Case Report

Incidentally Detected Metachronous Malignancy in Patients of Papillary Carcinoma of Thyroid Posthigh-Dose Radioiodine Therapy

Ayush Mishra, Vijay Singh, Yogita Khandelwal, Aswath Manikantan Smitha, David Jaya Prakash Kavali, Sukanta Barai

Department of Nuclear Medicine, SGPGIMS, Lucknow, Uttar Pradesh, India

Abstract

Thyroid cancer is one of the most common endocrine cancers. The most common histological subtypes are papillary and follicular variants; these are "differentiated thyroid cancers" and are associated with an excellent prognosis. The exact mechanism of thyroid cancer is not known. Several genetic alterations and environmental factors are found to be associated with this cancer. Patients with differentiated thyroid cancer are treated with postoperative radioactive iodine (RAI) therapy to ablate residual thyroid tissue and metastatic micro-foci. It is thought that after RAI, there is an increased risk of secondary malignancies such as lung, renal, and stomach cancer and lymphomas. However, the risk of secondary malignancy is not clear. They may be associated with genetic syndromes, environmental factors, and radiation exposure. The secondary malignancy may be detected incidentally during follow-up or present with signs and symptoms of that malignancy. There is no direct association between second malignancy and radiation exposure in I-131 therapies. We present a case series of five patients treated with high doses of I-131 for the remnant. The patients developed metachronous malignancies later in life.

Keywords: *Radioiodine ablation, secondary malignancy, thyroid cancer*

Introduction

Thyroid carcinoma is one of the most common malignancies of the endocrine system.[1] The majority belongs to well-differentiated thyroid cancers (papillary carcinoma of the thyroid, follicular cancer, etc.) and are relatively indolent, with a 20-year survival rate of 95%. These are related to long-term survival in a significant number of patients. Therapy options for differentiated thyroid cancer (DTC) have long consisted of total thyroidectomy, levothyroxine suppression therapy, and radioiodine I-131 therapy (RIT). RIT has been proven safe and effective therapy in the short term. However, any radiation exposure increases the stochastic probability of malignancy; owing to its radioactive nature and high biological half-life, it has been contemplated that I-131 exposure might lead to a higher risk for the occurrence of a second malignancy. Numerous cancers are thought to be induced by radiation exposure, based on epidemiologic studies involving environmental, medical, and occupational exposures.[2-5]

There is no unanimity in the literature regarding the second malignancy after I-131 therapy. A recent large-size study by Kim *et al*. enrolling 52,103 thyroid cancer patients who have received I-131 therapy showed a statistically significant rise in secondary cancer. These patients had a latent period ranging from months to years from radiation exposure to the development of malignancy. In general second primary malignancies are usually. However, there is also an increased incidence of salivary, kidney, breast, prostate, melanoma, non-Hodgkin lymphoma, leukemia, multiple myeloma, and brain cancer.[6]

However, an epidemiological study done by Piciu *et al*. stated that patients treated with I-131 therapy for thyroid cancers had no correlation with radioiodine's low and medium activities and the development of the second malignancy. They followed 1990 patients diagnosed with differentiated thyroid carcinoma (DTC) treated with thyroidectomy and adjuvant radioiodine therapy for a median surveillance duration of 182 months (range, 120–516 months).

How to cite this article: Mishra A, Singh V, Khandelwal Y, Smitha AM, Kavali DJ, Barai S. Incidentally detected metachronous malignancy in patients of papillary carcinoma of thyroid posthigh-dose radioiodine therapy. Indian J Nucl Med 2023;38:264-9.

