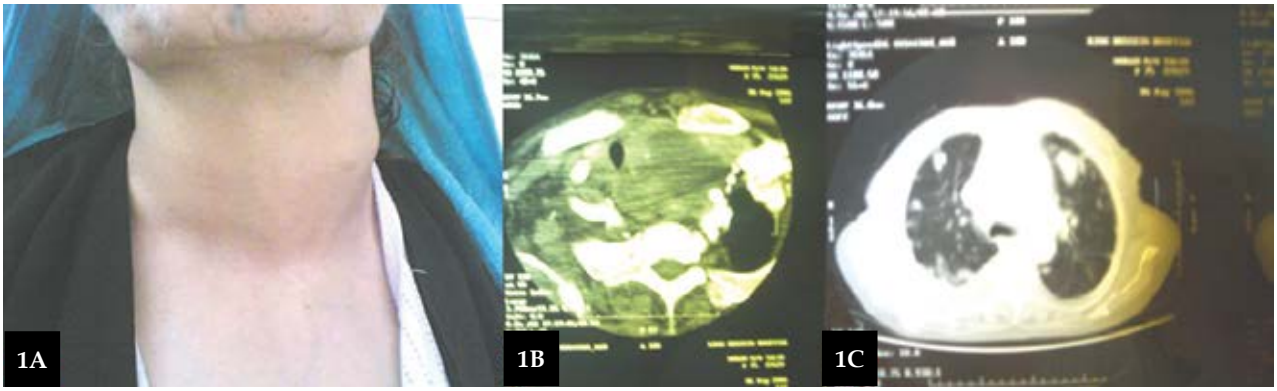

Figure 1A. *Large multinodular goitre with enlarged cervical lymph nodes;* **B.** *Neck CT-scan showing a large, heterogeneous, partially enhanced, ill-defined mass lesion with central necrosis in the left side of the neck extended from the level of the hyoid bone down the retrosternal area and medially reaching the right side of the cricoid cartilage;* **C.** *Chest and abdomen CT-scan shows multiple variable sized lung nodules in both lung fields and right-sided pleural effusion*

Rycina 1A. *Duże wole guzkowe z powiększonymi węzłami chłonnymi szyjnym;* **B.** *W obrazie TK szyi widoczna duża, niejednorodna, częściowo wzmacniająca się, słabo ograniczona zmiana z martwicą w części centralnej, znajdująca się po lewej stronie szyi i rozciągająca się od kości gnykowej sięgając w dół do okolicy zamostkowej, a w kierunku przyśrodkowym — do chrząstki pierścieniowatej;* **C.** *Obraz TK klatki piersiowej i jamy brzusznej z widocznymi licznymi guzkami o różnej wielkości w obrębie obu pól płucnych oraz prawostronny wysięk w jamie opłucnej*

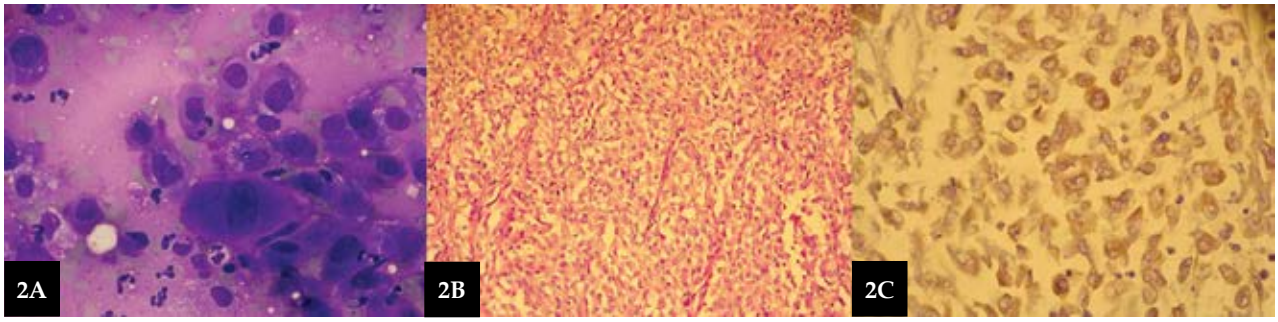

Figure 2A. *Thyroid fine-needle aspiration revealed a malignant process (medullary versus anaplastic carcinoma);* **B.** *Haematoxylin and eosin stain showing nests of spindle-shaped to polygonal cells of medullary carcinoma;* **C.** *Immunohistochemistry stain shows a positive cytoplasmic staining for calcitonin*

Rycina 2A. *Biopsja cienkoigłowa tarczycy ujawniła proces nowotworowy (rak rdzeniasty versus rak anaplastyczny tarczycy);* **B.** *W preparacie barwionym hematoksyliną–eozyną widoczne gniazda komórek wrzecionowatych i wielokątnych raka rdzeniastego;* **C.** *W preparacie barwionym metodą immunohistochemiczną widoczne dodatnie cytoplazmatyczne wybarwienia kalcytoniny*

examination confirmed MTC with anaplastic changes and positive calcitonin stain (Fig. 2C).