Address for correspondence:
Dr. Sukanta Barai,
Department of Nuclear Medicine, SGPGIMS,
Lucknow - 226 014,
Uttar Pradesh, India.
E-mail: danzig@rediffmail.com

Received: 22-11-2022
Revised: 17-02-2023
Accepted: 17-02-2023
Published: 10-10-2023

Access this article online

Website: www.ijnm.in

DOI: 10.4103/ijnm.ijnm_188_22

Quick Response Code:

The mean radiation dose from I-131 was 63.2 mCi (2338 MBq), with a range of 30 mCi (1111 MBq) to 90 mCi (3330 MBq).[7]

During the long term, follow-up patients treated with I-131 may present with other primary malignancies. Findings reported in previous studies have confirmed that there are risks of second primary malignancy (SPM) related to radiation dose, age, and latency.[8] There is a lack of evidence and significant bias in demonstrating this relationship.[9] It is hypothesized that the increased risk of SPM may be related to a genetic predisposition or treatment-related complication. The increased risk of SPM in papillary thyroid cancer (PTC) has been reported in several cancer registries and epidemiologic studies.[10-13] It is hypothesized that the increased risk of SPM may be related to a genetic predisposition or treatment-related complication. Radioactive iodine therapy (RAI), common adjuvant therapy for the management of PTC, typically the following surgery, has been a target of debate due to side effects such as sialadenitis, taste loss, and, most critically, SPM.

We followed more than 2500 patients registered under the nuclear medicine department from 1992 to 2022. We

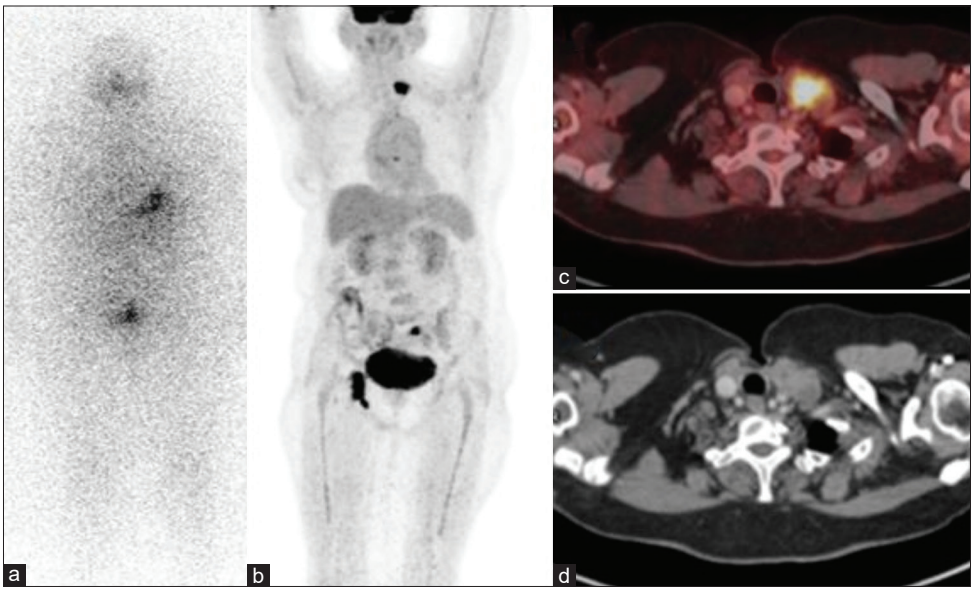

Figure 1: (a) I-131 scan showing no abnormal uptake, (b) F^{18} FDG PET/CT MIP showing abnormal uptake in the neck region, (c and d) Fused PET/CT images showing F18 FDG avid supra-mediastinal mass (metastasis from Ca right breast) and CT images showing soft tissue density mass, respectively. FDG PET/CT: Fluorodeoxyglucose positron emission tomography/computed tomography, MIP: Maximum intensity projection image

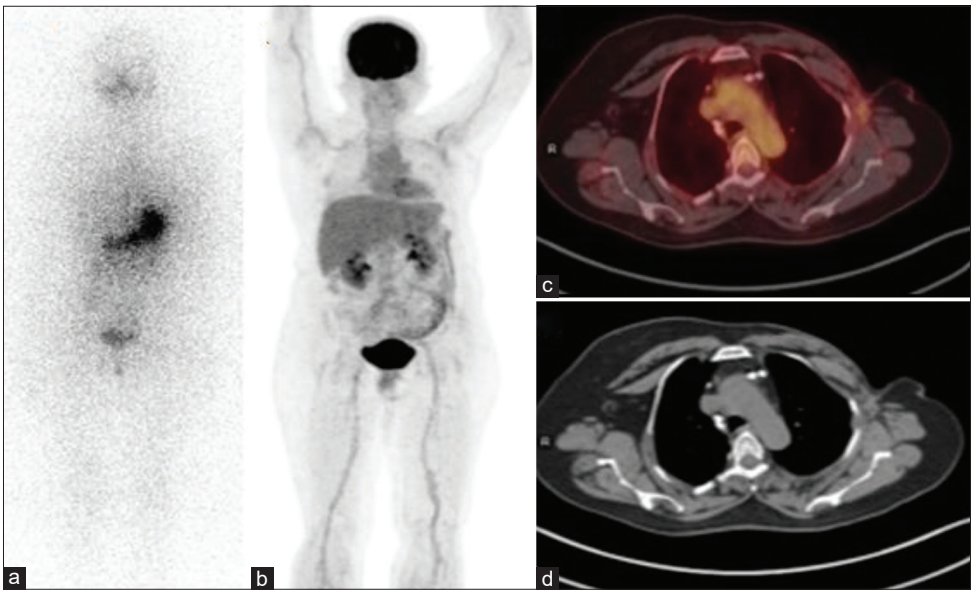

Figure 2: (a) I-131 scan showing no abnormal uptake, (b) F^{18} FDG PET/CT MIP showing abnormal uptake in the left axilla, (c and d) Fused PET/CT images showing F18 FDG avid left axillary mass (residual disease) and CT images showing soft tissue density lesion, respectively. FDG PET/CT: Fluorodeoxyglucose positron emission tomography/computed tomography, MIP: Maximum intensity projection image

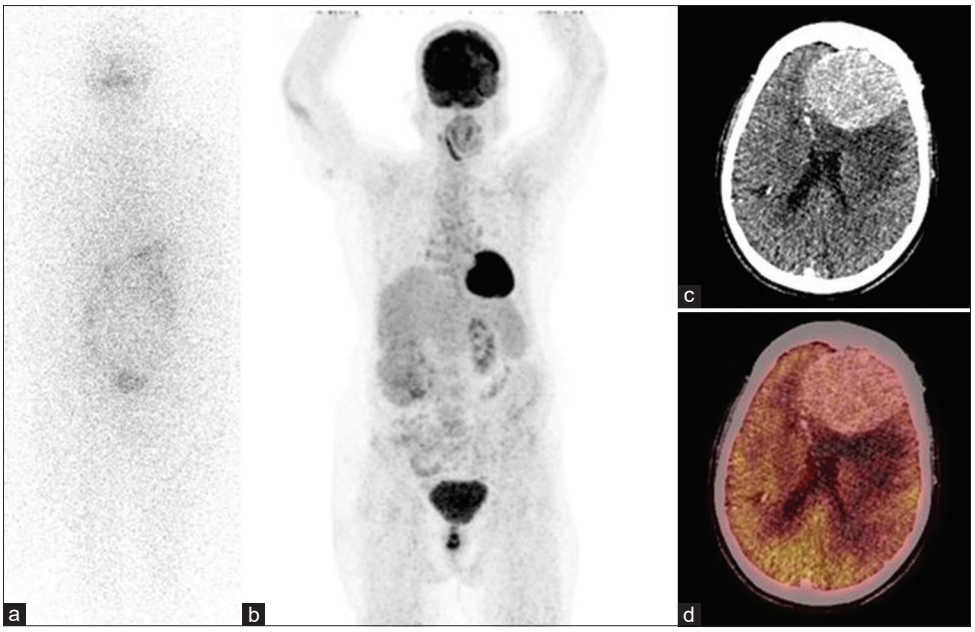

Figure 3: (a) I-131 scan showing no abnormal uptake, (b) F^{18} FDG PET/CT MIP showing increased uptake in the brain, (c and d) Fused PET/CT and CT images showing F18 FDG avid lesion soft tissue lesion in the left frontal lobe. FDG PET/CT: Fluorodeoxyglucose positron emission tomography/computed tomography, MIP: Maximum intensity projection image