Case 2 (see Table I)

A 65-year-old female patient, with a known case of bronchial asthma and diagnosed with toxic multinodular goitre in 2002. Due to early failure of medical therapy, she received 15 mCi RAI^{131} in 2003 and became euthyroid within six months. In April 2007 she presented with neck discomfort and sensation of suffocation. Physical examination revealed a hard thyroid nodule. Neck ultrasound showed a 2.5 x 3.0 cm heterogeneous thyroid nodule with spots of calcifications within the left thyroid lobe. Other smaller, homogeneous nodules < 1.3 cm, were found in both thyroid lobes Thyroid FNA biopsy revealed papillary thyroid cancer (PTC). She underwent total thyroidectomy, and the frozen section and histopathology confirmed the diagnosis of PTC with no capsular invasion (Fig. 3). Post-operative whole body I^{131} scan was negative. She did not receive radioactive iodine ablation after surgery. She is under regular follow-up with serial serum thyroglobulin levels that are < 0.1 ng/dL and no evidence of thyroid remnant tissue, or cervical lymphadenopathy on regular clinical and sonographic examination of the thyroid bed and neck. A whole body I^{131} scan was done in 2012 and it was negative. She is maintained on replacement suppressive therapy with levothyroxine 200 μg/day.

Case 3 (see Table I)

A 72-year-old male patient, ex-smoker, diagnosed with GD in 1996. He was treated with RAI^{131}, developed hypothyroidism one year later, and was given levothyroxine 100 μg daily. He was lost to follow-up at the endocrine clinic, but he remained under regular follow-up by a cardiologist for hypertension and ischaemic cardiomyopathy. In 2010, he was noticed to have lateral neck swelling. Neck US revealed a small hyperechoic nodule on the left side and another smaller one on the right side with multiple cervical LNs, the largest measuring 3.5 × 3 cm. The patient was referred to an endocrine clinic in December 2010 for further evaluation. Cervical LN biopsy under local anaesthesia revealed a metastatic papillary thyroid carcinoma. He was scheduled for high-risk surgery after thorough multi-disciplinary consultations in January 2011, but he had a decompensated congestive cardiac failure during this period and succumbed just before surgery because of new cardiac insult.

Discussion

The prevalence of thyroid nodules reaches up to 50% in late adulthood and represents a reservoir of potential malignancy to be investigated [13]. The majority of thyroid cancers (> 80%) are discovered in nodules less than 2 cm in the largest diameter. This high percentage is due to increased detection of thyroid cancers by increased surveillance and use of more sensitive diagnostic procedures [14]. The presence of thyroid nodule in a patient with Graves' disease has a malignancy rate of 16.9%, which is higher than in the general population [15]. Exposure to ionising radiation is a recognised precipitating factor for thyroid cancer [16]. Thyroid gland is highly susceptible to ionising radiation because of its position in the body and its ability to concentrate iodine [16]. The thyroid gland is amenable to the carcinogenic effect of radiation, and the risk of thyroid cancer decreases with increasing age at exposure with small risk above the age of 20 years [17].

Thyroid cancers after treatment with small doses of I^{131} for thyrotoxicosis are rare. Staffurth et al. reported a case of follicular thyroid cancer 15 years after a small dose of radioactive iodine (4 mCi) for Graves' disease [18].