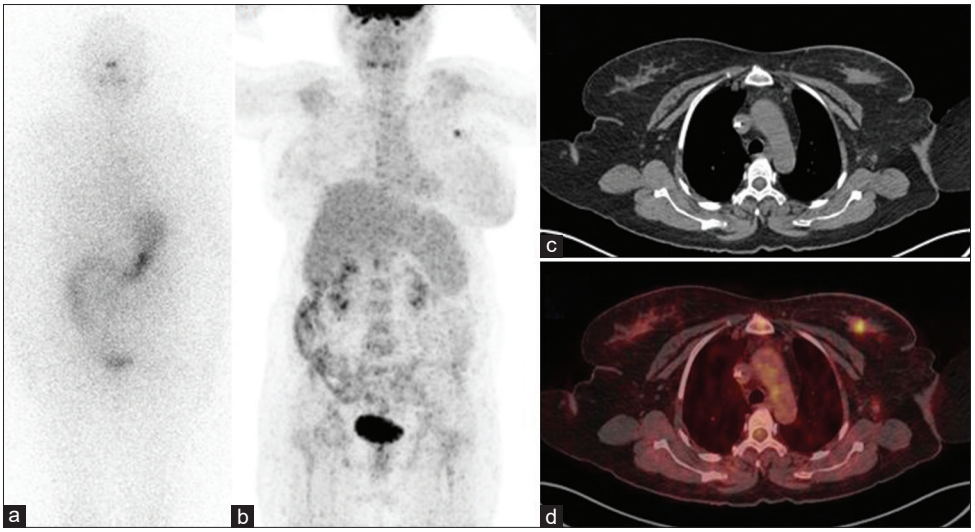

Figure 4: (a) I-131 scan showing no abnormal uptake, (b) F^{18} FDG PET/CT MIP showing abnormal uptake in the upper quadrant of the left breast, (c and d) Fused PET/CT images showing F18 FDG avid lesion in the left breast and CT images showing soft tissue density lesion, respectively. FDG PET/CT: Fluorodeoxyglucose positron emission tomography/computed tomography, MIP: Maximum intensity projection image

reviewed the departmental data retrospectively, and five patients were found to develop a SPM.

Patients particulars and history

A 66-year-old female with a history of anterior neck swelling was diagnosed with papillary carcinoma of thyroid. She underwent total thyroidectomy and was treated with 100 mCi of I-131 in October 2014. The patient was on regular follow-up and on tablet thyronorm 175 mcg. After 4 years, in 2018, she developed a lump in the right breast with nipple retraction and was diagnosed with infiltrating ductal carcinoma (IDC) subsequently on tru-cut biopsy of the right breast lump. She underwent breast conservation surgery in April 2018 and was ER/PR+ve and HER2nu−ve on histochemistry [Figure 1].

A 60-year-old female presented with neck swelling and was diagnosed with papillary carcinoma thyroid. She underwent a total thyroidectomy in 2007. She was treated with 40 mCi of I131 in 2008. The patient was on follow-up with 100 mcg of thyronorm and presented with left breast swelling in January 2022. Fine-needle aspiration cytology (FNAC) (January 11, 2022). She underwent left modified radical mastectomy, HPE-IDC [Figure 2].

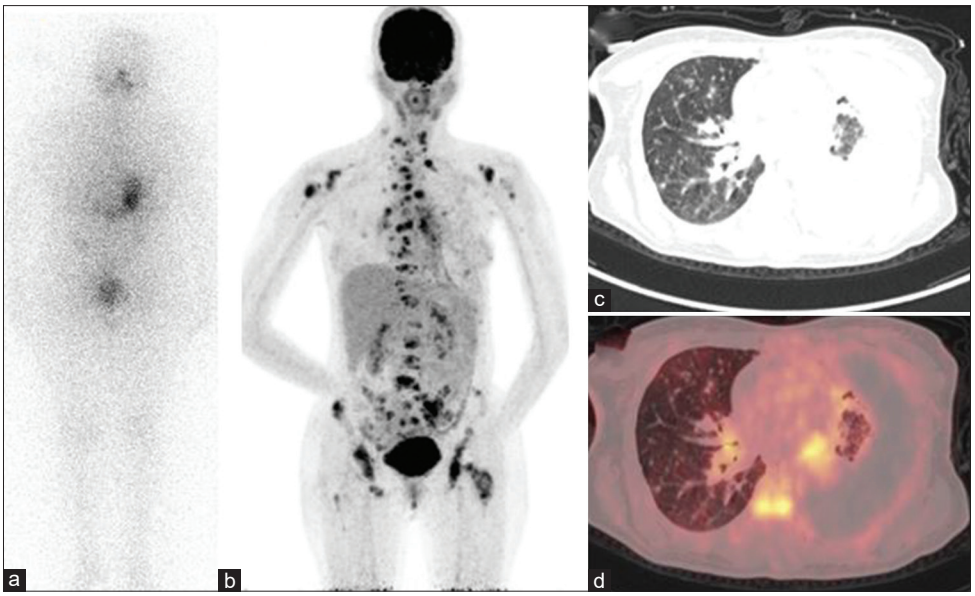

Figure 5: (a) I-131 scan showing no abnormal uptake, (b) F^{18} FDG PET/CT MIP showing extensive metastasis and mediastinal lesions, (c and d) Fused PET/CT images showing F18 FDG avid left pleural thickening and CT images showing left pleural effusion. FDG PET/CT: Fluorodeoxyglucose positron emission tomography/computed tomography, MIP: Maximum intensity projection image

A 52-year-old male presented with left neck swelling. He underwent left hemithyroidectomy. HPE-PCT (tall-cell variant). Completion thyroidectomy was done on May 15, 2015. 50 mCi of I-131 was given orally under supervision on July 23, 2015. The patient was advised suppression with 175 mcg of thyronorm and presented with a headache in September 2021. Contrast Enhance MRI- showed solid cystic extra-axial lesion in left temporal lobe which shows post contrast enhancement in solid component suggestive of meningioma Grade I [Figure 3].

A 48-year-old female patient presented with anterior neck swelling for the past 2 years. She underwent total thyroidectomy with left paratracheal dissection in October 2020. histopathological examination (HPE)- suggestive of multifocal PCT. She was treated with 100 mCi of I-131 on December 28, 2020. Susequently she complained of breast swelling in April 2022. Mammography – left breast – an irregular high-density mass with partly speculated and partly indistinct margins measuring 28 × 26 × 30 mm is seen in the upper outer quadrant in the middle third of the left breast. Intralesional fine pleomorphic and linear calcifications were also noted. Core biopsy and immunohistochemistry (IHC) – suggestive of IDC Grade II, ER/PR-Her-2-neu: 3 + Ki67 35%–40%. She underwent left breast conservation surgery on May 30, 2022, HPE [Figure 4].

A 41-year female presented with anterior neck swelling, diagnosed with papillary carcinoma thyroid. She underwent total thyroidectomy, followed by subsequent radioiodine therapy with 70 mCi of Iodine-131. The patient achieved remission and remained disease-free for 3 years when she developed right neck swelling and dyspnea. Computed tomography revealed severe left pleural effusion left lung mass in October 2019. FNAC from the right cervical swelling and cytopathology of the pleural fluid showed the presence of malignant cells. Biopsy of the cervical lymph node revealed metastatic adenocarcinoma with CK7 and TTF1 positive, and CK20 and thyroglobulin are negative. Mutation for epidermal growth factor receptor was positive. Diagnosis of carcinoma lung was established by combining radiological, histopathology, and IHC finding [Figure 5].

Discussion

Of five patients who developed a SPM in our study, three patients developed breast carcinoma, one patient developed lung cancer, and one developed meningioma. The old studies state that overall hematological malignancies are one of the most common malignancies. All five patients in our study developed solid malignancy, and none developed hematological malignancy. The average I-131 dose to the patient is 72 mCi ranging from 40 mCi to 100 mCi. There is no minimum and maximum amount of radiation that causes second malignancy.