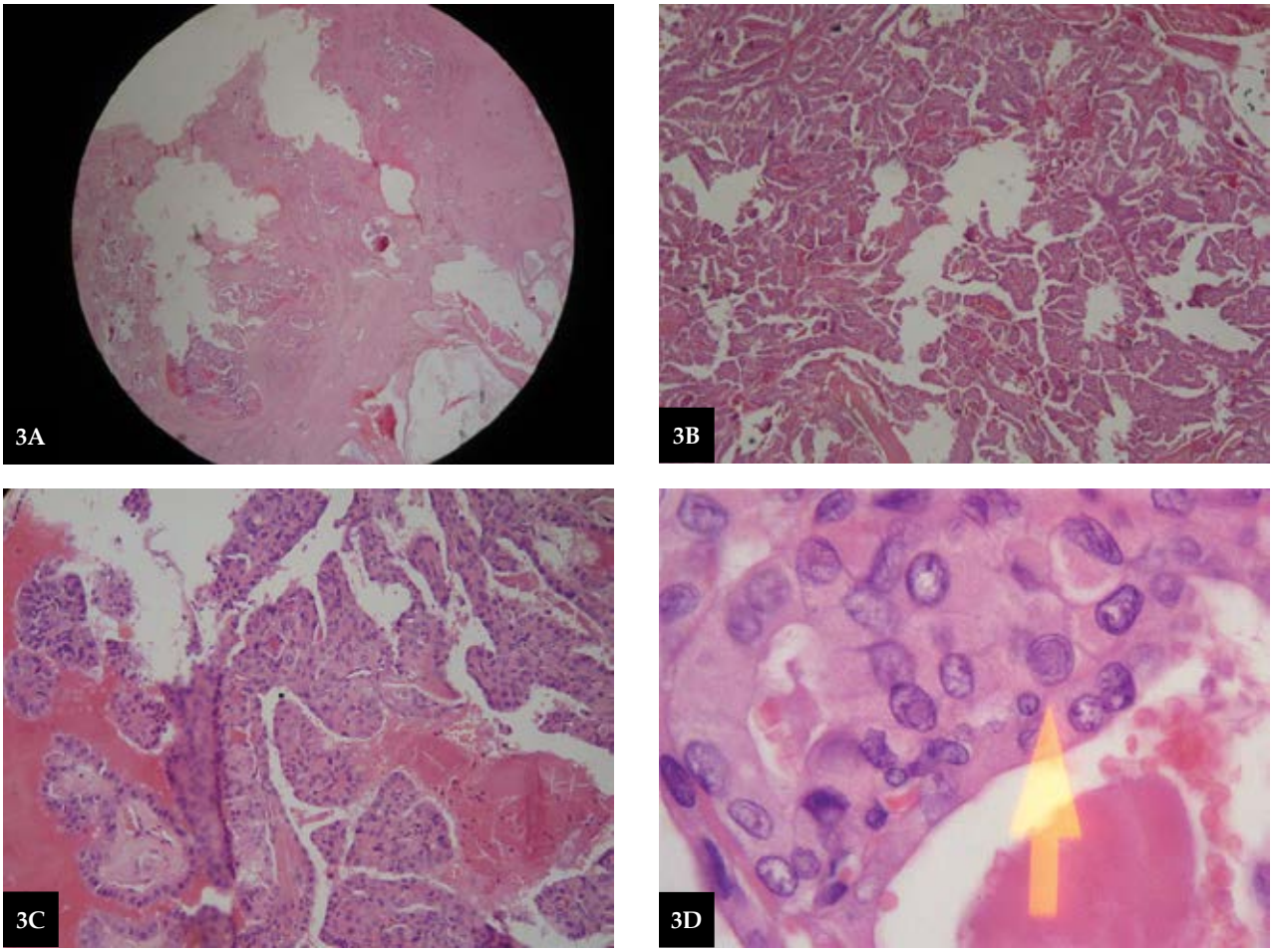

Figure 3 (A–D). *Showing the classic features of papillary thyroid carcinoma with multifocal lesions, papillae, grooves and clear nuclear features*

Rycina 3 (A–D). *Widoczne klasyczne cechy raka brodawkowego tarczycy z wieloogniskowymi zmianami, strukturami brodawkowatymi, rowkami oraz jasnymi jądrami komórkowymi*

RAI^{131} stimulates an increment in thyroid antibodies like TSH receptor stimulating antibodies [19] that play a significant role in thyroid carcinogenesis and angiogenesis [20]. Those antibodies can result in stimulation of thyroid tumour cell growth by activating endothelial cell growth factor [21]. The occurrence of thyroid cancer increased significantly in children who were exposed to ionising radiation 10 years after the Chernobyl accident [22], especially the occurrence of papillary thyroid cancer [23] .The commonest molecular lesion in these tumours are a rearrangement of the RET receptor tyrosine kinase proto-oncogene [23]. Ogawa et al. showed that treatment with radioactive iodine (RAI^{131}) deactivates the tumour suppressor gene that is commonly found in anaplastic thyroid cancer rather than differentiated thyroid cancer [24]. There are also some cytomorphological changes in thyroid follicular epithelium caused by radioactive iodine treatment, as reported by Stugis [25]. Radioactive iodine treatment plays a significant role in induction of cellular atypia with progressive metaplastic changes in patients with Graves' disease. This phenomenon is actually prominent in those who remain hyperthyroid after treatment with radioactive iodine [26].

Anaplastic thyroid cancer in hyperthyroid patients after an interval of time post radioactive iodine therapy was reported in only three cases, who were females and had received multiple doses of RAI^{131}. This cancer was elicited 12–20 years after RAI^{131} [26–28].

The Cooperative Thyrotoxicosis Therapy Follow-up Study concluded that thyroid cancer after radioactive iodine ablation developed in those people receiving lower rather than higher doses of RAI^{131} therapy [29]. The report of MTC post RAI^{131} for TMNG that developed anaplastic changes in patients who received a single dose of 25 mCi of RAI^{131} represents a unique association and has never been reported. Despite the fact that this report of a case series showed an increase in the relative risk of thyroid cancer and SMR in patients receiving radioactive iodine treatment for different causes of thyrotoxicosis, it should not exclude

I^{131} as an important modality of treatment. This series of cases highlights the importance of lifelong surveillance and monitoring for any structural changes in thyroid tissue to allow early detection of potentially curable cancer.

In conclusion, the prevalence of thyroid cancer post RAI^{131} is 1.136% in this cohort that received RAI^{131} and was followed-up for > 15 years. Radioactive iodine I^{131} is still a very effective therapy for hyperthyroidism, and the sporadic discovery of thyroid malignancy should not preclude the use of it. The development of MTC after radioactive iodine I^{131} was not reported previously. Unfortunately the patient did not live long enough for genetic studies to be done. These cases also highlight the importance of lifelong follow-up of patients treated with radioactive iodine to avoid such an association with probable grave outcome.

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