There was an increased incidence of SPM among patients diagnosed with PTC at a younger age. Radiation therapy, including RAI, is known to increase the risk of SPM, especially bone cancer, kidney cancer, hematologic malignancies, and prostate cancer, in multiple studies. This maybe because RAI accumulates in the bone marrow and is excreted through the kidneys. The salivary gland and breast express Na^+/I^- symporter, which promotes selective uptake of RAI.[14-16]

Even though the overall incidence rate was lower, patients who did not undergo any RAI still had an increased

incidence of SPM. This may be due to the genetic susceptibility of thyroid cancer patients. Studies suggest that the telomerase reverse transcriptase mutation and germline mutations of folliculin are associated with kidney cancer and PTC.[17,18] Mutations of CHEK2 are also associated with an increased risk of kidney, thyroid, prostate, and breast cancers.[19-21] In this study, 60% of patients developed breast carcinoma out of the SPM. It maybe due to more uptake of I-131 in the breast due to NaI symporter leading to more radiation exposure to the breast tissue. However, a dose of radiation to the patient does not correlate with developing a second malignancy. This incidence of cancers maybe due to genetic mutations like CHEK 2 inhibitors.

The recent advances in genomic diagnostics may enable tailoring screening strategies for patients with primary thyroid cancer for further risk of SPM. It is demonstrated decreased incidence of colorectal cancer in thyroid cancer survivors who did not undergo radiation therapy. There is evidence that a higher thyroid hormone level induces cell differentiation and mitigates tumor formation in colorectal cancer stem cells.[22] Since thyroid cancer survivors tend to be on TSH suppression therapy, they typically have higher thyroid hormone levels than their counterparts; this may unexpectedly lead to decreased incidence of colorectal cancer.

Thyroid carcinoma are more common in young patients with overalll good prognosis. The carcinogenic risk associated with the therapeutic administration of radioiodine needs to be quantified. Some organs are of particular concern because radioiodine is actively concentrated in the tissue (e.g., the salivary glands) or because they are the therapeutic route of administration (e.g., the digestive tract). Three factors on which radiation dose is delivered to healthy tissue depend on the administered activity, the uptake by the tissue, and the length of time that the isotope resides in the target tissue. Compared with the general population reference rates, an excess of 20%–90% of second cancer incidence after thyroid carcinoma has been observed in most large cohort studies.[23] An excess of second cancer in survivors of first cancer might result from detection and surveillance bias, shared genetic or environmental risk factors, or first cancer treatment.

Conclusion

Few instances of metachronous malignancy are noted after I-131 therapy. A study indicated that high radioiodine activity during thyroid carcinoma treatment probably increases the risk of future leukemia, salivary gland, digestive tract cancer, soft tissue, and bone sarcomas. However, no definitive association is noted. Nevertheless, we did not know the exact shape of the relationship between the activity administered and the risk of second cancer. We did not even know that metachronous malignancy is due to I-131 therapy or genetic mutation with syndromic involvement. Therefore, according to our study, although the risk of malignancy due to I-131 therapy is very low or I-131 therapy is very safe, we should plan radioiodine treatment very judicially and smartly by considering each factor. The risk–benefit ratio should be thoroughly considered before treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Mazzaferri EL, Kloos RT. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001;86:1447-63.
2. Kendall GM, Muirhead CR, Darby SC, Doll R, Arnold L, O'Hagan JA. Epidemiological studies of UK test veterans: I. General description. J Radiol Prot 2004;24:199-217.
3. Yoshinaga S, Mabuchi K, Sigurdson AJ, Doody MM, Ron E. Cancer risks among radiologists and radiologic technologists: Review of epidemiologic studies. Radiology 2004;233:313-21.
4. Hamatani K, Eguchi H, Ito R, Mukai M, Takahashi K, Taga M, *et al.* RET/PTC rearrangements preferentially occurred in papillary thyroid cancer among atomic bomb survivors exposed to high radiation dose. Cancer Res 2008;68:7176-82.
5. Zablotska LB, Nadyrov EA, Rozhko AV, Gong Z, Polyanskaya ON, McConnell RJ, *et al.* Analysis of thyroid malignant pathologic findings identified during 3 rounds of screening (1997-2008) of a cohort of children and adolescents from belarus exposed to radioiodines after the Chernobyl accident. Cancer 2015;121:457-66.
6. Kim C, Bi X, Pan D, Chen Y, Carling T, Ma S, *et al.* The risk of second cancers after diagnosis of primary thyroid cancer is elevated in thyroid microcarcinomas. Thyroid 2013;23:575-82.
7. Piciu D, Pestean C, Barbus E, Larg MI, Piciu A. Second malignancies in patients with differentiated thyroid carcinoma treated with low and medium activities of radioactive I-131. Clujul Med 2016;89:384-9.
8. de Vathaire F. The carcinogenic effects of radioiodine therapy for thyroid carcinoma. Nat Clin Pract Endocrinol Metab 2008;4:180-1.
9. Fallahi B, Adabi K, Majidi M, Fard-Esfahani A, Heshmat R, Larijani B, *et al.* Incidence of second primary malignancies during a long-term surveillance of patients with differentiated thyroid carcinoma in relation to radioiodine treatment. Clin Nucl Med 2011;36:277-82.
10. Teng CJ, Hu YW, Chen SC, Yeh CM, Chiang HL, Chen TJ, *et al.* Use of radioactive iodine for thyroid cancer and risk of second primary malignancy: A nationwide population-based study. J Natl Cancer Inst 2016;108:djv314.

11. Marti JL, Jain KS, Morris LG. Increased risk of second primary malignancy in pediatric and young adult patients treated with radioactive iodine for differentiated thyroid cancer. Thyroid 2015;25:681-7.
12. Clement SC, Kremer LC, Links TP, Mulder RL, Ronckers CM, van Eck-Smit BL, *et al.* Is outcome of differentiated thyroid carcinoma influenced by tumor stage at diagnosis? Cancer Treat Rev 2015;41:9-16.
13. Patel SS, Goldfarb M. Well-differentiated thyroid carcinoma: The role of post-operative radioactive iodine administration. J Surg Oncol 2013;107:665-72.
14. Wapnir IL, van de Rijn M, Nowels K, Amenta PS, Walton K, Montgomery K, *et al.* Immunohistochemical profile of the sodium/iodide symporter in thyroid, breast, and other carcinomas using high density tissue microarrays and conventional sections. J Clin Endocrinol Metab 2003;88:1880-8.
15. Dohán O, De la Vieja A, Paroder V, Riedel C, Artani M, Reed M, *et al.* The sodium/iodide symporter (NIS): Characterization, regulation, and medical significance. Endocr Rev 2003;24:48-77.
16. Dohán O, Carrasco N. Advances in Na(+)/I(-) symporter (NIS) research in the thyroid and beyond. Mol Cell Endocrinol 2003;213:59-70.
17. Dong L, Gao M, Hao WJ, Zheng XQ, Li YG, Li XL, *et al.* Case report of birt-hogg-dubé syndrome: Germline mutations of FLCN detected in patients with renal cancer and thyroid cancer. Medicine (Baltimore) 2016;95:e3695.
18. Bell RJ, Rube HT, Kreig A, Mancini A, Fouse SD, Nagarajan RP, *et al.* Cancer. The transcription factor GABP selectively binds and activates the mutant TERT promoter in cancer. Science 2015;348:1036-9.
19. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell 2014;159:676-90.
20. Siołek M, Cybulski C, Gąsior-Perczak D, Kowalik A, Kozak-Klonowska B, Kowalska A, *et al.* CHEK2 mutations and the risk of papillary thyroid cancer. Int J Cancer 2015;137:548-52.
21. Cybulski C, Huzarski T, Górski B, Masojć B, Mierzejewski M, Debniak T, *et al*. A novel founder CHEK2 mutation is associated with increased prostate cancer risk. Cancer Res 2004;64:2677-9.
22. Catalano V, Dentice M, Ambrosio R, Luongo C, Carollo R, Benfante A, *et al.* Activated thyroid hormone promotes differentiation and chemotherapeutic sensitization of colorectal cancer stem cells by regulating Wnt and BMP4 signaling. Cancer Res 2016;76:1237-44.
23. Sandeep TC, Strachan MW, Reynolds RM, Brewster DH, Scélo G, Pukkala E, *et al.* Second primary cancers in thyroid cancer patients: A multinational record linkage study. J Clin Endocrinol Metab 2006;91:1819-25.